



# TOOLKIT FOR RESEARCH AND DEVELOPMENT OF PAEDIATRIC ANTIRETROVIRAL DRUGS AND FORMULATIONS

WHO and UNITAID

in collaboration with IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) network, PENTA (Paediatric European Network for Treatment of AIDS) foundation and experts from the Paediatric Antiretroviral Working Group





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**ISBN 978-92-4-151436-1**

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**Cataloguing-in-Publication (CIP) data.** CIP data are available at <http://apps.who.int/iris>.

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Printed in Switzerland

# CONTENTS

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<b>Abbreviations</b> .....	iv
<b>Acknowledgements</b> .....	vi
<b>Introduction</b> .....	1
<b>Module 1: Trial design</b> .....	9
<b>Module 2: Pharmacokinetic modelling</b> .....	32
<b>Module 3: Pregnant and breastfeeding women</b> .....	45
<b>Module 4: Coinfections</b> .....	61
<b>Module 5: Acceptability</b> .....	78
<b>Module 6: Community engagement</b> .....	104
<b>Module 7: Target product profiles</b> .....	120
<b>Module 8: Product commercialization</b> .....	138
<b>Module 9: Regulatory filing</b> .....	148
<b>Module 10: Pharmacovigilance</b> .....	162
<b>Conclusion</b> .....	185

# ABBREVIATIONS

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<b>3TC</b>	lamivudine
<b>ABC</b>	abacavir
<b>ART</b>	antiretroviral therapy
<b>ARV</b>	antiretroviral
<b>AUC24 h</b>	24-hour area under the concentration–time curve
<b>C24 h</b>	24-hour plasma concentration
<b>CL</b>	clearance
<b>CYP</b>	cytochrome 450
<b>DTG</b>	dolutegravir
<b>EFV</b>	efavirenz
<b>EMA</b>	European Medicines Agency
<b>EU</b>	European Union
<b>FDA</b>	United States Food and Drug Administration
<b>FTC</b>	emtricitabine
<b>HBV</b>	hepatitis B virus
<b>HCV</b>	hepatitis C virus
<b>IMPAACT</b>	International Maternal Pediatric Adolescent AIDS Clinical Trials
<b>LPV/r</b>	lopinavir/ritonavir
<b>NRTI</b>	nucleoside reverse-transcriptase inhibitor
<b>PANNA</b>	Pharmacokinetics of Newly Developed Antiretroviral Agents in HIV-Infected Pregnant Women
<b>PENPACT</b>	PENTA 9/PACTG 390
<b>PENTA</b>	Paediatric European Network for Treatment of AIDS
<b>PEPFAR</b>	United States President’s Emergency Plan for AIDS Relief
<b>TAF</b>	tenofovir alafenamide
<b>TB</b>	tuberculosis
<b>TDF</b>	tenofovir disoproxil fumarate
<b>UGT</b>	uridine diphosphate-glucuronosyltransferase
<b>UNICEF</b>	United Nations Children’s Fund
<b>WT</b>	body weight



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# ACKNOWLEDGEMENTS

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The toolkit for research and development of paediatric antiretroviral drugs and formulations was developed under the leadership of the Treatment and care team in the HIV Department, WHO, and supported by the WHO Paediatric Antiretroviral Working Group. The project was led by Martina Penazzato (WHO Paediatric HIV Lead, Geneva, Switzerland) and coordinated by Claire Townsend (WHO consultant, Geneva, Switzerland). Each module was drafted by one or more co-authors (listed in each module), with input from other collaborators and the project team. Designated reviewers reviewed the modules, including at least one member of the Paediatric Antiretroviral Working Group and one external reviewer. Input from representatives of drug manufacturers and regulatory authorities was sought at key stages.

WHO and Unitaid thank everyone who contributed to developing this toolkit, including individuals from the Clinton Health Access Initiative, Drugs for Neglected Diseases initiative, Medicines Patent Pool, ICAP at Columbia University, the European Paediatric Formulation Initiative and the IQ Consortium Drug Product Working Group.

Specifically, we thank the following individuals for their input: Elaine Abrams (ICAP at Columbia University, New York, NY, USA), Sharon Nachman (State University of New York at Stony Brook, USA), Polly Clayden (HIV i-base, London, United Kingdom), Carlo Giaquinto (University of Padua, Italy), Marissa Vicari (International AIDS Society, Geneva, Switzerland) and Diana Gibb (University College London, United Kingdom).

Comments were also provided by the Division of Antiviral Products of the United States Food and Drug Administration and by representatives of the European Medicines Agency and members of the European Medicines Agency Paediatric Committee. Any views expressed in this publication by employees of the United

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The contents of this document do not necessarily reflect the official views of the United States Department of State.

The toolkit was developed with the financial support of Unitaid, the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network and the PENTA Foundation. The work of the Clinton Health Access Initiative on optimal antiretroviral drugs for children is made possible through the generous support of Unitaid.

## List of partner organizations

- International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network
- PENTA-ID Network
- Unitaid
- Drugs for Neglected Diseases initiative
- Clinton Health Access Initiative
- United Nations Children's Fund
- ICAP at Columbia University
- Elizabeth Glaser Pediatric AIDS Foundation
- Industry Liaison Forum
- United States President's Emergency Plan for AIDS Relief
- Collaborative Initiative for Paediatric HIV Education and Research
- Medicines Patent Pool





# INTRODUCTION

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# 1. BACKGROUND

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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

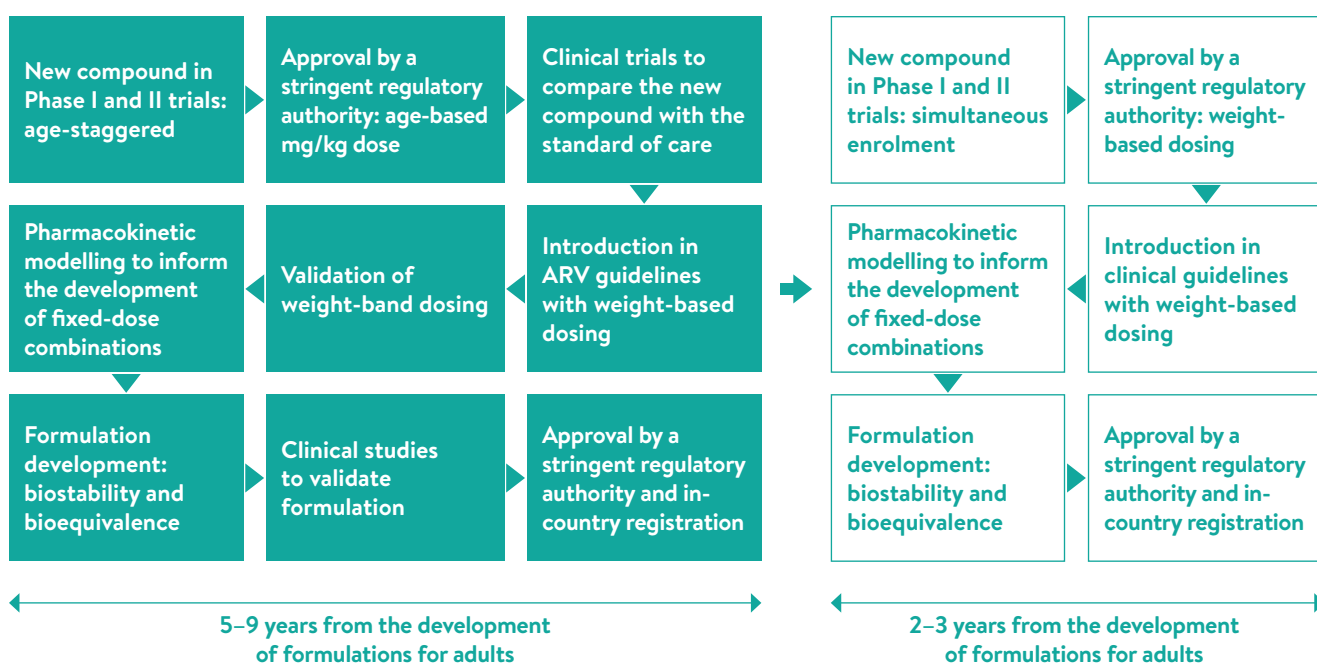
Research and development of formulations of ARV drugs for children has traditionally lagged behind those for adults, with delays of up to a decade (Fig. 1) (5). The development of drugs for children is often only considered once preclinical, Phase I and Phase II studies end, which can take many years. 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

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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:

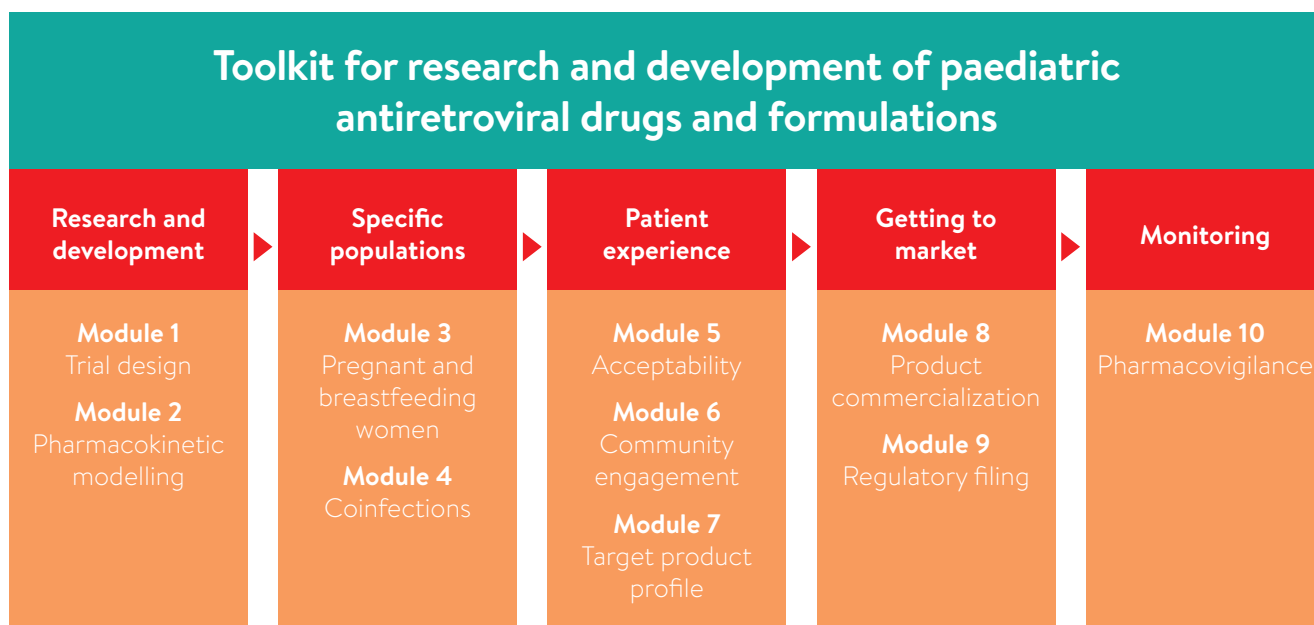
- innovator and generic drug manufacturers;
- researchers involved in research and development related to HIV drugs for children; and
- nongovernmental and other organizations with an interest in drug development.

### 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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# MODULE 1: TRIAL DESIGN

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# 1. INTRODUCTION

The overarching goal of this toolkit is to facilitate the treatment of children with HIV with the most efficacious medications. The selection of the right drugs and formulations given priority for development is based on target product profiles (see the module on target product profiles). Nevertheless, before an agent can be approved for use by regulatory bodies or included in national and global guidelines, data about dosing, safety and efficacy must be considered adequate in the intended population of children. This module reviews issues in selecting a clinical trial design to generate the necessary data about a candidate antiretroviral (ARV) drug for children as quickly and efficiently as possible.

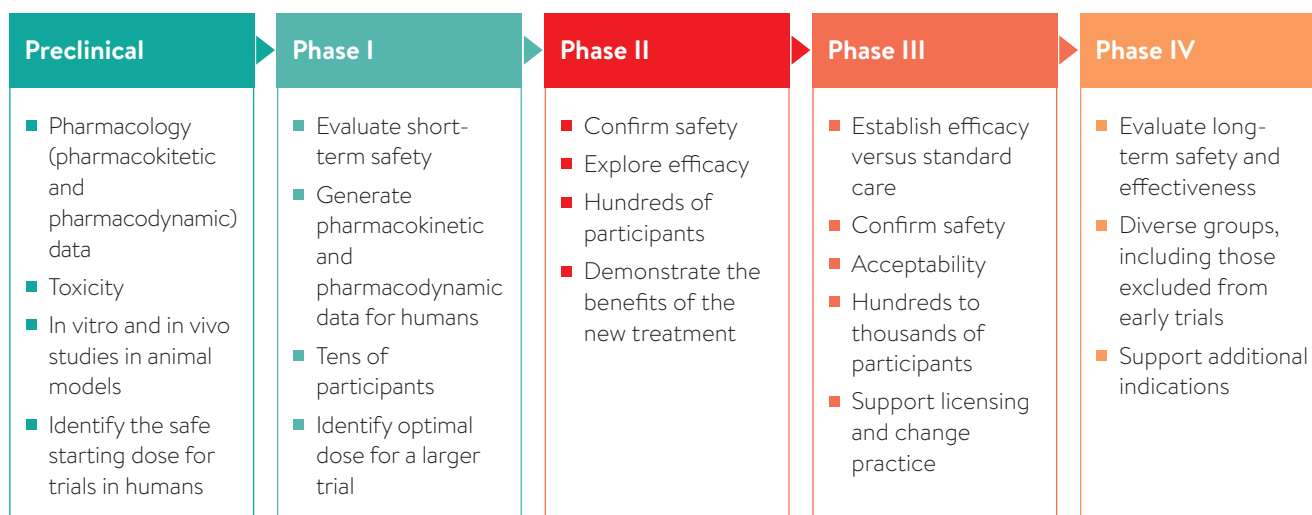
The development and evaluation of ARV drugs for children has historically been slow, with some agents being approved for children as long as a decade after they were approved for adults (1,2). The limited number of agents with age-appropriate ARV drug dosing and formulations for children has remained a key barrier to simplifying, harmonizing and implementing WHO treatment guidelines in low- and middle-income countries,

where most children with HIV live (1). To generate the timely data about modern ARV drugs needed for children in the fast-changing landscape of the ARV drug pipeline and dynamic treatment guidelines, clinical trials must be strategic, forward-thinking and efficient in implementation.

## 1.1 General considerations for HIV drug trials involving children

Clinical trials for drug development are classically divided into four phases: I to IV (Fig. 1.1). After preclinical study in the laboratory, a drug is generally first tested in humans in Phase I trials that generate key safety and pharmacokinetic and pharmacodynamic data for small numbers of participants. Phase I trials are generally dose-finding trials that might aim to establish the maximally tolerated dose for adults or identify the dosing for children that yields exposure equivalent to that of adults. Phase II trials confirm safety and explore efficacy to facilitate decisions about further development. Phase III trials are pivotal trials that confirm safety and

**Figure 1.1.** Phases of clinical trials



establish efficacy among a larger number of participants; Phase III data are generally required for regulatory approval of a new drug for adults. Phase IV trials generate data on long-term safety and/or efficacy for a new drug after it has been licensed in real-world conditions across different populations. Developing drugs for children and treatment optimization trials often combine features of different phases, commonly blending Phases I and II and Phases II and III.

Clinical drug trials can also be classified into two broad categories: regulatory and strategy trials.

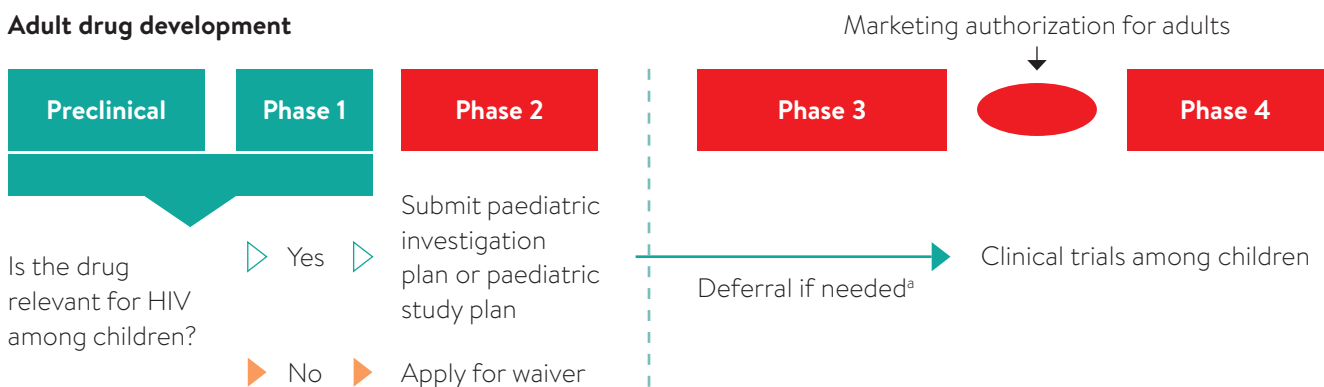
Regulatory trials are conducted for licensing applications that seek approval by stringent regulatory authorities and may include features of Phase I–III trials (dose-finding, safety and efficacy), depending on the extent to which the relevant data from adult studies can be extrapolated (see below). These trials generally focus on pharmacokinetics and safety and use age-appropriate drug formulations for children already tested in adults for bioequivalence with the adult formulations.

To secure approval for an agent for adults, stringent regulatory authorities such as the United States Food and Drug Administration (FDA) or European Medicines Agency (EMA) require pharmaceutical companies to either

submit plans to study the agent among children or request a waiver (3,4). The EMA calls a plan for study among children a paediatric investigation plan and the FDA calls it a paediatric study plan. Stringent regulatory authorities require a paediatric investigation plan or paediatric study plan for every new drug being developed for adults that is considered to be relevant for children. Paediatric investigation plans or paediatric study plans are required to be submitted early in drug development (3,4) and must be established before filing for the marketing authorization (Fig. 1.2 and the module on regulatory filing). Trials for developing and evaluating drugs for children are usually started once trials involving adults show substantial evidence of the efficacy and safety of the drug of interest. Waivers are difficult to obtain but can be granted if an agent is not thought to have a role in care for children and/or because it would be logistically impossible to study (such as finding eligible child participants being too difficult).

In determining which data are needed to support regulatory approval of an agent for use among children, it is critical to first ask what data can be extrapolated from adult trials and what data must be generated de novo in trials involving children. Fig. 1.3 summarizes FDA guidance on this topic. Depending on evidence-based assumptions on

**Fig. 1.2.** Timing of the development pathway for HIV drugs for children



<sup>a</sup>Additional efficacy and safety data for adults are needed before initiating studies among children.

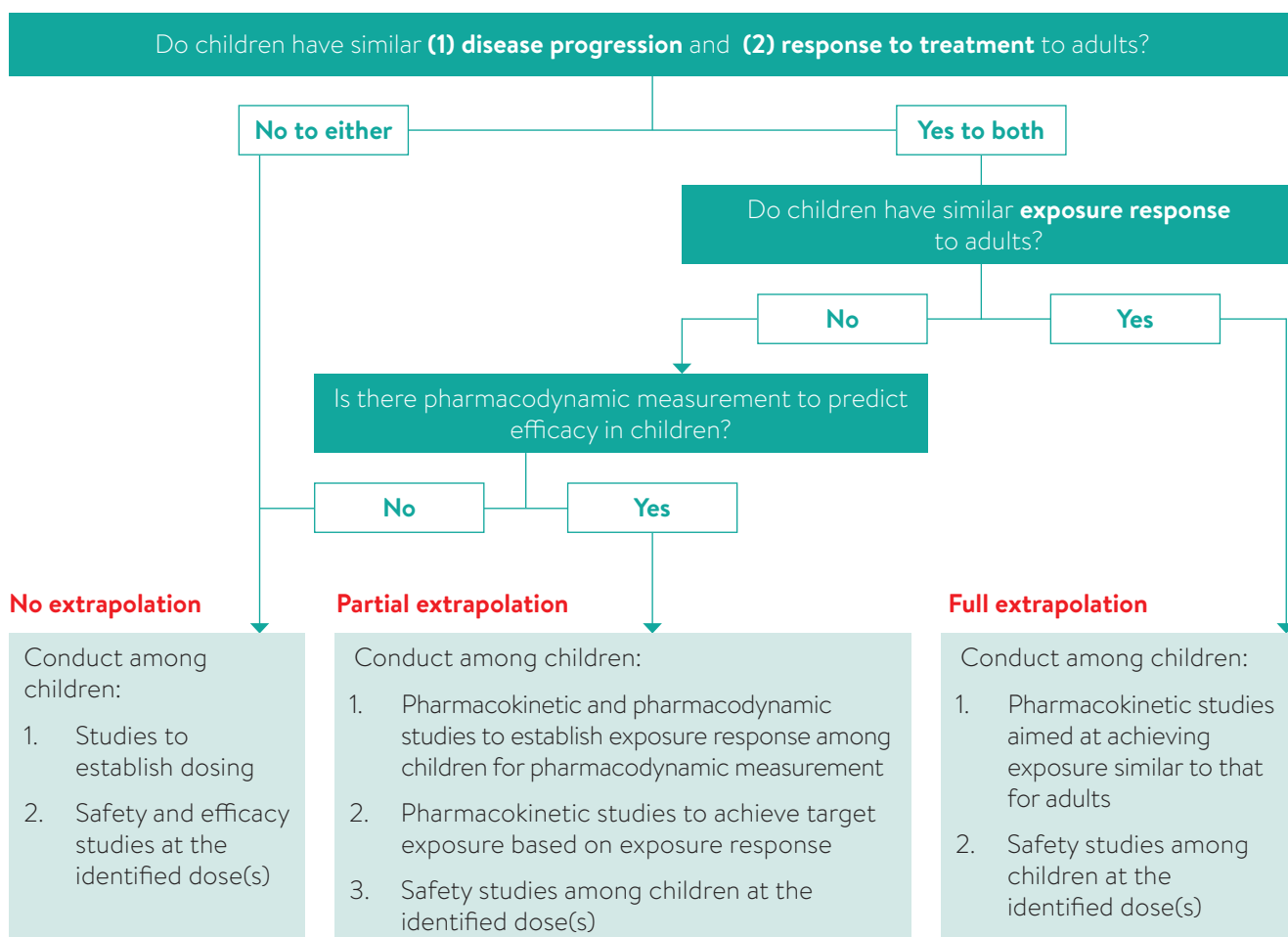
Source: reprinted from The Lancet Oncology, 14, Vassal G, Zwaan CM, Ashley D, Le Deley MC, Hargrave D, Blanc P et al., New drugs for children and adolescents with cancer: the need for novel development pathways, e117–24, Copyright (2013), with permission from Elsevier. (5)

the appropriateness of extrapolating efficacy from adult trials, the regulatory trials can differ in design, ranging from non-comparative studies evaluating pharmacokinetics and safety (extrapolation possible) to a randomized controlled trial, evaluating pharmacokinetics, safety and efficacy (no extrapolation possible). Some agents, such as immunomodulatory agents designed for cure strategies, may rely on mechanisms that cannot be reasonably extrapolated to children; these agents require more study, probably including evidence of efficacy for children, to be approved. Nevertheless, for studies of most ARV drugs that target the viral life cycle among children, it is generally accepted that progression of HIV, response to

treatment and exposure–response relationships are similar for children and adults, and efficacy evidence from adult Phase III trials can therefore be extrapolated to children. In other words, Phase I/II pharmacokinetic and safety non-comparative trials are generally considered sufficient to support regulatory approval of ARV drugs for children if the same exposure as for adults can be achieved.

In contrast to regulatory trials, strategy trials are used to evaluate various treatment approaches, such as the sequence of regimens for first-, second- and third-line therapy, treatment simplification and use of more pragmatic dosing compared with the standard of care and focus on

**Fig. 1.3.** Algorithm for planning and extrapolating studies for children



Sources: adapted from *General clinical pharmacology considerations for pediatric studies for drugs and biological products: guidance for industry 2014* (4) and Dunne et al. (6).

effectiveness (efficacy in the real world). Strategy trials aim to optimize drug delivery and uptake, to improve safety, adherence, acceptability or quality of life and to explore potentially better treatment options for children with coinfections. These trials can nest pharmacokinetic substudies to evaluate dosing differing from the licensed dosing, such as once-daily dosing (7–9) or more pragmatic dosing with a limited number of formulations to simplify procurement, prescribing and drug administration (10). Strategy trials are usually carried out after a stringent regulatory authority has already approved a drug, but the regulatory and strategy trials may overlap (Fig. 1.4) (10,11). Strategy trials often bridge a gap from the data required for regulatory approval to the data needed to inform clinical use and guideline development and address the existing knowledge gaps in pharmacokinetics and pharmacodynamics, pharmacogenomics and long-term age-specific toxicity. Given the cost and time to set them up, they must efficiently answer as many questions as

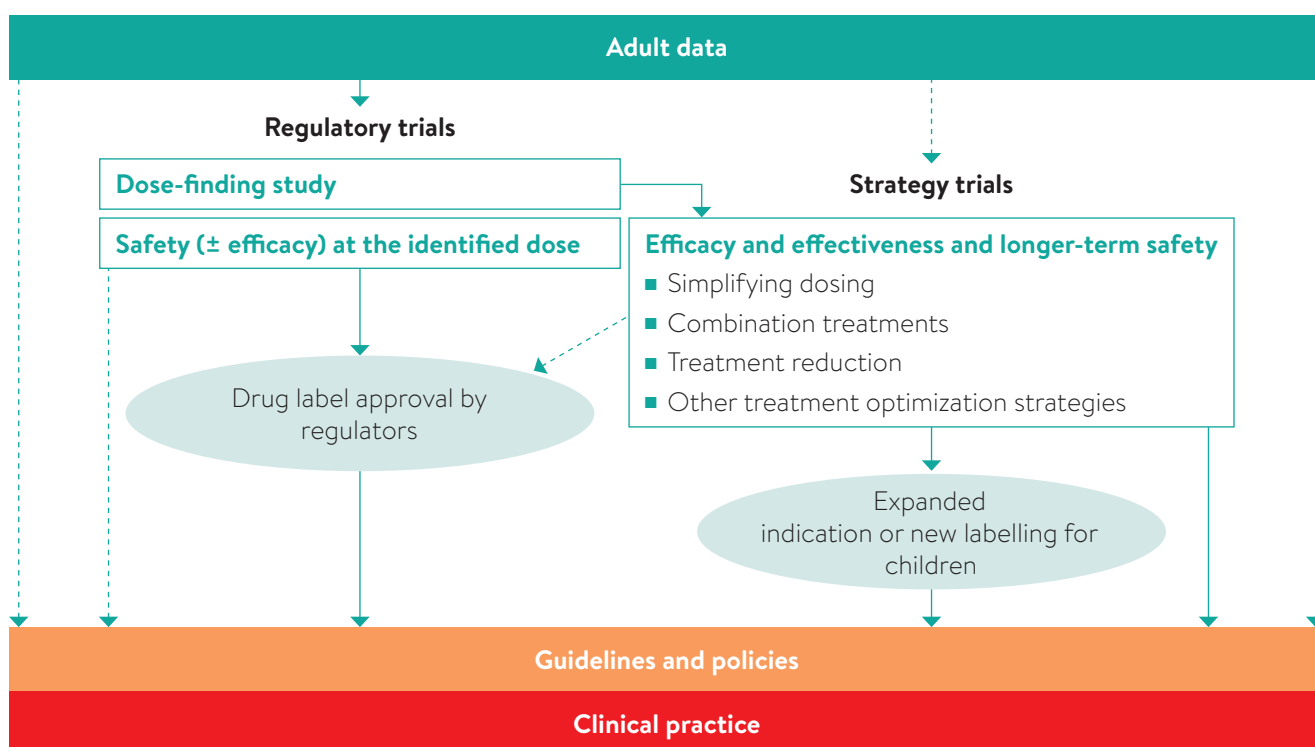
possible. Strategy trials are usually Phases III–IV and use randomized controlled designs, although single-arm designs can be also used when a randomized controlled trial is not feasible and the assumptions for thresholds for success or failure can be prespecified (12).

The effectiveness of an agent or regimen in real-world use is generally studied using large observational databases from clinical settings. Such studies can only be carried out once an agent has been approved and distributed for use in routine clinical care. These types of studies can be useful for modifying guidelines and informing new strategy trials (see the module on pharmacovigilance).

## 1.2 Approach to trial design

The process of any trial design starts with clarifying the key questions defining the main

**Fig. 1.4.** Developing drugs and optimizing treatment for children living with HIV: from dose-finding to clinical practice



objectives. Primary outcomes answer the most important questions and are measured by the primary endpoints. In trials evaluating drugs, a primary endpoint can be targeted drug exposure parameters, safety outcome (such as the proportion or rate of clinical and laboratory adverse events) or efficacy outcome (such as survival or absence of progression in HIV disease). A good endpoint should be clinically relevant, well defined and objective. Validated surrogate endpoints correlating with clinical outcomes are frequently used to speed up treatment evaluation (such as HIV-1 viral load suppression at certain time points). Many contemporary trials set a composite primary endpoint that combines clinical and surrogate endpoints. This enables the capture of a clinically relevant endpoint (such as death)

among people for whom surrogate endpoints could not be measured in time. Secondary endpoints measure other important outcomes for patients, clinicians and policy-makers, such as the safety, tolerability, adherence, acceptability and cost-effectiveness of the intervention.

Box 1.1 and Fig. 1.5–1.8 briefly summarize the trial designs, including advantages, limitations and examples. Ford et al. (13) provide more details on HIV strategy trials involving children.

Good design is one of the most important aspects of a clinical trial. Poor design could cause resources to be wasted or a promising treatment to be wrongly abandoned, and this is arguably unethical for trial participants who need new treatment options.

## **Box 1.** Examples of clinical trial designs

### **Open-label single-arm trial**

Single-arm trials are commonly used for initially assessing safety and efficacy of novel regimens (Phases I and II) before proceeding to evaluation in a randomized controlled trial. They are also used when randomized controlled trials are not feasible (such as evaluating treatment in a small population with specific characteristics). In these trials, pre-specified safety and efficacy thresholds based on previous trials are used for comparing with the experimental intervention (12). The advantages of the design are small size and often short trial duration, whereas disadvantages include limited generalizability and comparability with the results of previous trials, since the difference with the set threshold can result from other factors than the studied intervention (12).

The design is also commonly used for pharmacokinetic and safety evaluation of drugs for children when (1) disease progression, (2) response to treatment and (3) response to exposure are assumed to be similar among children and adults (6). The trials start with the initial estimated doses for each age- or weight-based cohort using modelling and simulation that target exposure similar to those for adults. The sample size for evaluation of drug exposure is determined by variability (standard deviation) of the pharmacokinetic parameter of interest. The estimates of variability can be obtained from different sources, including pharmacokinetic studies in adults, physiologically based pharmacokinetic models, previous pharmacokinetic studies involving children and pharmacokinetic studies of drugs with similar physiochemical and metabolic characteristics (14). One approach to estimate the sample size would be to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for each subgroup of children to achieve at least 80% power (15). Two approaches for data analysis can be used: a standard non-compartmental pharmacokinetic approach and a population pharmacokinetic approach. The FDA (4) has provided further guidelines on dose selection, sample size and data analysis for children.

Evaluating safety at the selected doses aims to assess any signals of toxicity identified in animal studies and trials involving adults. However, trials involving children are generally not required to be powered for assessing specific adverse reactions in a statistically rigorous way. The sample size is often determined by the size of the affected population; a sample size of 100 patients across a range of ages is commonly considered as a minimum requirement, since it provides some confidence that a specific adverse reaction is observed at least once in the trial if the true rate is at least 3% (16). The length of follow-up for chronic infections is usually 24–48 weeks. Longer-term safety monitoring may be warranted if there are growth and development concerns. The trials can also provide supportive (non-confirmatory) efficacy results that can be indirectly compared with the current standard of care based on previous trials. IMPAACT (International Maternal, Pediatric, Adolescent AIDS Clinical Trials) P1066 was a Phase I and II open-label multicentre trial evaluating the dosing and safety of multiple raltegravir formulations for children (17,18). The shortcomings of this approach become apparent if the initial studied dose does not reach the target, causing the trial to be extended. Parallel dose-ranging short pilot studies and adaptive designs can provide valuable solutions (see below).

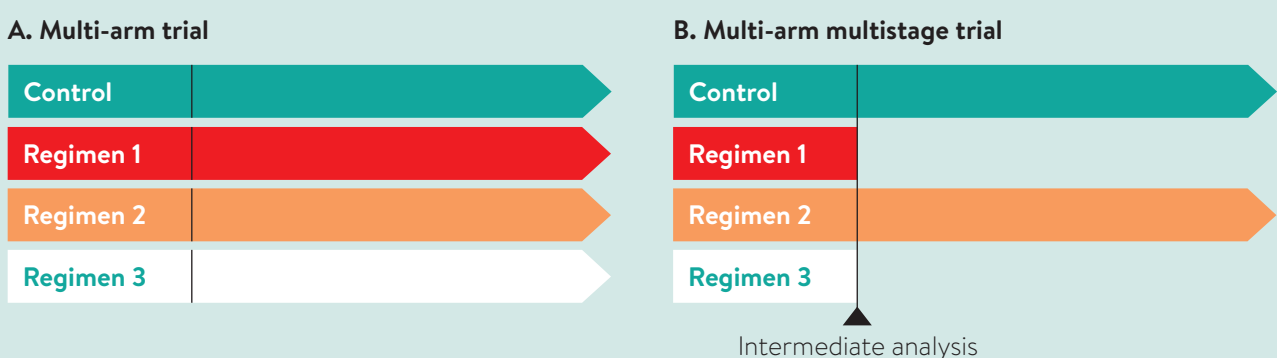
### Traditional randomized controlled trials

A randomized controlled trial is a gold standard for evaluating various treatments. In a traditional two-arm trial, participants are randomly allocated to one of the treatment arms: intervention or control. The control arm receives current standard of care, alternative treatment or, if appropriate, placebo. Although the parallel design enables rigorous comparison of two treatments, randomized controlled trials can be costly and laborious to perform and should therefore generally be reserved for questions that will clearly change management. The PROMOTE paediatric trial randomized children to non-nucleoside reverse-transcriptase inhibitors or lopinavir-based antiretroviral therapy (ART) (19).

### Multi-arm trials (Fig. 1.5)

Participants are randomized to one of several interventions or control. The design is more efficient than a two-arm randomized controlled trial because the same control group can be compared with each of the interventions (multiple pairwise comparisons) and because testing multiple interventions increases the chance of a positive answer. Like randomized controlled trials, multi-arm trials are large and costly to perform and should generally be reserved for evaluating several pressing questions or multiple agents. CHAPAS-3 was a three-arm trial comparing stavudine, zidovudine and abacavir as part of regimens based on non-nucleoside reverse-transcriptase inhibitors and powered for toxicity as primary outcome (20).

**Fig. 1.5.** Multi-arm trials and multi-arm multistage trials



### Multi-arm multistage trials

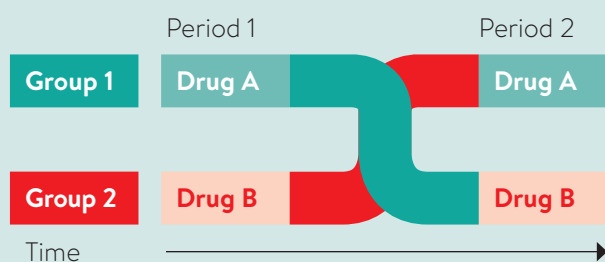
Multi-arm multistage trials are adaptive trials with multiple arms and stages that include predefined lack-of-benefit analysis at the interim stages based on intermediate outcome (Fig. 1.5B). A multi-arm multistage trial can compare multiple treatments (or different doses) and drop less-effective arms at the interim stages. The design offers efficiency benefits and enables direct comparison between arms, reduces the total number of participants and duration of the trial and saves money by performing one trial instead of several. It can also accommodate seamless transition from Phase I to II or II to III and streamline experimental treatment evaluation. The design has a few practical difficulties, requiring that several experimental treatments be available at the same time and buy-in from pharmaceutical companies to compare their treatments. Multi-arm multistage trials may not be suited for all diseases, since a short-term intermediate outcome predicting treatment effect should exist that correlates with the final outcome. Funding applications and planning the trial implementation may be challenging because of the uncertainty of the final sample size and duration unless certain adjustments to the design are made (21). The TAILor trial is an ongoing multi-arm multistage trial evaluating different doses of telmisartan for reducing insulin resistance among adults living with HIV receiving ART (22).

### Crossover trials (Fig. 1.6)

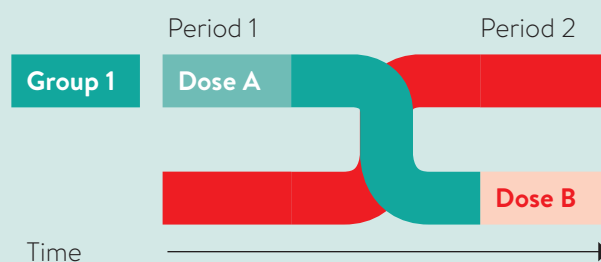
Each participant receives the intervention, and comparator, in series. The design increases the statistical power derived from a small number of participants, since there are no differences between participants that may influence the response to treatments. However, the design works poorly for agents with long washout periods or when long-term effects are of interest, and the design is biased towards including participants who tolerate the interventions. Crossover design can be used in pharmacokinetic studies when different drug formulations, different combinations or different doses are evaluated. One example is the ODYSSEY tuberculosis (TB) pharmacokinetic substudy that aims to compare exposure to a standard dolutegravir (DTG) dose to double-dose DTG co-administered with rifampicin (10).

Fig. 1.6. Crossover studies

#### A. Classical crossover study



#### B. Crossover pharmacokinetic study

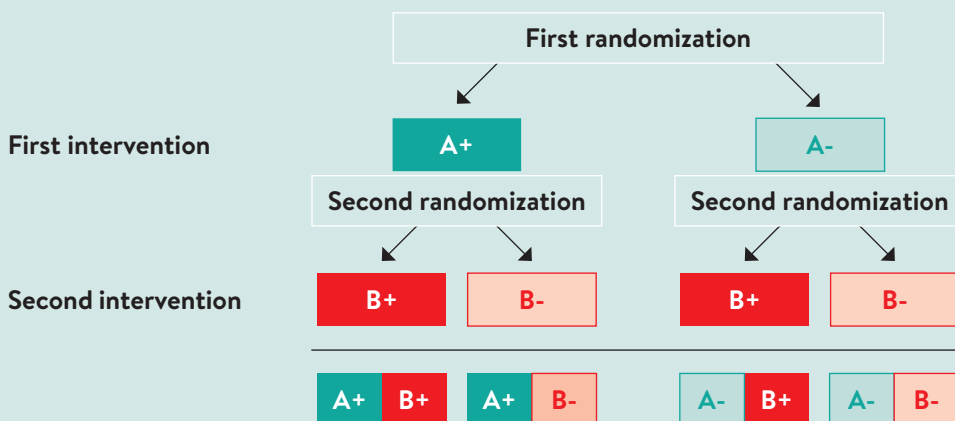


### Factorial randomized controlled trials (Fig. 1.7)

Participants are randomized to two (or more) independent interventions. The interventions are then analysed separately and tested for interaction. Factorial designs are efficient in facilitating multiple comparisons but can be underpowered if interactions exist. ARROW is an example of a factorial trial that compared three ART regimens (first randomization) and two monitoring strategies (second randomization) (23).



**Fig. 1.7.** Factorial randomized controlled trial



A, B: allocated interventions; +: randomized to receive intervention;  
 -: randomized to receive standard of care.

**Cluster randomized controlled trials (Fig. 1.8)**

Groups of individuals, not individuals themselves, are randomized to intervention or control, but outcomes can still be measured at the individual level. The design is appropriate when an intervention cannot be feasibly given to some members of a group but not others without contamination. For example, several large trials examining the impact of universal ART have randomized by community-level clusters; it would not have been feasible for providers and patients to not be aware of, and influenced by, differential approaches to ART initiation within their communities (24). The primary disadvantage of cluster randomized controlled trials is that they can become very large, since the power for comparison is driven by the number of clusters and not simply the number of participants.

**Fig. 1.8.** Cluster randomized controlled trial



Randomization of groups of individuals (households and communities) rather than individuals.  
 A, B = allocated interventions

Source: adapted from a personal communication from Elizabeth Chappell, University College London, 2017.

**Basket trials**

Basket trials include separate but related trials into one operation. They may evaluate the same intervention in different patient groups. Basket trials can be efficient by utilizing one protocol and regulatory approval for all trials and increasing combined power across the trials, but they can be large and costly. IMPAACT P1060 is a paediatric HIV trial that used this approach; it included two randomized controlled trials comparing lopinavir- to nevirapine-based ART among infants with and without perinatal nevirapine exposure (25,26).

## Box 1.2 Superiority, equivalence and non-inferiority

Comparative trials are designed to demonstrate superiority, equivalence or non-inferiority.

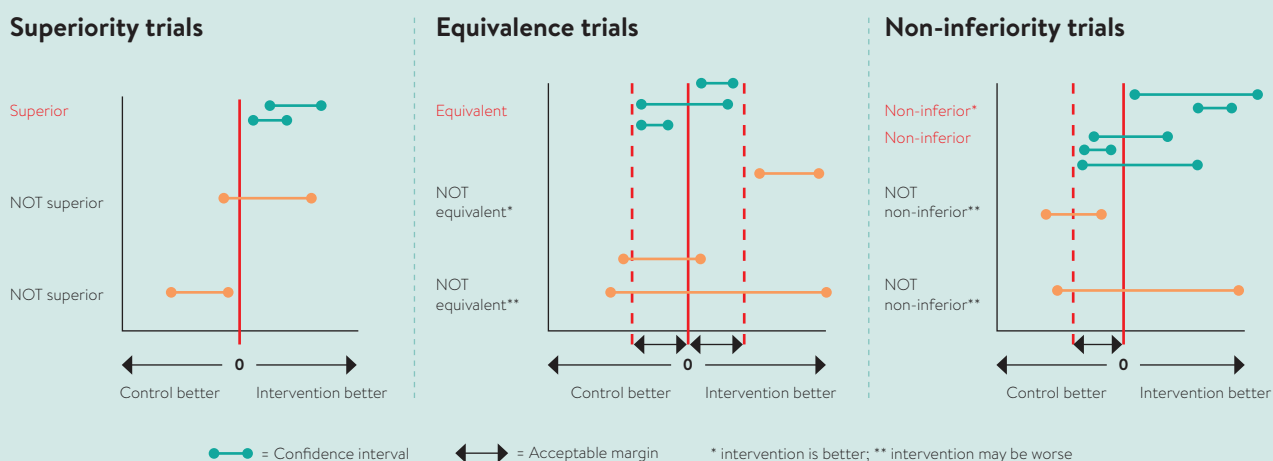
Superiority trials are designed and powered to demonstrate that one treatment is better than another, but proving superiority may be difficult if the primary outcome for the comparator is already very good. A failed superiority trial cannot be interpreted to mean equivalence or non-inferiority of the interventions.

Equivalence trials aim to show that treatments are neither better nor worse than another, with effects differing by no more than a pre-specified amount (margin). Equivalence trials can be used to confirm the bioequivalence of formulations (such as fixed-dose combinations and component drugs or dispersible and film-coated tablets). The acceptable margin is prespecified as the design phase. The stringent regulatory authorities may specify certain margins for the regulatory studies based on statistical and clinical reasoning of what represents a clinically significant difference between the formulations.

Non-inferiority trials aim to demonstrate that a treatment is no worse than (or at least as good as) an existing treatment and that the difference in favour of existing treatment does not exceed a pre-specified amount (margin). These types of trials are used if there are other assumed benefits over the comparator, such as fewer side-effects, easier administration and/or less expensive production. One advantage of non-inferiority trials is that an intervention may be shown to be not only non-inferior but also superior.

Fig. 1.9 shows the differences between superiority, equivalence and non-inferiority with examples of how to interpret the results.

**Fig. 1.9.** Superiority, equivalence and non-inferiority trials



Source: adapted from a personal communication from Elizabeth Chappell, University College London, 2017.

## 2. CHALLENGES

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Many pressures and operational challenges impede the implementation and completion of clinical trials of ARV drugs for children.

### **2.1 Pharmaceutical companies have limited incentives to support trials among children**

Pharmaceutical companies generally have minimal financial incentives to fund trials of new agents for children given the limited market potential. The high costs of running the trials, higher risk of liability compared with adults and more restrictive regulatory requirements, which can be inconsistent between major stringent regulatory authorities, further discourage the companies from conducting trials of ARV drugs among children.

### **2.2 Difficult to recruit and enrol children**

Clinical trials of ARV drugs can be slow to recruit children because fewer children than adults living with HIV are able to participate in studies. Ethical concerns and attempts to protect children from the excessive risks of using a new agent frequently result in strict inclusion criteria. Adults provide their own consent, accepting potential risks, whereas children rely on their parents or guardians and ethical review boards to represent their interests. Trials enrolling children must ensure an acceptable risk-benefit ratio and ideally provide a real prospect of individual benefit. This can result in narrow inclusion criteria for children (for example, treatment-experienced children with few other options) that restrict recruitment. Children living with HIV are often orphans living with non-parental guardians, presenting a challenge to enrolment given regulations governing who can consent to children participating in research.

### **2.3 Challenges in enrolment make decisions about sample size difficult**

A classical randomized controlled trial designed to show benefits in efficacy over standard care requires a relatively large sample size and may result in a prolonged recruitment period and high costs, especially when involving multiple sites across multiple countries. In contrast, trials with small sample sizes risk being underpowered and yielding inconclusive results, leading to a missed opportunity for detecting clinically relevant outcomes and a substantial waste of resources.

### **2.4 Staggered approach for dose-finding studies can slow down completion**

Dose-finding trials that step down into younger age bands (12–18 years, 6–12 years, 2–6 years, 4 weeks to 2 years, birth to 4 weeks) were designed to avoid exposing young children to adverse events from age-specific differences in drug absorption and metabolism, but their staggered approach can greatly extend the study duration.

### **2.5 Landscape of ARV drug options is rapidly changing**

Finally, the landscape of drug options is rapidly changing, and new agents and fixed-dose combinations requiring assessment of drug-dose ratios separately for children are constantly entering the market. This raises the need for rapid study of new agents in children but conversely means that trials (or agents) can become obsolete before they are completed.

## 3. SOLUTIONS

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Designing a study of a candidate drug for children living with HIV requires carefully considering the main questions, objectives and data requirements for (1) regulatory approval purposes and/or (2) the place of the studied drug or regimen in the current or future treatment options.

This in turn informs the choice of trial designs, and of the possible options, the most efficient design that maximizes the generation of evidence should be selected.

Once the design has been decided, one must consider the suitable sites for recruitment and operational logistics to conduct the trial. During the process, potential funders, collaborators and regulators must be engaged.

Although these steps are presented serially here, they often occur simultaneously, since each step depends on others. A key element to efficiently designing and conducting clinical trials is that all potential stakeholders are involved throughout the process of developing the study. Close collaboration will align the trial design as closely as possible with the objectives of funders, regulators and clinicians. Such collaboration requires extra effort to coordinate but increases the likelihood that a trial will be funded, perform efficiently and generate the information needed. Suggested approaches to expedite a trial of a new drug or treatment regimen among children living with HIV are highlighted below.

### 3.1 Evaluate what data are required

It is important to be judicious and specific in deciding exactly what data are needed to support a candidate agent for inclusion in treatment

options for children living with HIV. It is useful to start by evaluating the current clinical context, the ages and settings for children and where current choices fall short (Box 1.3).

Ideally, trials evaluate the dosing scheme and formulations that will be most relevant for the intended population. Although individual mg-per-kg dosing of liquids might yield the most precise pharmacokinetic exposures, trials should aim to use age-appropriate formulations and weight-band dosing that are more practical for implementation globally and endorsed by WHO (2). Fixed-dose formulations should be ideally evaluated in the same study once weight-band dosing is confirmed.

Carefully reviewing the safety data from studies among adults is also critical. Were there adverse events that might be particularly significant for children and require additional tests or long-term safety evaluation in the trial, such as for nervous system and mental reactions and bone toxicity?

Efficacy data can be extrapolated from adult studies, since the EMA and FDA now recognize that, for HIV disease in particular, pharmacokinetic data demonstrating similar drug exposure to those among adults can be used to generalize clinical efficacy to children (3,4). A regulatory clinical trial evaluating the efficacy of a drug for children has the potential to delay the regulatory approval of the drug. An extrapolation algorithm suggested by the FDA (4) and later discussed by Dunne et al. (6) is a useful tool in making the decision about what type of trials are required among children for drug approval (Fig. 1.3). Once dosing has been established, additional strategy trials may also be needed among children to evaluate pragmatic dosing and inform the role of the drug in wide clinical settings.

### Box 1.3 Questions to consider when planning a clinical trial

- For what ages and settings will this drug be most relevant?
- Are there specific reasons to be concerned that the efficacy of this drug for children differs from adults, or is relying on adult efficacy data reasonable?
- What outcomes or margin of improvement would result in this agent replacing current options?
- What are the safety concerns about this agent and how might they differ for children versus adults?

## 3.2 Start drug trials for children early

Research communities should advocate studying new agents among children as soon as reassuring safety data are available from adult trials, mitigating possible risks from exposure to new medicines with careful safety monitoring in the context of a clinical trial. Whenever possible, Phase II trials should begin among children before Phase III trials among adults end (27).

## 3.3 Use efficient trial designs and consider innovative options

Several design principles can expedite the performance of clinical trials of agents to treat children living with HIV.

- **Use physiologically based pharmacokinetic modelling to select the test dose.** The doses tested in trials are often classically derived by extrapolating from weight-based doses in the adjacent age groups. Maturation changes in drug metabolism and non-linear relationships between weight and drug

availability among children may affect dose determination. Incorporating preclinical data about drug disposition (metabolism, volume of distribution and clearance) in physiologically based pharmacokinetic modelling can increase the precision in dose selection and help with weight-band dosing. Physiologically based pharmacokinetic modelling has been used to study antiretroviral drugs (28) and holds particular appeal for determining the doses for children (29,30) and neonates (31) (see the module on pharmacokinetic modelling).

- **Study multiple ages and weight bands**

**simultaneously.** Unless there are specific physiological or safety reasons to be concerned about a drug for children, moving rapidly into studying children is reasonable. The dramatic changes in certain metabolic pathways in the first days and week of life necessitate careful and distinct approaches to determining the dose. Nevertheless, outside the neonatal period, agents with good safety profiles and well characterized metabolic pathways could be studied across wide age and weight ranges simultaneously. As described above, pharmacodynamic and pharmacokinetic modelling can increase the safety and efficiency of identifying starting doses. Pilot pharmacokinetics among a few children per weight band could also aid pharmacokinetic modelling and allow a more precise prediction of the dose for the study determining the dose (11).

- **Study adolescents alongside adults or include them in late-phase adult trials.** Adolescents have been successfully included in cancer clinical trials with adults (32). Studying older children in parallel with adult trials proved to be possible in the DTG development programme, which enabled for the first time licensing of a new ARV drug for children weighing  $\geq 30$  kg at the same time as for adults. Ideally, the late-phase adult trials should include adolescents older than 12 years, which could save substantial resources.

■ **Take advantage of washout data to design trials for neonates.** With rapid changes in metabolism and drug clearance, neonates are especially challenging to dose correctly (see the module on pharmacokinetic modelling). The washout data generated from the study of drug levels among infants exposed to agents transplacentally can provide insight into the clearance of new agents by neonates, informing the modelling for dosing neonates. For example, IMPAACT P1026s has used an opportunistic design to characterize the washout of many ARV drugs among neonates, adding new arms when new ARV drugs come into use for adults (33); data from the 1097 study were instrumental in establishing the pharmacokinetics and safety of raltegravir for full-term neonates (34).

■ **Assess acceptability and feasibility within the initial dose-finding and safety studies.** Acceptability and feasibility are important characteristics for implementing formulations in diverse populations. It is important to evaluate them at early stages of drug development for children (2) and ideally incorporate them into clinical trials. See the module on acceptability for more details.

■ **Carefully choose the most appropriate design and consider innovative statistical methods and trial designs to increase efficiency.** Multi-arm randomized controlled trials, crossover trials and factorial and basket trials use financial and patient resources more efficiently than traditional two-arm randomized controlled trials. Adaptive trial designs and innovative analysis offer additional efficiency gains (Box 1.4).

Many conventional trial designs are static and rely on pre-specified enrolment criteria, interventions and comparisons. By contrast, adaptive designs enable changes in trial design based on interim data while preserving statistical integrity (35,36). The FDA has endorsed adaptive designs since 2006 (37) for use in developing and evaluating drugs (38,39). They can potentially increase efficiency by enabling power and sample sizes to be re-estimated and arms to be added and deleted and overall increasing the likelihood that a study will achieve its aim (36). A multi-arm multistage design has been successfully used in ongoing cancer and TB trials (40,41), and in the TAILor trial on reducing insulin resistance among adults living with HIV and receiving ART (26).

#### Box 1.4 Examples of adaptive designs and innovative statistical methods

■ **Multi-arm multistage designs.** Multi-arm multistage designs use adaptive methods and enable multiple agents to be compared with a single control group (Fig. 1.4B). Planned interim analysis enables unpromising arms to be dropped and new arms to be added while preserving the integrity of the trial. Multi-arm multistage designs can thus shorten the development process without compromising safety and efficacy by increasing the power for identifying the best clinical benefit of the drug product under investigation. A multi-arm multistage design could serve as a master protocol to examine the efficacy of new ARV drugs among children. Multi-arm multistage designs allow elements of Phase II trials such as determining dose to be combined with Phase III trials examining efficacy.

■ **Bayesian methods.** Evidence from previous studies, including adult studies, can be borrowed to inform predictions and reduce the sample size. Data gathered within the trial are also used to adjust the sample size and modify the trial's design while the trial is being carried out. Bayesian methods have the potential to make the trial design more efficient by increasing power and precision and can help to accelerate the completion of trials.

Although several statistical, logistical and operational complexities make multi-arm multistage trials difficult to implement (42,43), many HIV clinical trials among adults and children have adaptively modified some aspects of their design to respond to a changing context or intermediate results received, including expanding the inclusion criteria (10,11), modifying the dose (10,11) and adding randomization (21,44). A recent single-arm PHPT-5 trial on ARV drug regimen intensification for preventing intrapartum mother-to-child transmission of HIV among mothers presenting late in pregnancy used a Bayesian approach (45). The trial evaluated the efficacy of adding single-dose nevirapine during labour to maternal triple lopinavir/ritonavir-based ART and using triple ART prevention for infants instead of zidovudine prophylaxis. Historical data from previous randomized controlled trials in the same setting were used to generate the prior distributions of mother-to-child transmission probabilities. Prospective data from the trial were used to estimate the posterior predictive distribution, which confirmed the probability of superiority of the intensified prevention of vertical transmission over the standard of care (45). When large randomized controlled trials are not feasible and the predictions can be borrowed from trials involving adults or previous ones involving children, a Bayesian approach should be considered to confirm the studied treatments.

### 3.4 Pool research resources

Pooling the data and resources within large research collaborations can mitigate the challenge of recruitment for trials among children. Multicentre networks have productively performed in trials on cancer (46), rheumatology (47) and HIV (48,49) among children. Two large paediatric HIV networks (PENTA and IMPAACT) have been successfully working together in conducting the PENPACT-1 (PENTA 9/PACTG 390) trial (50) and, more recently, in linking Phases II and III trials to accelerate the evaluation of DTG treatment among children (10,11).

### 3.5 Align trials among children and harmonize the approval process

When different groups are studying the same agent, the study designs should be aligned so that the results can be easily compared and be complementary to address various data gaps. For regulatory trials, the companies may choose to work together early with clinical experts to optimize their design of paediatric investigation plans and paediatric study plans to generate clinically relevant data that are feasible to obtain and meet the regulatory requirements. The WHO-led Paediatric Antiretroviral Working Group and Paediatric ARV Drug Optimization groups have pharmacological, clinical trial and regulatory expertise and offer scientific advice on paediatric investigation plans and paediatric study plans free of charge. Drug developers should also consult the FDA and EMA on their trials among children (see the module on regulatory filing).

Alignment of regulatory requirements and linkage between the main stringent regulatory authorities in the process of reviewing submitted trial data for a specific drug may considerably accelerate drug development for children (see the module on regulatory filing).

Efficient collaboration and a harmonized approach are needed between policy-makers, the paediatric HIV research community, the pharmaceutical industry and regulatory agencies to streamline the process of developing ARV drugs for children.

### 3.6 Community engagement

The community, including study participants, their caregivers and their clinicians should be involved early in designing a trial and throughout operation. Their perspectives can yield critical insight into the incentives and barriers to recruitment and participation in clinical trials among children (see the module on community engagement).

## 4. CASE STUDIES

The integrase inhibitor DTG is currently being assessed in two trials among children. IMPAACT P1093 is a single-arm trial evaluating DTG dosing and safety among children for licensing purposes (11). ODYSSEY is a strategy trial, studying the efficacy and safety of DTG in first- and second-line ART for children in various settings (10) (Table 1.1).

IMPAACT P1093 is a Phases I and II, multicentre, open-label, non-comparative intensive pharmacokinetic and safety trial of DTG among children. Full extrapolation of efficacy from adult trials was considered appropriate. Data on bioequivalence for adults between formulations were used to guide dosing, and physiologically based pharmacokinetic modelling was used to estimate the doses required to reach the effective exposure targets. The study team consulted the FDA on the design and exposure targets before the trial started and as the study progressed. Various age-appropriate formulations for children, including film-coated tablets, granules and dispersible tablets, are being evaluated. The trial initially used staggered age cohort enrolment, starting with adolescents 12–17 years old followed by children 6–11 years old. To streamline the evaluation of DTG for

younger children, simultaneous enrolment was later implemented in the younger age cohorts.

ODYSSEY is a Phases II and III randomized controlled trial evaluating the efficacy and safety of DTG-based ART for children in various settings. It uses a basket design: ODYSSEY A recruits children starting first-line ART and ODYSSEY B children starting second-line ART. ODYSSEY has a few nested pharmacokinetic substudies, aiming to evaluate pragmatic dosing for children using a minimal number of formulations across the age range and using WHO weight-band dosing. ODYSSEY is also assessing DTG dosing for children coinfecting with TB. The trial is producing data complementary to that from P1093, aiming to inform policy-makers on pragmatic treatment options and streamline access to DTG for children living in various settings.

Collaboration between IMPAACT P1093, ODYSSEY and ViiV Healthcare included early sharing of information on dosing between ongoing studies and paved the way to aligning the dosing for younger children in ODYSSEY and to expanding the possibilities for studying practical treatment approaches.

**Table 1.1.** Summary of IMPAACT P1093 and ODYSSEY trial details

	IMPAACT P1093	ODYSSEY
Registration numbers	IND 110847 DAIDS-ES 11773 EudraCT 2010-020988-20 NCT01302847	ISRCTN91737921 EudraCT 2014-002632-14 NCT02259127
Study design	Phases I and II, multicentre, open-label pharmacokinetic, safety, tolerability and antiviral activity of DTG in combination regimens among infants, children and adolescents living with HIV-1. Stage I evaluates the short-term tolerability and safety of DTG, allowing the selection of a dose in stage II. Stage II provides long-term safety, tolerability, and supportive efficacy data for DTG	An open-label, multicentre, randomized (1:1), non-inferiority, Phases II and III, 96-week, two-arm clinical trial to compare the efficacy and toxicity of DTG plus two nucleoside reverse-transcriptase inhibitors versus the standard of care among children younger than 18 years old living with HIV-1 who are starting first-line ART (ODYSSEY A) or switching to second-line ART (ODYSSEY B)



	<b>IMPACT P1093</b>	<b>ODYSSEY</b>
Participants	Children living with HIV 4 weeks to 18 years old	Children living with HIV 4 weeks to 18 years old
Number of participants	About 160	700
Interventions	All participants receive age-appropriate DTG formulations as part of their combination ART regimen Dosing is by age and WHO weight bands	DTG + two nucleoside reverse-transcriptase inhibitors (DTG arm) versus standard of care (standard of care arm) in first-line and second-line ART regimens Dosing is by WHO weight bands
Primary outcome(s)	Dose for each DTG formulation that achieves similar exposure to the 50-mg once-daily adult dose of DTG Safety and tolerability of DTG at 24 and 48 weeks Steady-state pharmacokinetics of DTG in combination with optimized background therapy and DTG dose determination achieving targeted 24-hour area under the concentration–time curve (AUC <sub>24 h</sub> ; primary pharmacokinetic endpoint) and 24-hour plasma concentration (C <sub>24 h</sub> ; secondary pharmacokinetic endpoint)	Treatment failure (clinical or viral) by 96 weeks, estimated using time to the first occurrence of: <ul style="list-style-type: none"> <li>■ Insufficient viral response, defined as &lt;1 log<sub>10</sub> drop at 24 weeks</li> <li>■ HIV-1 RNA ≥400 copies/ml at or after 36 weeks, confirmed by next visit</li> <li>■ Death due to any cause</li> <li>■ Any new or recurrent AIDS-defining event (WHO stage 4) or severe WHO stage 3 event</li> </ul>
Main secondary outcomes	Viral response at 24 and 48 weeks Immune response by 24 and 48 weeks Change in HIV-1 genotype and phenotype and other optimized background therapy compounds in children experiencing viral failure DTG exposure, its variability and clinical covariates affecting DTG disposition using intensive and sparse sampling and population pharmacokinetic analysis Extended long-term (≥48 week) safety and tolerability Relationship between DTG exposure and antiviral activity	Efficacy outcomes <ul style="list-style-type: none"> <li>■ Treatment failure (clinical or viral) by 48 weeks</li> <li>■ New resistance mutations</li> <li>■ Clinical events (new or recurrent severe WHO stage 3 or 4 events and death)</li> <li>■ Immune recovery (change in CD4 or CD4:CD8 ratio)</li> </ul> Safety outcomes <ul style="list-style-type: none"> <li>■ Severe adverse events, grade 3 or 4 clinical and laboratory events and events of any grade leading to ART modification</li> </ul> Quality of life, adherence and acceptability
Duration	48 weeks, followed by long-term safety follow-up that will last at least three years	All participants will be followed until the last recruited participant reaches week 96
Sponsor	United States National Institutes of Health	PENTA Foundation
Funder	ViiV Healthcare and United States National Institutes of Health	ViiV Healthcare

## 5. SUMMARY

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Improving access to optimal ART for children will require strategic clinical trial programmes that address drug development and ART optimization priorities set by the collaborative global Paediatric ARV Drug Optimization initiative (51). Many pressures and operational challenges specifically impede the development and completion of clinical trials to develop ARV drugs for children. Pharmaceutical companies have minimal financial incentives to fund trials of new agents for children given the limited market potential. Clinical trials are slower because fewer children are able to participate in studies than adults. Classical approaches to dose-finding for children are slow. Attempts to minimize the risks of using a new agent for children can result in very narrow inclusion criteria.

Dose-finding trials that step down into younger age or weight bands were designed to minimize the risk of adverse events from age-specific differences in drug absorption and metabolism, but this staggered approach greatly extends the study duration. Finally, the landscape of drug options is rapidly changing; new agents and fixed-dose combinations requiring assessment of drug-dose ratios separately for children are constantly entering the market. This raises the need for rapid study of new agents for children, but conversely means that trials (or agents) can become obsolete before they are completed.



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## 6. KEY CONSIDERATIONS

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- Identify the key data needed to give children access to a prospective ARV drug.
  - Identify the minimum data needed for regulatory approval, remembering that Phase III efficacy trials are generally not required for ARV drugs that have been studied in adults.
  - Work with clinicians, community members and experts to identify the key efficacy or formulation data needed from strategy trials to inform clinical guidelines.
- Start ARV drug trials among children as soon as possible while Phase III trials among adults are underway.
- Use innovative trial designs and procedures for efficiently generating data.
  - Apply physiologically based pharmacokinetic modelling to help in selecting the dose.
  - Study multiple ages and weight bands simultaneously, unless there are specific physiological or safety reasons to be concerned about a drug for children.
- Ensure early and ongoing collaboration between policy-makers, the pharmaceutical industry, regulatory agencies, community members and paediatric HIV researchers to streamline the selection and completion of essential clinical trials and accelerate the development of ARV drugs and the optimization of treatment for children.
  - Study adolescents alongside adults or include them in late-phase trials for adults.
  - Use washout data from neonates.
  - Include acceptability and feasibility study within the initial dose-finding and safety studies.
  - Carefully choose the most appropriate design and consider innovative statistical methods and trial designs to increase efficiency.

## 7. ACKNOWLEDGEMENTS

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Comments were also provided by the Division of Antiviral Products of the United States Food and Drug Administration and by representatives of the European Medicines Agency and members of the European Medicines Agency Paediatric Committee. Any views expressed in this publication by employees of the United States Food and Drug Administration or the European Medicines Agency, or members of the European Medicines Agency Paediatric Committee, are their own and may not be understood or quoted as being made on behalf of or reflecting the position of the United States Food and Drug Administration or of the European Medicines Agency or any of its committees or working parties.

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A high-angle photograph of a woman sitting on the floor, smiling warmly at the camera. She is wearing a vibrant pink sari with a white floral pattern and a blue blouse with a floral design. She has a red bindi on her forehead and a nose ring. She is holding two young children. One child, a toddler in a yellow shirt, is looking towards the camera. The other child, a baby, is nestled in her arms, wrapped in a pink cloth. The background is a plain, light-colored floor.

# MODULE 2: PHARMACOKINETIC MODELLING

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# 1. INTRODUCTION

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Two main factors underpin the pharmacokinetic differences between adults and children requiring dose adjustments: body size and maturation (1).

The effect of body size on drug disposition is well described using the theory of allometric scaling, which predicts a non-linear relationship between drug clearance and body size. Because of this non-linearity, children generally need a larger dose in mg/kg than adults.

In addition, the pharmacokinetics for children younger than two years and neonates can differ considerably from that for older children because of developmental differences in the physiological processes underlying drug absorption, distribution, metabolism and excretion (2). In particular, since metabolic pathways are immature, the values of drug clearance tend to be smaller than body size alone would predict.

Although the effect of body size is similar for all drugs and quite predictable (3), the effects of maturation depend on the drug and need to be specifically investigated. Thus, before any antiretroviral (ARV) drug can be used among neonates, an appropriate neonatal dosing regimen with an appropriate formulation needs to be studied and neonatal safety assessed (4). Neonates and young infants require ARV medicine for both preventing mother-to-child transmission of HIV and for treating HIV infection. The module on trial design and the module on pregnant and breastfeeding women further discuss issues related to safety and pharmacokinetic studies involving neonates.

When designing a pharmacokinetic trial, one needs to consider the method used for data analysis, since several options are available, each with their own advantages and disadvantages depending on the scenarios.

- Non-compartmental analysis is very easy to implement and summarizes the pharmacokinetic profiles in terms of the area under the concentration–time curve and maximum concentration but can only be applied when an intensively sampled pharmacokinetic profile is available for each subject (5).
- Population pharmacokinetic analysis is often the preferred analysis when performing intensive blood sampling is not feasible, for example, in young children, including neonates (6). Population pharmacokinetic analysis involves a mathematical model-based approach suitable with sparse or opportunistically sampled drug concentration data. Population pharmacokinetic analysis estimates primary pharmacokinetic parameters such as clearance and volume of distribution, possibly including in the model the effect of individual covariates (such as body weight and age) on these pharmacokinetic parameters.
- Physiologically-based pharmacokinetics is a complex predictive tool integrating into an in silico platform information about both human physiology and the chemical and physical characteristics of the drug under study (7). This tool is designed to work with very little or no clinical data but only provides an extrapolated prediction.

## 2. CHALLENGES

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Data on pharmacokinetics, safety and efficacy for adults are needed before drugs can be studied among children. Pharmacokinetic studies among children are further delayed when dose-finding studies are performed in sequential age cohorts (see the module on trial design).

### 2.1 Establishing initial drug doses

Establishing initial drug doses for neonates and other children is especially challenging, since the effects of both body size and the maturation of metabolic pathways on a drug's pharmacokinetic properties need to be considered. Moreover, specific considerations are required when designing pharmacokinetic studies among children, including identifying the optimal drug exposure targets, calculating the number of children needed in each age group or weight band and ensuring that ethically appropriate blood sampling and volumes are drawn.

### 2.2 Fixed-dose combinations

ARV drugs are now commonly co-formulated in fixed-dose combinations, which simplifies dosing and enhances adherence to treatment. Creating fixed-dose combination tablets for children is also desirable but presents several challenges. For example, the effect of body size and even more so that of maturation on each drug within a novel fixed-dose combination often differ, and thus the optimal ratio between the drugs in the fixed-dose combinations may not be equivalent across all weight bands.

### 2.3 Influences on drug bioavailability

Factors unique to infants and other young children may influence drug bioavailability. These factors include feeding mode and schedule, differences in fed and fasted states and modifications to formulations to facilitate drug intake, such as splitting or crushing tablets intended to be swallowed whole. Strategies that avoid having to break tablets across dosing weight bands are advocated. Drug–drug interactions among children living with HIV are common, but data cannot be directly extrapolated from adult studies since the extent of the interaction can differ in children.

### 2.4 Palatability and changes in drug doses

Poor palatability of ARV drug formulations can be a particular challenge for treating children, and frequent changes in drug doses are confusing for caregivers and children. Nevertheless, frequent dose changes may be unavoidable for drugs, especially for neonates and other young children, which are metabolized or eliminated through pathways with rapid maturation.

It is critical to minimize delays in generating pharmacokinetic and safety data for novel ARV drugs and/or formulations involving neonates and other children.

## 3. SOLUTIONS

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Below are some considerations and solutions to the common challenges encountered when designing pharmacokinetic trials assessing ARV drugs for children and adolescents.

### 3.1 Identifying ARV drug exposure targets

Maintaining ARV drug exposure within therapeutic limits is critical. If ARV drug concentrations are too low, they may fail to achieve viral suppression, whereas if they are too high, they may be associated with drug toxicity. The pharmacokinetic targets for efficacy and safety for children are usually extrapolated from studies performed among adults.

In general, ARV drugs are licensed and used for children based on studies of relatively small numbers of children whose primary outcomes are drug safety and pharmacokinetics. Dosing in these studies is designed with the goal of achieving plasma drug concentration targets equivalent to those established for adults, although the assessment of viral outcomes among the participating children will provide some evidence that the drug concentration targets remain appropriate for children.

### 3.2 Optimal design of pharmacokinetic studies involving children

Unless a drug is intended solely or primarily for children, studies involving children cannot be done until data are available on pharmacokinetics, safety and efficacy for adults. The aim of a dose-finding pharmacokinetic study involving children is to determine with sufficient precision the pharmacokinetics for children of different ages, consistent with guidelines provided by regulatory authorities (8). Adolescents are sometimes included as part of initial adult studies, followed

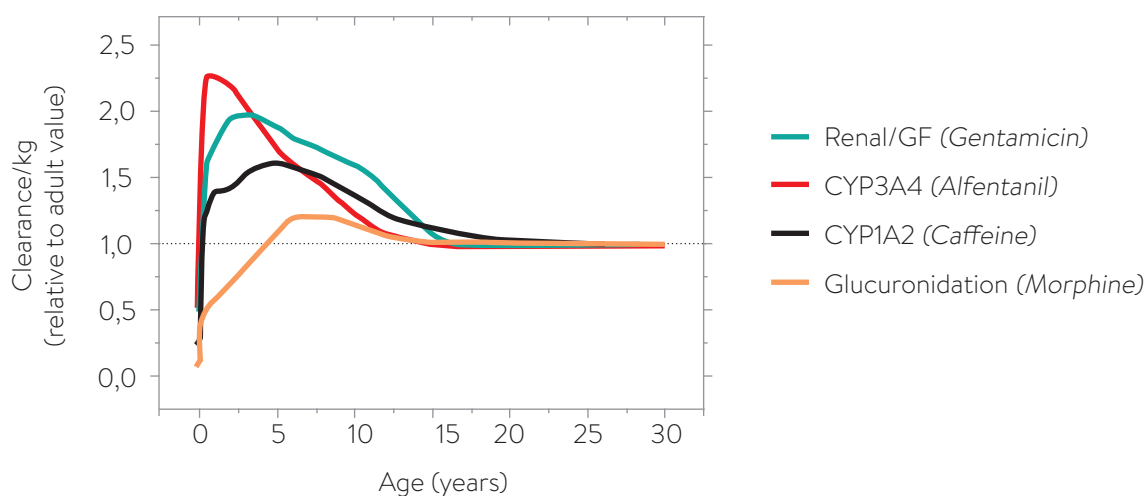
by studies among children, starting with the oldest age group and progressing to younger cohorts once reassuring pharmacokinetic and safety data are available for older cohorts.

The choices specific to a pharmacokinetic study of children include the number of children in each age or weight group and the number of blood samples to draw per subject for each pharmacokinetic profile. The number of children in each age or weight group will determine the precision with which typical values of clearance and volume of distribution parameters in each group can be estimated. For example, age bands are generally smaller for smaller ages (such as <3 months, 3–6 months, 6–12 months, 12–24 months, 2–6 years and 6–12 years), to account for the fact that the greatest developmental changes happen in the first months and years of life. Similarly, since the effect of maturation is stronger for younger children (Fig. 2.1), a larger sample size will be required in the youngest age or weight bands.

For the same reason, the lowest degree of variability would be expected among adolescents, with the main effect being body weight, and the variability would then be comparable to that observed for adults. The total number of subjects in each weight and age band will depend on the specific drug and its reported between-subject variability. An online tool is available to calculate this sample size, based on information about the pharmacokinetics of the drug for adults, the information about its main metabolic pathways and the level of variability observed (9).

The number of blood samples drawn in each pharmacokinetic profile will affect the precision with which the individual pharmacokinetic parameters are estimated for each subject in the study. Further, ethical constraints limit the total volume of blood that can be collected from a child (11), so sensitive drug assays are needed that require minimal plasma volumes (10–50 µL). The

**Fig. 2.1.** Effect of age on drug clearance



Created based on data from: Edginton et al. (10). The lines represent the clearance of drugs through different pathways normalized to body weight and relative to adult reference values.

blood-sampling schedule depends on how the data will be interpreted. If non-compartmental analysis (5) is planned, a more intensively sampled profile and strict adherence to the sampling schedule are necessary.

In addition, the entire dosing interval should be covered to accurately calculate the drug exposure (such as area under the concentration–time curve) at steady state. If a population pharmacokinetic approach is to be used, the sampling can be more sparse and less rigid, as long as accurate information is kept about the timing of all samples and doses (even on the days before the blood-sampling visit). Model-based approaches may also have stronger power to determine estimates of pharmacokinetic parameters, because the data from all age bands can be pooled together and analysed jointly.

To optimize the timing of the samples within the schedule, a state-of-the-art approach is to apply optimal design theory (12). Briefly, using a model-based approach, software tools are available that can provide an optimal sampling schedule expected to maximize the information collected in the study. Alternatively, a general rule of thumb comprises drawing a pre-dose sample one around the expected time of maximum concentration and

then cover the rest of the curve, aiming to have at least 2–3 samples in the expected terminal phase of the profile. Ideally, the last sample should be drawn as late after the dose as logistically feasible, but avoiding a time range with a high chance of observing values below the lower limit of quantification of the assay.

Interim analysis is advised to assess the exposure and determine as soon as possible whether the observed exposure with the selected dose is in accordance with the predicted values.

### 3.3 Model-based approaches to establish dosing for initial pharmacokinetics and safety studies among children

Body size and maturation are the two main factors causing the difference in pharmacokinetics between adults and children ( $1\text{mg/kg}$ ). These factors are best accounted for using model-based approaches such as population pharmacokinetics or physiologically based pharmacokinetics. The effect of body size can be predicted well using allometric scaling theory (13), which affects all drugs in the same way. The volume of distribution is scaled linearly with body weight, whereas

clearance (CL) has a non-linear relationship with body weight (WT) (with an exponent of 3/4), as outlined in the following equations:

$$V_i = V_{std} \cdot \left(\frac{WT_i}{WT_{std}}\right)^1 \quad CL_i = CL_{std} \cdot \left(\frac{WT_i}{WT_{std}}\right)^{\frac{3}{4}}$$

Given the reference adult values of  $CL_{std}$  and  $V_{std}$ , which relate to an adult of reference body weight  $WT_{std}$  (such as 70 kg), the expected values of  $CL_i$  and  $V_i$  for a person of weight  $WT_i$  are calculated according to the formulas above. With the estimate of clearance for a particular weight, the dose can be calculated to achieve a target drug exposure for adults (such as the area under the curve using the classic formula area under the curve = dose/clearance).

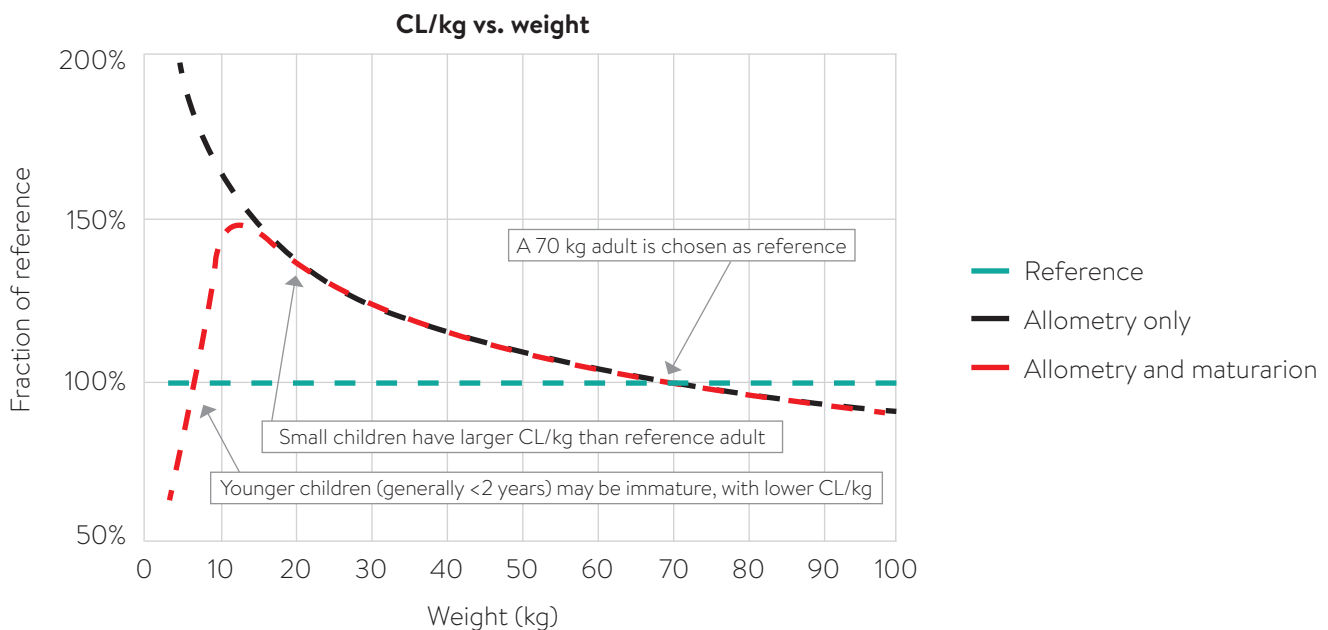
Because of this nonlinear relationship between body weight (a surrogate for size) and drug elimination, children generally need a higher mg/kg dose than adults, as shown in Fig. 2.2. Thus, if a dose for children is extrapolated from adults to children using a constant mg/kg, this will generally cause underexposure in children. In addition,

a drug's half-life ( $T_{1/2}$ ) tends to be shorter for children, as the ratio between clearance and the volume of distribution will be larger with smaller body size. This may require, for example, splitting what is a single daily dose in adults into two separate doses for children.

The effects of body size on clearance and the volume of distribution, respectively, are expected to affect all drugs similarly. Allometric scaling of these parameters is crucial in predicting the suitable dose for children older than two years. For this reason, the use of allometric scaling as a best-guess reasonable assumption has been advocated (3). Allometric scaling can be applied to simple tools to provide predictions of ARV drug exposure across the weight range of children, such as with the WHO dosing tool to explore optimal drug ratios for fixed-dose combination tablets for children (14).

For children younger than two years, metabolic pathways are generally not yet mature and therefore not operating at full capacity compared with those of adults. Because of this maturation effect, clearance values for infants tend to

**Fig. 2.2.** Changes in clearance (CL/kg) versus body weight



The green horizontal line represents the reference clearance/kg for a 70-kg adult. The black dashed line shows the effect of allometric scaling alone, without maturation. The pink line shows the combined effect of allometric scaling and maturation.

be smaller than body size alone would predict (Fig. 2.2). The maturation profile may vary greatly between drugs (Fig. 2.1), but if the drug elimination pathways are known, one can use literature information about their maturation and use population pharmacokinetics or physiologically based pharmacokinetics to predict a starting dose (15). However, the prediction of a starting dose will still need to be validated, especially in children younger than one year. Since metabolic pathways mature during fetal development, a more accurate description can be obtained using conception age and not postnatal age, to account for the effect of prematurity.

When determining the optimal dose to use for young children, other factors need to be considered besides the maturation of clearance. The volume of distribution may also be different among very young children since body composition changes during the first months of life, and the speed and extent of absorption (bioavailability) may also change because of differences in the size and motility of the gastrointestinal tract and changes in gastric pH (16,17)

### **3.4 Washout studies in neonates to inform dose selection**

Studies in neonates are often performed only after data are available from studies of young infants. Washout studies of the elimination of a drug in neonates that was acquired across the placenta following administration of the drug during pregnancy provides an assessment of the rate of drug elimination in the first days of life, informing dose size selection for initial studies with direct neonatal dosing in the first days of life (see the module on pregnant and breastfeeding women). In vitro studies of the effect of the drug on bilirubin binding may also be conducted before studies of dosing in neonates to ensure that administering the drug to neonates will not result in an increased incidence of kernicterus resulting from the displacement of bilirubin from albumin (18–20).

### **3.5 Effect of fed and fasted states on drug bioavailability among neonates and other young children**

Generating pharmacokinetic data for novel ARV formulations for children in the fed state by using healthy adults is standard practice. For neonates and other young children, consideration should be given to investigating the impact of regional and age-related infant feeding practices, especially in highly endemic countries. Pharmacokinetic data in the fasted state are also equally important to understand the potential impact on drug exposure if no or only a little food was provided. Population pharmacokinetics or physiologically based pharmacokinetic modelling may aid in assessing how food affects drug concentrations, including issues of malnutrition, among neonates and other infants.

### **3.6 Bioavailability studies of ARV drugs among children**

Bioequivalence of novel formulations to be used in children must be assessed. Such studies are often performed initially among adults but should also be assessed among children, since adult bioequivalence studies of some ARV formulations for children did not predict bioavailability problems that were revealed when these formulations were administered to children (21,22).

### **3.7 Investigating modifications of novel formulations for adults and children is critical**

The shift from individual liquid formulations to small dispersible and chewable fixed-dose combination tablets has been a major achievement and has greatly helped families in low- and middle-income countries in administering complex drug combinations to their children daily. However, it is critical to carefully consider how drugs will be administered in a real-life setting across children's age continuum, and efforts to collect pharmacokinetic data

following different modes of administration would be beneficial. Although less common today, modifying the mode of administering fixed-dose combination tablets for adults or children has been necessary to facilitate administration to children, such as splitting or crushing tablets for adults or children that should be swallowed whole (21). Such manipulation of a formulation can significantly affect bioavailability (23). The possible interactions with excipients should also be considered in the formulations of co-administered drugs (24). In this context, proactively performing pharmacokinetic studies of new drug formulations for adults and children among healthy volunteers would be beneficial in helping to clarify how the formulations can be safely modified, if at all, in the clinic and home settings.

### **3.8 Palatability of ARV formulations for children is paramount**

Developing solid formulations is favoured over developing liquid formulations. For example, the recent introduction of a pellet formulation of lopinavir/ritonavir has helped to simplify dosing, although taste issues remain (25,26). In general, flavoured or taste-masked formulations are preferred, and pharmacokinetic and acceptability studies of these formulations in children must be undertaken.

### **3.9 Dosing strategies should be simplified when possible**

Simplifying drug-dosing strategies to achieve target drug exposure is of critical importance in successfully administering drugs to children. WHO weight-band dosing guidelines have helped to simplify dosing, and pharmacokinetic studies among children living with HIV should be undertaken to assess drug exposure and safety with dosing regimens that use these standard weight bands. For example, the IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) P1083 study assessed the WHO weight-band dosing of lopinavir/ritonavir

for children (27). Nevertheless, frequent dose changes may be unavoidable for drugs that are metabolized or eliminated through pathways with rapid maturation, such as raltegravir among neonates (see the section on case studies).

### **3.10 Giving priority to fixed-dose combination formulations for children**

The WHO paediatric dosing tool (14) enables the joint display of the exposure of several drugs within a fixed-dose combination across weight bands and allows for graphical comparison. A more sophisticated computer optimization method selecting both optimal tablet size and ratio between the ingredients has recently been proposed for tuberculosis (28). A model-based analysis was recently used to determine the optimal drug ratio for a fixed-dose combination abacavir + lamivudine + efavirenz tablet for children and is discussed in the section on case studies (29).

### **3.11 Drug–drug interactions may differ for children versus adults**

Pharmacokinetic data on drug–drug interactions for adults may be used to inform which drugs should not be co-administered to children because of a risk of too high or too low drug exposure. However, drug–drug interactions between ARV drugs and commonly prescribed non-ARV drugs that are expected to interact (for example, because of a common metabolic pathway or substrates for the same drug transporters) should be assessed among children as well. Since such interactions may differ between adults and children, dosing adjustments must be investigated among children. One example of such a difference was observed with the reduction in lopinavir exposure with the co-administration of rifampicin as part of tuberculosis treatment. Doubling lopinavir/ritonavir doses when co-administered with rifampicin resulted in therapeutic lopinavir exposure for adults, but not for children (30,31) (see section 2.1 of the module on coinfections).

## 4. CASE STUDIES

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The following section describes two case studies highlighting the pharmacokinetic challenges often encountered when designing clinical trials involving children.

### 4.1 Raltegravir for neonates

Raltegravir was the first HIV integrase strand transfer inhibitor to be licensed and the first to be available with a formulation suitable for use among neonates. Raltegravir is metabolized by uridine diphosphate-glucuronosyltransferase (UGT) 1A1, which is also the major enzyme responsible for metabolizing bilirubin. Bilirubin glucuronidation is very slow immediately after birth but accelerates dramatically over the first days and weeks of life, and raltegravir metabolism is expected to follow the same developmental pattern.

Studies were conducted to safely and efficiently investigate the pharmacokinetics of raltegravir among neonates and establish an appropriate neonatal dose. An *in vitro* study of the effect of raltegravir on bilirubin binding showed that raltegravir would have no clinically significant effect on bilirubin binding at typical therapeutic concentrations but could cause potentially harmful effects at concentrations 50–100 fold higher than typical therapeutic concentrations (18). A study of washout pharmacokinetics of raltegravir among neonates following maternal dosing during pregnancy demonstrated that raltegravir elimination was highly variable and extremely prolonged in the first days of life (32). An initial dosing study of two single raltegravir doses during the first week of life, one during the first 48 hours of life and a second at around seven days of life, confirmed that raltegravir elimination was extremely slow immediately after birth but accelerated during the first week of life.

These data were combined with pharmacokinetic data for raltegravir from infants older than one month, and a raltegravir population pharmacokinetic model was developed. Simulations were performed evaluating raltegravir exposure with different dosing regimens during the first six weeks of life, with a goal of selecting a regimen that would provide therapeutic plasma target concentrations while avoiding potential toxicity throughout the first month of life (33). The suggested regimen (1.5 mg/kg once a day for the first week of life, 3 mg/kg twice a day for weeks 2–4 and 6 mg/kg twice daily during weeks 5–6) was then evaluated in a study of daily raltegravir dosing among neonates. This study demonstrated that this dosing regimen met the raltegravir target concentrations (34) and led to United States Food and Drug Administration (FDA) licensing of raltegravir for neonates in November 2017.

Raltegravir was the first ARV drug to be licensed for neonates since emtricitabine was licensed in 2005. A study of the pharmacokinetics of raltegravir among low-birth-weight infants is now being planned.

### 4.2 Determining the optimal strength of a novel abacavir + lamivudine + efavirenz formulation for children

The 2016 WHO consolidated ARV drug guidelines (35) recommend a combination of abacavir (ABC), lamivudine (3TC) and efavirenz (EFV) as the preferred first-line ARV regimen for children weighing 10–35 kg (about 3–10 years old). So far, no fixed-dose combination tablet of ABC + 3TC + EFV for children is available; however, several generic manufacturers have said that they intend to develop this formulation. The first step in developing this fixed-dose combination for children was to determine the



optimal dose of each drug within the fixed-dose combination tablet to provide appropriate dosing of each component across all WHO weight bands through simple dose increments. However, the individual dosing recommendations for ABC, 3TC and EFV do not have equal incremental increases in dosing by weight, leading to different drug ratios across the WHO weight bands. These differences in dosing are a consequence of the different rates of maturation of the elimination pathways for the individual drug components.

Pharmacokinetic data supporting the optimal strength of an ABC + 3TC + EFV fixed-dose combination tablet for children are needed.

Recently, population pharmacokinetic analysis was performed using data pooled from multiple clinical trials and therapeutic drug monitoring datasets from countries around the world (29). Simulations revealed that a fixed-dose combination of ABC + 3TC + EFV for children of 150 + 75 + 150 mg provides the most effective and safe concentrations across the WHO weight bands.

Manufacturers can now move forward to develop this strength tablet, but subsequent pharmacokinetic studies are needed to confirm that optimal drug exposure of each component is achieved in the target population of children.

## 5. SUMMARY

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- Although efficacy for children can generally be extrapolated from that of adults, pharmacokinetic and safety studies are necessary to establish appropriate dosing for children.
- Initial doses in trials for children require understanding the (non-linear) effect of body size and maturation. Modelling and simulation tools are increasingly used to inform initial dose selection.

## 6. KEY CONSIDERATIONS

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- Model-based approaches should be used to help inform dosing in young children. Such data will be critical to support performing pharmacokinetic dose-finding studies in children simultaneously across weight and age bands rather than using the standard 'staggered' or 'step-down' approach.
- Model prediction for infants younger than four weeks are less precise due to the rapid maturation of metabolic pathways during the first month of life. For newly approved ARVs, performing washout studies in neonates will provide key data to inform dose selection and in turn accelerate dosing-finding studies in this vulnerable population.
- Developing robust population pharmacokinetic models using available data in children living with HIV should be prioritized to help determine which strength and/or ratios of novel fixed-dose combination tablets for children manufacturers should develop.
- Pharmacokinetic studies in children should be undertaken to assess drug exposure and safety with dosing regimens that use standard WHO weight bands.

## 7. ACKNOWLEDGEMENTS

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# MODULE 3: PREGNANT AND BREASTFEEDING WOMEN

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# 1. INTRODUCTION

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The number of children newly infected with HIV has decreased by 47% since 2010, although 160 000 children acquired HIV in 2016 (1). This decline is mainly related to treating women living with HIV for their own health and to reduce the risk of vertical HIV transmission (2). Combination antiretroviral therapy (ART) is a highly effective strategy for preventing the vertical transmission of HIV, reducing the risk from 20–45% to less than 1% in non-breastfeeding populations (3). However, information on antiretroviral (ARV) drug pharmacokinetics and maternal and fetal safety during pregnancy, as well as placental transfer, distribution into breast-milk and infant exposure are required before pregnant and lactating women can safely and effectively use these drugs.

Unfortunately, pregnant and breastfeeding women are generally excluded from pre-marketing clinical drug development programmes (4). In the past decade, the United States Food and Drug Administration (FDA) has continued to emphasize the need for including women (pregnant and non-pregnant) in development programmes, issuing guidance for industry on establishing pregnancy registries and drafting guidelines for conducting pharmacokinetic and pharmacodynamic studies among pregnant women and draft guidance for studies among lactating women (5,6).

Nevertheless, no current legislation or regulations formally provide incentives for or mandate drug studies among pregnant women (7). Several post-marketing surveillance initiatives and clinical trial networks (usually in the form of public–private partnerships) investigate the pharmacokinetics and report

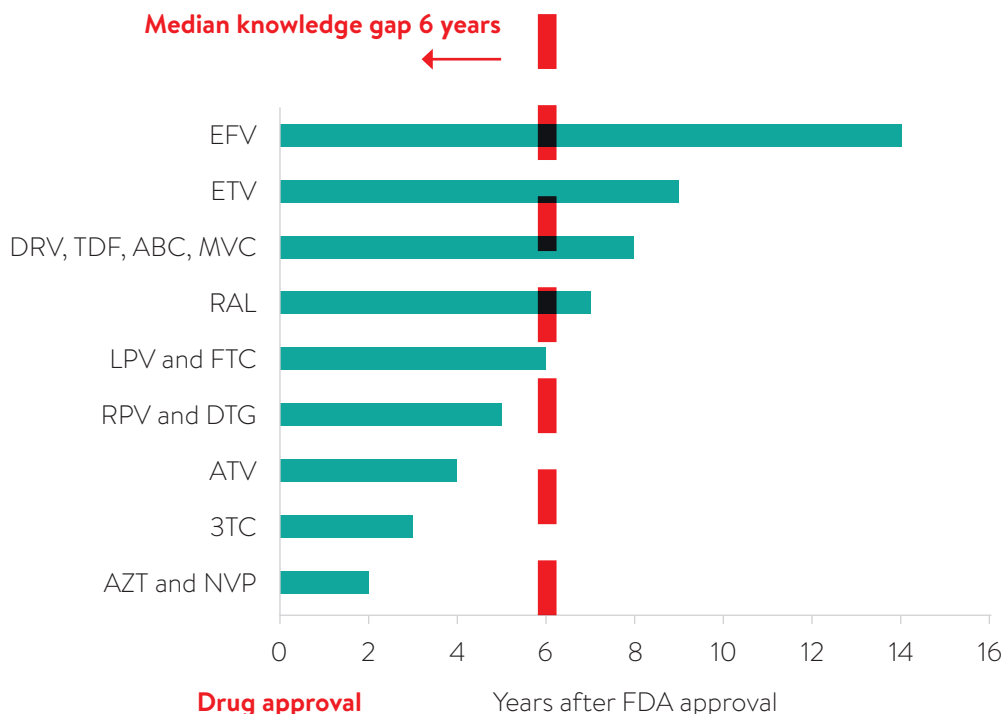
on the safety of ARV drugs during pregnancy (8–10). Nevertheless, the data from these studies usually become available years after FDA licensing. Looking at clinical trials reporting on the pharmacokinetics and safety of the main ARV drugs during pregnancy, the median time to first data (the time between FDA approval and publication of the first prospective clinical trial) exceeds six years.

Partly depending on treatment alternatives, many pregnant and breastfeeding women and potentially their (unborn) infants inevitably use (or have used) untested ARV drugs. Untested here refers to the fact that health-care professionals had no data available on pharmacokinetics and safety during pregnancy or breastfeeding to inform treatment strategies (4). Excluding pregnant and lactating women from participating in medical research results in a lack of knowledge about the risks and potential benefits of products that will be available for their use once on the market.

Early data on the pharmacokinetics and safety of ARV drugs in pregnancy and lactation gathered under rigorous scientific conditions are critically needed. This would place fewer women and their fetuses at risk compared with the much larger number of pregnant and lactating women who are exposed when drugs reach the market without evaluation (11).

In short, including pregnant and breastfeeding women in clinical research is critically important, and the period between FDA approval and the first clinical pregnancy and lactation data should be minimized or eliminated (Fig. 3.1).

**Fig. 3.1.** Time between approval and the first published pharmacokinetic data in pregnancy for various ARV drugs



## 2. CHALLENGES

Research involving and treatment of pregnant and breastfeeding women raises ethical and scientific questions. Although regulatory agencies encourage the study of drugs among pregnant and breastfeeding women, they are generally excluded from drug development programmes, leading to knowledge gaps when drugs come to market. Nearly all drugs are licensed without any data describing their use in pregnancy, including safety for the mother and child when used during pregnancy and breastfeeding, whether effective exposure is achieved during pregnancy with standard nonpregnant adult dosing and to what extent the drug crosses the placenta and is excreted in breast-milk. The lack of research leads to pregnant and breastfeeding women and

their infants using ARV agents that have not been tested on them.

### 2.1 Ethical concerns about exposing pregnant women and their fetuses to ARV drugs being developed

Since the risks to the fetus and the infant posed by most new chemical entities or approved drugs cannot be sufficiently ruled out, pregnant and breastfeeding women are generally excluded from (pre-marketing) clinical trials (12,13). Although no one questions the relevance of these ethical considerations, this leads to the following point.

## **2.2 ARV drugs are widely used “untested” among pregnancy and breastfeeding women**

Since pregnant women are excluded from clinical trials during the development phase, a substantial knowledge gap remains regarding the pharmacokinetics and safety of ARV drugs during pregnancy, placental transfer of agents and transfer into breast-milk following drug marketing. Consequently, many pregnant and breastfeeding women will inevitably use (or have used) “untested” ARV drugs.

## **2.3 Using ARV drugs in pregnancy may be associated with birth defects or other adverse birth outcomes: preterm birth, fetal growth restriction and gestational diabetes**

An essential element of pregnancy-related clinical pharmacology is the effect on the fetus of mothers using therapeutic agents. Maternal drug effects, such as an increased risk of preterm labour or impaired maternal glucose homeostasis, may profoundly affect the well-being of the fetus. Individual drugs cross the placenta to a greater or lesser extent, exposing the fetus to potential direct therapeutic and/or toxic drug effects. Exposure during the first trimester may impact fetal organogenesis and result in teratogenicity, although to date there is no confirmed association between exposure to ARV drugs and increased birth defect rate (10).

Fetal (or placental) exposure to ARV drugs may provide beneficial effects such as pre-exposure prophylaxis to mother-to-child HIV transmission but may also result in fetal toxicity, such as bone marrow suppression or mitochondrial dysfunction (14).

## **2.4 Physiological changes in pregnancy may affect exposure to ARV drugs, and these changes may change drug efficacy**

Pregnancy is associated with a wide range of physiological, anatomical and biochemical changes that substantially influence the pharmacokinetics of therapeutic agents (15–18). Pregnancy is associated with prolonged gastric transit time, nausea and vomiting and dietary alterations that may alter drug absorption. Drug distribution may change in pregnant women because of changes in body composition, blood volume, protein binding and expression of transporters. Activity of drug metabolizing enzymes may increase during pregnancy (such as cytochrome 450 (CYP) 3A and uridine diphosphate-glucuronosyltransferase (UGT) 1A4) or decrease (such as CYP 2C19), affecting the intrinsic clearance of ARV drugs. Increases in cardiac output, renal blood flow and glomerular filtration rate during pregnancy may increase the elimination of renally cleared drugs.

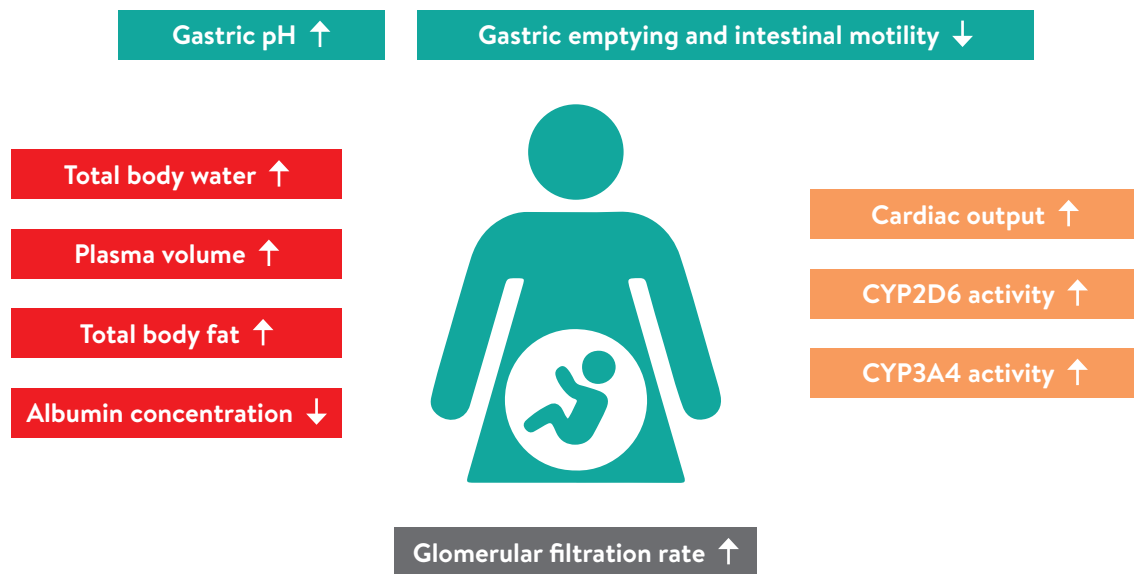
In combination, these changes may result in alterations during pregnancy of the unbound pharmacologically active concentration of drug at the target site, leading to changes in drug response. Studying the pharmacokinetics of ARV drugs among pregnant women is necessary to ensure adequate drug exposure in this vulnerable population (Fig. 3.2).

## **2.5 Placental transfer, fetal exposure and disposition into breast-milk are unknown**

Physiologically, placental transfer is the main determinant of fetal exposure (20). Quantifying fetal exposure is key for evaluating potential fetal toxicity and therapeutic effect, since fetal exposure may have benefits in providing pre-exposure prophylaxis against maternal virus (14). In general, quantifying human fetal exposure is not straightforward, since the fetus itself is not accessible for sampling throughout



**Fig. 3.2.** Pregnancy, physiology and pharmacokinetics



Created based on data from: Abduljalil et al. (19).

pregnancy, so assessment of fetal drug exposure is generally limited to cord blood sampling at the time of delivery. Cord-to-maternal plasma concentration ratios are often computed based on time-matched samples collected at the time of delivery to provide a measure for fetal drug exposure relative to exposure in the mother. However, these relationships can be misleading because of the time-dependent distributional kinetics of drugs across the placenta (that is, placental transfer may vary during gestation).

Cord blood sampling provides the best available proxy for fetal exposure in humans, but the data resulting from cord blood sampling are generally limited to a single sample collected at one time point late in pregnancy. This sampling limitation complicates population pharmacokinetic analysis of such data (21,22). Data on fetal exposure from animal models may be informative but of limited translational value because of interspecies variability in placental structure and function (23,24).

Transmission of HIV from mother to child after birth via breast-milk remains a major problem

in regions where formula feeding is not safe, affordable or practical. The provision of maternal ART through the period of breast-feeding has been shown to significantly reduce breast-milk HIV transmission by reducing breast-milk HIV concentrations and/or by providing prophylaxis to the infant who ingests the ARV drugs present in breast-milk (25).

Waitt et al. (26) investigated whether infant exposure to ARV drugs during breastfeeding is quantitatively important. They concluded that this might be the case for some nucleoside reverse-transcriptase inhibitors and non-nucleoside reverse-transcriptase inhibitors but not for protease inhibitors.

Exposure to ARV drugs during breastfeeding could result in toxicity to the infant. Should the infant acquire HIV infection via breast-milk, infant exposure to low concentrations of ARV drugs during the breastfeeding period could result in the infant developing ARV drug resistance, limiting future therapeutic options (27,28).

## 3. SOLUTIONS

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Adequate ART for mother and child during and directly after pregnancy is vital in preventing mother-to-child HIV transmission. The following approaches and solutions can be used to ensure adequate treatment. Following these recommendations, information will become available for health-care professionals on adequate treatment regimens during pregnancy in a timely, informative and efficient manner.

### 3.1 Ethical concerns about exposing pregnant women and their fetuses to ARV drugs being developed

Regulatory authorities and ethical committees should require and support the inclusion of pregnant women in pre-marketing clinical trials. At the very least, women enrolled in Phase II or III clinical trials should not be removed from the study drug if they become pregnant during the trial, if preclinical reproductive toxicology studies were negative. Fortunately, the consensus is shifting, and support for including pregnant women before marketing is growing (11,13).

Incentives from regulatory authorities are important to include pregnancy as part of the clinical development plan for ARV drugs, given the substantial anticipated use among women of childbearing age. This plan should ensure that the necessary data are obtained through studies in pregnancy and/or breastfeeding to support the use of drugs in pregnant women, including:

- safety data from both mother and child, with long-term follow-up after in utero and/or breast-milk exposure; and
- pharmacokinetic and pharmacodynamic data: viral load monitoring, CD4 counts, pharmacokinetics in pregnancy, placental passage, passage into breast-milk and exposure of neonates and other infants.

Dedicated clinical pharmacology studies involving pregnant and lactating women can be initiated once initial safety and efficacy have been demonstrated among non-pregnant adults (4). These studies could include the women from pre-marketing trials and continue to include more pregnant women for adequate power with respect to a prespecified clinical endpoint, such as undetectable viral load at delivery. These studies may be opportunistic (women who become pregnant while receiving a specific drug can be included without changing treatment) or may be intervention studies (search for the optimal dose in pregnancy) initiated by academia or the pharmaceutical industry. To accelerate inclusion rates and include women in the settings where the disease is most prevalent, these studies should be performed in relevant populations in both high-income and low- and middle-income countries. Centres of excellence should be established in the low- and middle-income countries.

### 3.2 Using ARV drugs in pregnancy may be associated with birth defects or other adverse birth outcomes: preterm birth, fetal growth restriction and gestational diabetes

The safety of ART and pregnancy outcomes should be closely monitored during pharmacokinetic studies that include pregnant women. However, clinical studies specifically designed to detect safety issues during pregnancy require large numbers of study subjects and are therefore not feasible. Instead, post-marketing surveillance studies are used that follow women and newborns exposed to ARV drugs during pregnancy, such as the Antiretroviral Pregnancy Registry (<http://www.apregistry.com>). For sufficient power to detect

relevant effects (mainly birth defects), these studies typically require hundreds of subjects exposed to these agents (10). Guidance on designing and executing these studies is described elsewhere (29). This post-marketing surveillance should be supported and monitored more closely from a regulatory perspective (see the module on pharmacovigilance).

### 3.3 Clinical pharmacology studies of ARV drugs among pregnant women

In clinical studies with ARV drugs that include pregnant women, the following data should be collected:

- viral loads during pregnancy and postpartum;
- maternal safety during pregnancy;
- birth outcome: gestational age, birth weight, congenital abnormalities and HIV infection status;
- full pharmacokinetic profiles in the second and third trimesters and postpartum;
- if protein binding is substantial, unbound plasma concentrations should be determined;
- additional single time-point plasma samples can be taken throughout the course of pregnancy (such as at every visit) to identify temporal changes during pregnancy;
- cord and maternal blood sample at delivery, ideally for all included subjects; and
- washout samples of ARV drugs from infants following delivery (see the module on pharmacokinetic modelling).

Although pharmacodynamics are monitored and should be reported (such as viral load or toxicity), absolute differences are usually small, and detecting such effects would require more sophisticated trial design and including much larger numbers of pregnant subjects. Hence, pharmacodynamics as the primary endpoint in such studies is generally unfeasible. For this reason, the primary endpoints of clinical pharmacology studies of ARV drugs among

pregnant women are typically pharmacokinetic under the assumption that pharmacokinetic parameters such as total drug exposure are informative and predictive for ARV drug efficacy and safety.

As such, these studies should be powered to detect relevant differences in the primary pharmacokinetic endpoints of interest. These typically include total drug exposure, maximum concentration over a dosing interval and/or concentration at the end of the dosing interval and depend on what parameter correlated best with the pharmacodynamics in previous pharmacokinetic and pharmacodynamic studies involving non-pregnant adults. These pharmacokinetic parameters can be estimated by non-compartmental analysis and, if needed, also by population pharmacokinetic modelling, with the major advantage that such an approach enables interpolation when the dose being investigated is deemed inadequate during pregnancy.

This is in accordance with the FDA guidance on designing pharmacokinetic studies in pregnancy, in which they recommend that “the dose should [be adjusted to] produce a comparable range of unbound plasma concentrations of drug or active metabolites in both controls and pregnant patients” (5). Pregnancy effects can be determined by the comparability of exposure of non-pregnant (control) and pregnant people by means of no-effect boundaries for the ratio of a pharmacokinetic parameter, an approach sometimes referred to as the bioequivalence method. For this approach, the null hypothesis is that pregnancy has a clinically relevant effect on the pharmacokinetic parameter of interest. If the 90% confidence interval for the ratio falls within the no effect boundaries (typically 80–125%), the null hypothesis can be rejected, and it is reasonable to conclude that pregnancy has no clinically relevant effect and no dose adjustment is needed.

The no-effect boundaries are preferably set based on well established pharmacokinetic and pharmacodynamic relationships for efficacy and safety. However, these relationships are

not always readily available, and setting these boundaries can therefore be challenging. Since pregnancy is a temporary condition, boundaries somewhat wider than the conservative bioequivalence boundaries can be acceptable (such as 70–143% or wider), especially if the therapeutic window is relatively wide and variability is large. Prespecifying these boundaries for the primary pharmacokinetic endpoint and powering the study accordingly are crucial. Further guidance on setting the no-effect boundaries and ensuring the inclusion of sufficient subjects for adequate statistical power is provided elsewhere (30).

### 3.4 Placental transfer and infant washout

To assess fetal exposure, cord blood samples and maternal samples should be taken at delivery (ideally for all included subjects). In addition, for compounds with substantial anticipated fetal exposure based on preclinical data, it is recommended to collect serial washout samples after birth from neonates exposed to the ARV drugs in utero. This sampling is especially important for compounds metabolized by enzymes that are known to be immature in neonates (see the module on pharmacokinetic modelling). Depending on the half-life of the compound, serial neonatal plasma samples should be collected, with the duration of sampling based on an estimate of likely half-life among newborns. Because many neonate enzyme systems are immature, half-life might be substantially prolonged (31).

### 3.5 Disposition into breast-milk

When postpartum women included in clinical trials are breastfeeding, simultaneous maternal and infant plasma samples and breast-milk samples should be collected. In all samples, both viral load and concentrations of the ARV drug can be assessed. This sampling may be performed at standard postpartum visits, such as at 2, 6, 14 and 24 weeks postpartum. Preferably whole milk

should be used for the analysis, since this is what the infant is ingesting.

### 3.6 Preclinical placental transfer

During the preclinical phases of drug development, parallel to or shortly after reproductive toxicology studies, the ex vivo human cotyledon perfusion model can be used to investigate the placental transfer of ARV drugs (14). These experiments use term placentas obtained immediately following delivery and could be outsourced to institutes (typically academic medical centres) that have such models in place. The results of such studies can provide information about the fetal exposure to the ARV drug of interest, but such studies are limited to late pregnancy.

### 3.7 Modelling and simulation

Given the limited participation of pregnant women in clinical studies, leading to few data in pregnancy, modelling and simulation may facilitate understanding of pregnancy-related clinical pharmacology.

Population pharmacokinetic modelling can be helpful to quantify the sources of variability, handling sparse data, dealing with non-linearity, facilitating the pooling of data sets from studies with unbalanced design, trial simulation and interpolation (such as simulation of other dosing regimens in the target population). For this approach to be successful requires certain clinical data from the target population of pregnant women. These models can then be used for stochastic simulation to evaluate the drug exposure (or other secondary pharmacokinetic parameters of interest) during pregnancy, for example, to evaluate the frequency of individual drug exposure below a certain target.

If the dose studied appears inadequate, the model can be used for simulating secondary pharmacokinetic parameters following alternative dosing regimens. This can inform

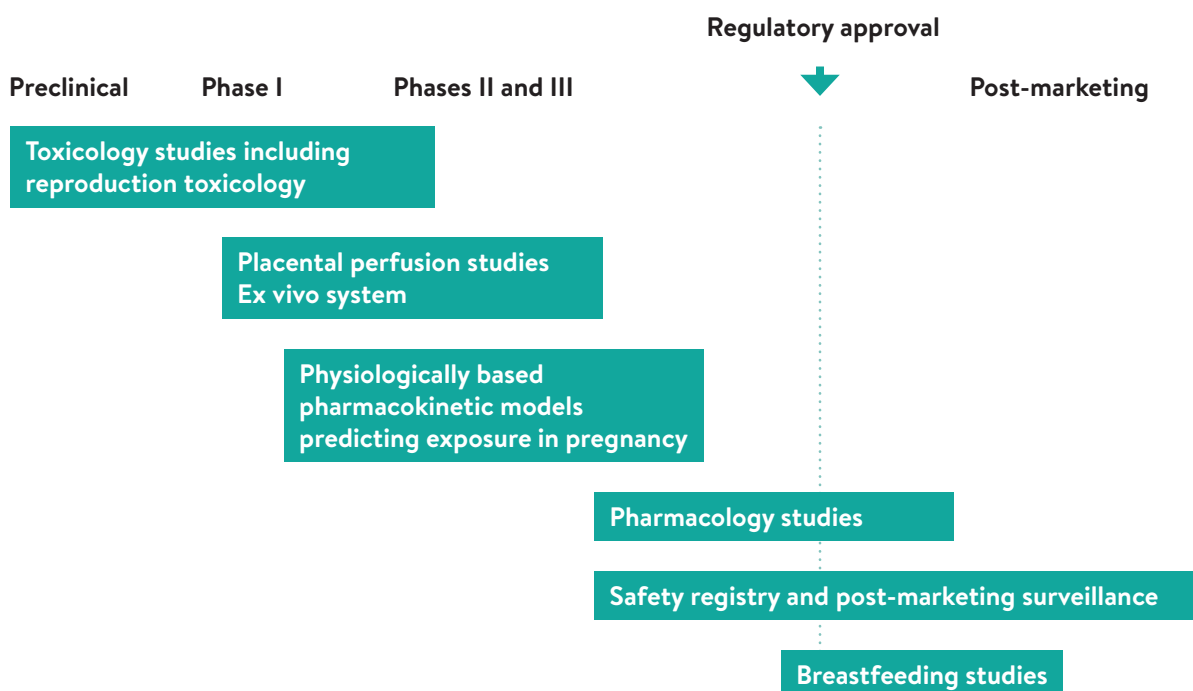
follow-up studies investigating dose adjustments during pregnancy (32). Further, this approach can be used for optimizing design and clinical trial simulation. This enables optimization of sampling schedule throughout the course of pregnancy, which could provide information about the temporal change of pharmacokinetics during pregnancy (33). Further, it could guide the plan of analysis for a clinical study, inform the choice of primary outcome measures and determine the number of women that should be included for adequate statistical power.

Full bottom-up approaches, such as physiologically based pharmacokinetic modelling, use mechanistic information, including system-related parameters (such as organ volumes, blood flows and tissue composition) and drug-related parameters (such as intrinsic metabolic clearance or drug ligand affinity). These parameters are combined in systems of differential equations that are based on a pragmatic compartmental structure describing the anatomy, physiology and biochemistry of the pregnant women. This approach enables the way the body processes a

drug to be simulated in a mechanistic manner, taking molecular processes as a starting-point. Consequently, it provides comprehensive and integrated understanding of the pharmacokinetics and pharmacodynamics of a drug and can be completed even in the complete absence of clinical data in the target population (by extrapolation).

For example, fetal exposure can be quantitatively predicted by physiologically based pharmacokinetic modelling (21,22). Placental transfer can be parameterized using an in vitro-to-in vivo extrapolation approach based on clearance values or rate constants from ex vivo human cotyledon perfusion experiments. These parameters can then be integrated in fetal-maternal whole-body physiologically based pharmacokinetic models to predict fetal exposure. Following such an approach, recent studies successfully predicted fetal exposure based on human placental transfer (20,33,34). Later, this can be verified with cord blood and matched maternal blood samples collected at birth in clinical studies (Fig. 3.3).

**Fig. 3.3.** Studies involving pregnant women in developing drugs



## 4. CASE STUDIES

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Currently, most pharmacokinetic studies among pregnant women living with HIV are conducted by two clinical trial networks: 1) the International Maternal Pediatric Adolescent AIDS Clinical Trial (IMPAACT) Network protocol P1026s and 2) Pharmacokinetics of Newly Developed Antiretroviral Agents in HIV-Infected Pregnant Women (PANNA) network (8,9). These studies follow an opportunistic design and perform intensive pharmacokinetic sampling during pregnancy and postpartum. Together they have conducted intensive pharmacokinetic sampling on more than 1000 pregnant and postpartum women receiving more than 25 ARV drugs. Most recently, these networks reported the pharmacokinetics of rilpivirine and dolutegravir among pregnant women living with HIV (35,36). Pharmaceutical companies sometimes conduct and publish similar studies (37). Such studies routinely conduct cord blood sampling. Less frequently, washout data from infants is collected. Several neonate washout studies have been performed, especially in case of in utero exposure to drugs metabolized by UGT. Examples are studies performed by the IMPAACT Network with raltegravir, dolutegravir and elvitegravir (31,36,38).

Although not yet standard practice, the design of these studies would also be ideal for assessing breast-milk disposition (when national guidelines allow for breastfeeding). Waitt et al. (26)

systematically reviewed the pharmacokinetic studies investigating the transfer of ARV drugs to breast-milk and subsequently to the infant.

The ARIA study (NCT01910402) is a progressive example of how to manage women enrolled in Phase II trials who become pregnant. In this study, sponsored by the pharmaceutical industry, women who become pregnant during the study are allowed to continue study drugs with informed consent and are included as a separate arm in the study (NCT02075593). This demonstrates the growing awareness, implementation and future opportunities for (pre-marketing) clinical research that includes pregnant women.

Ex vivo human cotyledon perfusion experiments have also been conducted, and the literature has been reviewed (14). The placental transfer of the HIV integrase inhibitor dolutegravir was evaluated in an ex vivo human cotyledon perfusion model (39). ARV drug placental transfer has been integrated into physiologically based pharmacokinetic models and fetal exposure has also been predicted (20,33,34).

The major database for collecting safety information for ARV drugs during pregnancy is the Antiretroviral Pregnancy Registry, where pregnancy exposures and outcomes are reported on a voluntary basis.

## 5. SUMMARY

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Pregnant and breastfeeding women are mainly excluded from clinical research, resulting in the use of “untested” ARV drugs by pregnant and breastfeeding women and their infants. Including pregnant and breastfeeding women in clinical research is critical, and the period between FDA approval and the first clinical pregnancy and lactation data should be minimized or eliminated.

The recommendations provided here will assist in effectively evaluating all aspects of clinical pharmacology that are required for safe and effective treatment of women living with HIV and their children and to optimize pharmacotherapy during pregnancy. This will facilitate more timely and quantitative information on safe treatment strategies for pregnant and breastfeeding women living with HIV.

## 6. KEY CONSIDERATIONS

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- Placental transfer should be studied during the preclinical phases of drug development using techniques such as the ex vivo human cotyledon perfusion model.
- Regulatory authorities and ethical committees should require and support the inclusion of pregnant women in pre-marketing clinical trials. At the very least, women enrolled in Phase II or III clinical trials should not be removed from the study drug if they become pregnant during the trial.
- Clinical pharmacology studies of ARV drugs among pregnant and lactating women should be executed according to the high standards and requirements stated in this toolkit.
- Modelling and simulation should be used to facilitate understanding pregnancy-related clinical pharmacology and to inform clinical studies involving pregnant women.
- Cord blood samples and maternal samples should be taken at delivery to assess fetal exposure, and washout samples in neonates should be taken to assess neonatal elimination.
- Postpartum lactating women should be included in clinical trials, and breast-milk transfer from mother to infant should be assessed.
- The safety of ART and pregnancy outcomes should be closely monitored during pharmacokinetic studies that include pregnant women and by post-marketing surveillance studies.

## 7. USEFUL RESOURCES

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### FDA and EMA guidance for industry

#### EMA

- The exposure to medicinal products during pregnancy: need for post-authorisation data  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/11/WC500011303.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf)

#### FDA

- Establishing pregnancy exposure registries  
<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071639.pdf>
- Pharmacokinetics in pregnancy – study design, data analysis, and impact on dosing and labelling  
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072133.pdf>
- Clinical lactation studies – study design, data analysis, and recommendations for labelling  
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072097.pdf>

### Perinatal guidelines for treating women living with HIV

- Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States  
<https://aidsinfo.nih.gov/guidelines/html/3/perinatal/0>
- BHIVA guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review)  
<http://www.bhiva.org/pregnancy-guidelines.aspx>
- European guidelines for treatment of HIV-positive adults in Europe  
<http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html>

### WHO guidelines

- Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition  
[http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1)



## Other

- Antiretroviral Pregnancy Registry <http://www.apregistry.com>
- International Maternal Pediatric Adolescent AIDS Clinical Trial (IMPAACT) Network protocol P1026s <https://clinicaltrials.gov/ct2/show/NCT00042289>
- Pharmacokinetics of Newly Developed Antiretroviral Agents in HIV-Infected Pregnant Women (PANNA) network [www.pannastudy.com](http://www.pannastudy.com) and <https://clinicaltrials.gov/ct2/show/NCT00825929>
- European Placental Perfusion Network <https://www.facebook.com/EuropeanPlacentalPerfusionGroup>
- ARIA study at clinicaltrials.gov <https://clinicaltrials.gov/ct2/show/NCT02075593>; pregnancy substudy <https://clinicaltrials.gov/ct2/show/NCT01910402>
- Guidance for industry: establishing pregnancy exposure registries <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071639.pdf>

### Key publications with open access

- Pregnancy-associated changes in pharmacokinetics: a systematic review <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002160>

## 8. ACKNOWLEDGEMENTS

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# MODULE 4: COINFECTIONS

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# 1. INTRODUCTION

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Much of the morbidity and mortality caused by HIV infection is related to immunosuppression from poorly controlled HIV infection and subsequent disease from opportunistic coinfections. Coinfections usually require their own treatment, which may have implications for the antiretroviral therapy (ART) regimen because

of the potential for combined toxicity and drug–drug interactions. Proactively considering what key coinfections and their treatment imply for developing antiretroviral (ARV) drugs for children is therefore prudent. Coinfections of particular interest include tuberculosis (TB), hepatitis B virus (HBV) and hepatitis C virus (HCV).

## 2. COINFECTION WITH TB AND HIV

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The global burden from TB, a disease caused by *Mycobacterium tuberculosis*, is enormous, with an estimated 10.4 million incident cases worldwide resulting in 1.4 million deaths in 2015, making it the single most deadly infectious disease globally (1). The burden of TB among children has been underestimated historically, but more recent attempts have revised the estimated number of incident TB cases among children substantially upward. As many as 1 million children are estimated to develop TB globally each year (1).

Case-fatality rates of untreated TB are as high as 44% among HIV-uninfected children older than 5 years and are significantly higher among children living with HIV, even when appropriately treated for TB (2). An estimated 210 000–240 000 children died from TB in 2015, making TB one of the top 10 causes of child mortality (2). Notably, the children most at risk for poor outcomes from TB, infants and other young children, are also the group for whom predicting drug–drug interactions is most difficult and for whom child-friendly formulations are the most important.

There are several important reasons to specifically consider TB coinfection in developing ARV drugs and formulations for children. First

is the substantial epidemiological overlap of TB and HIV in many settings. There are many reasons for this overlap, including at least in part the increased risk people living with HIV have of developing TB. The highest burden of childhood TB remains in sub-Saharan Africa and South-East Asia, where most children with HIV live, so coinfection is likely in many settings (2).

Even in settings with a low TB burden, children with HIV have a much higher risk of developing TB (3). Although ART reduces this risk substantially, people living with HIV receiving ART remain at increased risk of developing TB compared with children without HIV.

Second, TB remains one of the most important causes of mortality among children living with HIV worldwide. HIV infection potentially complicates the diagnosis of TB among children and increases the risk of morbidity and mortality. Efforts to reduce mortality among children living with HIV must therefore necessarily consider TB and work to ensure the optimal co-treatment of both infections.

Third, co-treatment of TB with ARV drugs introduces the potential for additive adverse effects. The recommended first-line treatment

regimen for drug-susceptible TB is a two-month intensive phase with rifampicin, isoniazid and pyrazinamide with or without ethambutol followed by a four-month continuation phase of isoniazid and rifampicin (4). Although children generally tolerate these TB medications well, they may cause hepatotoxicity, rash and other adverse effects, which overlap with the adverse effects of many ARV drugs.

Finally, and critically important for drug development, is the potential for drug–drug interactions (5). Rifampicin, a key TB drug uniquely capable of sterilizing TB lesions, shortening treatment and preventing relapse, is also a potent inducer of cytochrome p450 enzymes and important transporter proteins (5–8). These rifampicin-induced interactions may result in drastically reduced exposure of some ARV drugs, potentially jeopardizing their efficacy and also increasing risk for acquiring ARV drug resistance (5,9).

ARV drugs without clinically significant interactions with rifampicin would be ideal agents, but this is not possible for many ARV drugs currently in use and in development. Rifabutin, an alternative rifamycin to rifampicin, does not affect concentrations of protease inhibitors. However, protease inhibitors potently inhibit rifabutin’s metabolism, and a small study of co-treatment among children was stopped early because of neutropaenia (10); this interaction and the safety of co-treatment with rifabutin and protease inhibitors needs to be studied further. In the absence of studies addressing the use of ARV drugs among children with TB, this important subpopulation may be receiving suboptimal ART; early inclusion of children with TB and HIV coinfection in studies of emerging ARV drugs is thus vitally important.

Because of the epidemiological overlap and importance of TB as a cause of morbidity and mortality among children living with HIV, the development of ARV drugs for children must ensure that co-treatment with TB is safe and effective.

## 2.1 Key challenges

The key consideration in developing ARV drugs for children from the perspective of TB and HIV co-treatment is to establish whether the ARV drug of interest and TB medication, primarily rifampicin, have drug–drug interactions. If drug–drug interactions are present, then the extent of the interaction should be characterized for children. For clinically significant interactions, alternative dosing should be established and formulations developed that will maintain target exposures of the ARV drug. Safety of the ARV drug, at the proposed dose to be used for co-treatment, must also be established for children co-treated for TB and HIV.

To establish these objectives, studies are needed among children, such as Phase I and II trials. Data from adults establishing the presence and degree of expected drug–drug interactions are highly informative for studies of children. However, drug–drug interactions may differ among children because of differences in developmental pharmacokinetics or formulations.

An important example is lopinavir/ritonavir (LPV/r), the key component of ART for children younger than three years. In contrast to adults, children given doubled doses of LPV/r combined with rifampicin-based TB treatment do not achieve adequate LPV exposure. This appears to result from differences in absorption among young children and is potentially related to the formulation for children (11,12). This highlights the need to study drug–drug interactions among children when developing formulations for children. Although adding additional ritonavir (super-boosting LPV to a 1:1 ratio of LPV/r) supports adequate LPV concentrations for children (13), lack of a suitable ritonavir formulation limits the adoption of this approach. Studies are therefore needed among children living with HIV, but these studies face several critical challenges.

### 2.1.1 Delays in initiating studies involving children

There are substantial delays in studying ARV drugs more generally among children (14). TB is often an exclusion criterion in early-phase studies of ARV drugs involving children that aim to establish the dose and safety of these drugs among children. In some ways this is sensible, since drug–drug interactions with components of TB treatment and the additional safety concerns may be problematic for emerging ARV drugs. In fact, trials of ARV drugs among children with TB are often not done at all, or if they are, it is only after the safety and optimal dosing of a drug has been established among children living with HIV but not TB. This leads to very long delays until sufficient experience is accumulated. Since the field is moving rapidly and new and better drugs are constantly being developed, by the time studies of children are underway or completed, the data are less clinically relevant since other newer ARV drugs have already taken priority. There is little incentive to include children coinfecting with TB and HIV in early-phase trials, since manufacturers do not and are not required to seek market authorization for use in TB and HIV co-treatment.

### 2.1.2 Lack of appropriate formulations for children

The lack of appropriate formulations for children is a major barrier to studying drug–drug interactions between TB medications and ARV drugs. Suitable formulations are often not available early in the drug development process, when these studies should be undertaken. In addition, the presence or extent of drug–drug interaction may depend on the formulation itself: as described above, for LPV/r, double-dosing with rifampicin for adults results in adequate LPV concentrations, but the liquid formulation results in low exposure for children (11).

Even when appropriate ARV formulations are available, the altered dosing that may be required

to address the interaction may further complicate formulation issues. If the components of a fixed-dose combination tablet are differentially affected by the interaction, alternative single-drug formulations of one or more components may be required. An example is the need for super-boosting LPV/r with additional ritonavir when co-administered with rifampicin for children coinfecting with TB and HIV. Additional ritonavir is needed to increase the ratio of LPV/r from 4:1 to 1:1; however, the ritonavir formulation for children is a poorly palatable liquid requiring refrigeration, which has limited the uptake of this strategy in many low- and middle-income countries.

### 2.1.3 Challenges of recruiting children for studies

Recruiting children to high-quality studies of TB and HIV co-treatment is increasingly challenging, despite the continued significance of TB coinfection to morbidity and mortality among children living with HIV. As services for preventing the vertical transmission of HIV continue to reach more children in better functioning health systems, where generally the capacity for implementing the required studies of children is concentrated, fewer children acquire HIV. Children in these studies who do become infected with HIV and develop TB are often those who have complicated social situations and have slipped through the existing services, often for the same reasons that make them challenging participants to enrol and keep in trials. In health programmes with gaps in preventing vertical transmission and other health services, although more children acquire HIV and TB, the capacity to enrol them into studies is often compromised.

### 2.1.4 Developmental pharmacokinetics and other design considerations

The maturation of many physiological processes during the first few years of life has the potential to greatly affect the pharmacokinetics of



drugs, sometimes in ways that are difficult to predict (15,16). Not surprisingly then, drug–drug interactions may also vary by age. Pharmacogenomic differences may also influence the degree and direction of drug–drug interactions (17). To account for this large potential variability, sample sizes must therefore be large enough to characterize pharmacokinetics and establish optimal doses across ages.

Drug–drug interactions between the ARV drug of interest and other ARV drugs may also complicate study design. If the optimal dose of an ARV drug administered with TB drugs is unknown, then it cannot be considered a component of a fully active ART regimen. In this case, the ARV drug being studied may be added on to a fully active standard ART regimen. However, existing recommended regimens contain medications such as efavirenz (EFV) or LPV/r, which may also interact with the ARV drug of interest, complicating the characterization of interactions with TB treatment.

## 2.2 Proposed solutions

### 2.2.1 Start studies and develop formulations for children earlier

Delays in evaluating novel ARV drugs among children coinfecting with TB and HIV must be reduced. One approach is to enable children living with HIV who develop TB while participating in trials of novel ARV drugs to have pharmacokinetic sampling and short-term safety monitoring after starting antituberculosis treatment, rather than immediately going off the study (see section 2.3 on the Odyssey trial). Dosing of the ARV drug in such a study can be based on the drug–drug interaction studies of adults. This opportunistic approach may not be formally powered to characterize such drug interactions but may provide meaningful data in an efficient and timely way. The risk of such an approach depends on the degree of expected drug–drug interactions based on preclinical and adult studies.

Potential risks to the participants from this approach, such as insufficient viral suppression because of unexpected interactions resulting in low ARV drug exposure, require careful management. The risk would likely be low if the ARV drug of interest was only given for a short period after starting TB treatment to perform pharmacokinetic sampling; the time taken for the interaction to mature, because of induction of enzymes and transporters, would need to be considered. Other ARV drugs could be added to the regimen so that the drug of interest is not relied on for viral suppression. Interim pharmacokinetic analyses could inform dosing in these trials once they open, further reducing risk.

There are other opportunities to accelerate studies among children. Many ARV drug trials involving children use an age de-escalation strategy, starting with older children and with progressively younger children enrolled in a stepwise fashion as data on safety and optimal dosage emerge. In this case, a trial of the ARV drug for TB and HIV co-treatment could be developed in parallel to a main trial, with age cohorts opening once safety and the optimal dosage have been established among children living with HIV but not TB rather than waiting until the entire trial is completed before opening a trial among children coinfecting with TB and HIV.

Suitable formulations for children must be developed much sooner and must consider potential drug–drug interactions among children coinfecting with TB and HIV.

### 2.2.2 Facilitate more rapid recruitment for studies

Ensuring more rapid recruitment for studies of children coinfecting with TB and HIV requires continued support for trial and clinical research capacity in settings with a high burden of both diseases. Multicentre studies involving multiple study sites in countries with a high burden of TB and HIV coinfection may provide the best opportunity to recruit efficiently. Studies should be designed as pragmatically as possible without

sacrificing safety, to avoid making eligibility criteria so strict as to be a barrier to enrolment in the study.

### 2.2.3 Pool data

Although it has its limitations, pooling data from multiple trials or studies that collect pharmacokinetic and safety data for co-treated children on the ARV drug of interest may provide data more rapidly than a single large adequately powered trial. This would also make opportunistic collection of data in trials (see section 2.2.1) potentially more useful. A collaborative mechanism to facilitate such data sharing and pooling would be a useful advance.

### 2.2.4 Use pharmacometrics

Pharmacometric methods may be very useful in TB and HIV co-treatment. Models can be used to appropriately scale data from drug–drug interaction studies of adults to better estimate optimal doses for co-treatment among children. This approach is likely to provide reasonable

estimates down to two years of age. For children younger than two years, there is more uncertainty because of developmental changes in pharmacokinetics and formulation effects.

Physiologically based pharmacokinetic modelling is becoming increasingly sophisticated and may improve dosage estimation among children younger than two years. This approach is likely to make studies more efficient by reducing the frequency of dosage adjustments and also by requiring fewer participants and fewer sampling time points to meet the study objectives. This is critically important, given the challenges of recruiting to these studies. In addition, population pharmacokinetic modelling is a powerful tool for pooling data across studies and subpopulations.

### 2.2.5 Consider the data required to make recommendations about co-treatment

There are clearly challenges to generating the relevant data needed to inform treatment recommendations for infants and other



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children coinfecting with TB and HIV. Even when suboptimal data are available, health-care workers need guidance based on the best available evidence. A pragmatic approach to developing treatment recommendations is needed, in which generating the highest-quality data is encouraged but the practical challenges in implementing studies in this population are considered. For guideline drafting, such organizations as WHO should consider developing a consensus about the highest-priority data and minimum data required to make treatment recommendations. Clear communication of this to researchers and industry could inform choices about how to most efficiently use resources and recruit children coinfecting with TB and HIV into research studies.

### **2.2.6 Collaboration and coordination between disease areas**

Both TB and HIV therapeutics are rapidly developing. Changes in optimal medications, doses or formulations in either disease area have potentially important implications for children co-treated for TB and HIV. Improved communication between experts and drug developers in these areas will help anticipate potential challenges and develop timely and effective solutions. Focus on key ARV drugs that could be combined into 2–3 regimens for TB and HIV co-treatment, as identified by expert consensus and key organizations such as WHO, may help in setting priorities for limited resources.

## **2.3 Case studies**

### **ODYSSEY trial**

The ODYSSEY trial is a randomized controlled trial of dolutegravir (DTG)-based ART versus the standard of care (therapy based on protease inhibitors or non-nucleoside reverse-transcriptase inhibitors) among children living with HIV (ClinicalTrials.gov identifier NCT02259127). DTG is a new, highly potent

integrase inhibitor increasingly used as a key ARV drug among treatment-naïve and -experienced people living with HIV. It is metabolized by the UDPG1 and CYP3A4 enzyme systems, so drug–drug interactions are expected with rifampicin.

A Phase I drug–drug interaction study among healthy adult volunteers showed that 50 mg of DTG given twice daily along with rifampicin resulted in only slightly higher exposure than with the currently recommended 50-mg once-daily dose of DTG (18); however, questions remain about the optimal dolutegravir dose for TB and HIV co-treatment (19). Children who are treated with rifampicin for TB when entering the trial or who develop TB while in the trial will be eligible for a small TB pharmacokinetic substudy. While on rifampicin, these children will receive DTG twice daily (rather than once daily) and will have pharmacokinetic sampling for DTG while on rifampicin and then again when rifampicin has been stopped. This efficient approach uses the opportunity of having children coinfecting with TB and HIV in an already planned trial to generate critically needed data on DTG dosing in co-treated children. This practical solution should be replicated in other trials.

### **Pharmacokinetics of LPV/r superboosting among infants and other young children coinfecting with HIV and TB**

This study, sponsored by the Drugs for Neglected Diseases initiative, was a multicentre, open-label, non-randomized, prospective, noninferiority study to compare the pharmacokinetics of LPV administered with superboosting (LPV/r 1:1) and concurrent rifampicin treatment or with standard boosting (LPV/r 4:1) without concurrent rifampicin treatment and to assess the safety, tolerance and viral effect of superboosting among infants and other children coinfecting with HIV and TB weighing >3 kg and ≤15 kg. Preliminary data from the study, completed in 2016, demonstrated non-inferiority for superboosting with concurrent rifampicin treatment and standard dosing without rifampicin regarding

through LPV/r concentrations below target values. The trial identified several challenges and important lessons:

- Despite the pragmatic design, enrolment was slow, and strategies to improve study accrual are thus needed.
- Most children were ART naive.
- Treatment was failing for many children receiving ART, necessitating additional time and resources to be spent on supporting adherence and ensuring that there was no resistance.
- Better strategies are needed to assess adherence.
- Tolerability and acceptability should be assessed proactively (personal communication, Helena Rabie, Stellenbosch University, Cape Town, South Africa, September 2017) (see the module on pharmacokinetic modelling for additional information on this and related studies).

## 2.4 Future issues

Until recently, there has been little change to TB treatment, with no new TB drugs entering the treatment landscape. However, largely as a response to the problem of multidrug-resistant TB (defined as resistance to both isoniazid and rifampicin), this is changing. Repurposed medications, such as clofazimine and linezolid, are being introduced into multidrug-resistant treatment regimens. Further, two new medications for TB, bedaquiline and delamanid, have conditional approval for treating multidrug-resistant TB among adults. Bedaquiline, a diarylquinoline that inhibits mycobacterial ATP-synthase, is metabolized by CYP3A4, resulting in significant drug–drug interactions with EFV (estimated 52% reduction in bedaquiline concentrations) and LPV/r (three-fold increase in bedaquiline exposure) but not nevirapine (20,21).

Delamanid, a nitroimidazole compound that inhibits mycobacterial cell wall synthesis, is not expected to have significant interactions with ARV drugs, but it is partly metabolized

by CYP3A4. Its primary metabolite DM-6705, responsible for most of its QT-prolonging effect, is also metabolized by CYP3A4 (22). Potential drug–drug interactions and safety among children co-treated with ARV drugs and these medications must be characterized. The trials of bedaquiline involving children have been substantially delayed, opening only in 2016, and the trials of delamanid involving children completed enrolment at the end of 2017. However, neither trial included children living with HIV. Trials involving children with HIV are beginning to be set up through the IMPAACT (International Maternal Paediatric Adolescent AIDS Clinical Trials) Network, but this delay has important implications for children living with HIV, especially for bedaquiline, for which clinically significant drug–drug interactions are expected.

In addition, these and other new and repurposed medications have shown the potential in preclinical studies to shorten TB treatment (23–25), and there is thus much work ongoing to develop shorter regimens for drug-susceptible TB with combinations of these medications. These medications will therefore probably find a more prominent role in TB treatment, and ensuring that these medications can be used safely and effectively for children coinfecting with TB and HIV is even more crucial. Leaders in developing both TB and HIV drugs for children must be aware of the advances in both fields that have implications for likely future treatment regimens for both diseases.

## 2.5 Useful resources

Chapters 4 and 5. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. Geneva: World Health Organization; 2016 (<http://www.who.int/hiv/pub/arv/arv-2016/en>, accessed 22 May 2018).

## 3. COINFECTION WITH HBV AND HIV

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Chronic HBV infection affects 5–20% of the 36 million people living with HIV worldwide, and the burden of coinfection is highest in South-East Asia and sub-Saharan Africa (26). In countries with high endemicity (seroprevalence >8%), where implementation of birth and infant HBV vaccination has been suboptimal, vertical transmission remains the main route of HBV transmission for children, followed by horizontal transmission. Horizontal transmission includes from child to child, within the household and within the extended family as well as transmission through inoculation of minute amounts of blood or fluid during medical, surgical and dental procedures through poor injection safety and traditional practices (such as scarification or circumcision). In countries with low HBV endemicity and/or in which the prevention of vertical transmission through infant vaccination has been widely implemented, HBV infection is uncommon among children.

The 2016 WHO consolidated guidelines on the use of ARV drugs (27) recommend that children coinfecting with HIV and HBV be given priority for ART because of the increased risk of fibrosis progression, cirrhosis and hepatocellular carcinoma. WHO recommends that children with chronic hepatitis B and clinical evidence of cirrhosis be treated for HBV regardless of alanine aminotransferase levels, hepatitis B e antigen status or HBV DNA levels. Antiviral treatment options for children with HBV include interferon  $\alpha$ , pegylated interferon- $\alpha$ -2a and the nucleoside and nucleotide analogues lamivudine, adefovir, entecavir and tenofovir (28).

### 3.1 Key challenges

No published studies on HBV treatment among children have included children coinfecting with HIV and HBV, and no antiviral drugs are labelled

for the treatment of children coinfecting with HIV and HBV.

The recommended first-line nucleoside reverse-transcriptase inhibitors tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) (or emtricitabine (FTC)) in adults and adolescents are active against HBV. Among children 3–9 years old, the first-line nucleoside reverse-transcriptase inhibitors are abacavir (ABC) + 3TC or TDF + 3TC. However, ABC + 3TC is preferred because TDF causes significant bone and renal toxicity. Further, TDF formulations for younger children are not widely available and, to date, there are no TDF-containing fixed-dose combinations for children. Nevertheless, children coinfecting with HIV and HBV should be treated with a TDF-based regimen, and if ARV drugs need to be replaced because of HIV drug resistance, TDF with 3TC or FTC should be continued together with the new ARV drugs.

Tenofovir alafenamide (TAF) has good efficacy among adults living with HIV, with much less bone and renal toxicity. Although limited data exist on HIV and HBV coinfection, the 2017 European guidelines on HBV infection (29) recommend a TAF-based ART regimen for adults coinfecting with HIV and HBV. TAF is currently available in the adult formulations of fixed-dose combinations for children and adolescents weighing over 35 kg.

### 3.2 Proposed solutions

#### Including adolescents in trials involving adults coinfecting with HIV and HBV

To speed up the availability of antiviral drugs for HBV, one solution could be including adolescents in trials involving adults coinfecting with HIV and HBV. Adolescents can usually take the same dose as adults, since the

pharmacokinetics are similar, and there is therefore no need to wait until trials for adults are completed before starting ones for adolescents.

### **Development of TAF for younger children**

TAF is about to become one of the main nucleoside reverse-transcriptase inhibitors for children living with HIV and HBV in the United States and Europe. The development of TAF for children weighing less than 35 kg, with appropriate formulations and fixed-dose combinations for children, should be a priority. This would allow the optimal treatment of HBV among children coinfecting with HIV and HBV.

### **Development of TDF formulations for younger children**

TDF formulations for younger children and TDF-containing fixed-dose combinations for children are needed. However, if the development of TAF for children is given priority, the development of TDF formulations for younger children and TDF-containing fixed-dose combinations for children will be less crucial.

## **3.3 Case studies**

### **Trial of TAF for HBV among adolescents**

A trial is ongoing on TAF among adolescents 12–17 years old monoinfected with HBV (ClinicalTrials.gov identifier NCT02932150).

### **TAF switch studies among adults**

A trial is ongoing on the safety and efficacy of switching from TDF and/or other oral antiviral treatment to TAF among adults monoinfected with HBV (ClinicalTrials.gov identifier NCT03180619).

## **3.4 Useful resources**

- Guidelines for the prevention, care and treatment of people with chronic hepatitis B infection. Geneva: World Health Organization; 2015 (<http://www.who.int/hiv/pub/hepatitis/hepatitis-b-guidelines-policy/en>, accessed 22 May 2018).
- European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol.* 2017;67:370–98.
- Chapter 5. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. Geneva: World Health Organization; 2016 (<http://www.who.int/hiv/pub/arv/arv-2016/en>, accessed 22 May 2018).

## 4. COINFECTION WITH HCV AND HIV

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In 2016, HCV affected an estimated 5–15% of the 36 million people living with HIV, rising to 90% among people who inject drugs. Low- and middle-income countries have the highest burden of coinfection. HCV-related liver disease progresses more rapidly among people living with HIV. All adults coinfecting with HIV and HCV should therefore be considered for HCV treatment.

The decision to start ART among children and adolescents coinfecting with HCV should follow the same principles as in HIV monoinfection. Potential harmful effects of ARV drugs include their hepatotoxic effects. For most people coinfecting with HIV and HCV, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury. In treating people coinfecting with HIV and HCV, considering the potential risk of drug–drug interactions between HIV and HCV treatment regimens is also very important. People receiving ongoing HIV treatment should have stable viral control of HIV infection before initiating HCV treatment.

Children coinfecting with HCV and HIV have a lower rate of spontaneous clearance of HCV, are more commonly HCV viraemic and have higher alanine aminotransferase values than HCV-monoinfected children (30,31). Treatment in the past with interferon-based treatment with ribavirin was very difficult for children because of side-effects such as depression as well as severe anaemia, thrombocytopenia and neutropenia. Further, those old regimens yielded low rates of success among children and even lower among children coinfecting with HCV and HIV (32).

The newer, all-oral direct-acting antiviral HCV regimens produce similar and very high rates of sustained viral response among adults regardless of HIV status. Thus, direct-acting antiviral HCV therapy has substantially simplified the treatment of people coinfecting with HIV and HCV. There

are fewer drug–drug interactions between direct-acting antiviral HCV regimens and ARV drugs, and sustained viral response rates with direct-acting antiviral HCV therapy among people living with HIV are higher than 95%, even for those with previous HCV treatment failure or advanced fibrosis. People coinfecting with HIV and HCV therefore no longer need to be considered a special, difficult-to-treat population.

### 4.1 Key challenges

The United States Food and Drug Administration and European Medicines Agency recently approved sofosbuvir + ledipasvir, which is indicated for the treatment of adolescents 12 years of age and older or weighing at least 35 kg with HCV genotype 1, 4, 5 or 6 infections without cirrhosis or with compensated cirrhosis. The decision was mainly based on a Phase II, multicentre open-label study of 100 adolescents with chronic genotype 1 HCV infection treated for 12 weeks with the adult formulation of sofosbuvir ± ledipasvir (400/90 mg daily).

Sustained viral response was documented for 98% of participants: the regimen was safe and well tolerated, with no grade 3 or 4 adverse events reported. The combination of sofosbuvir + ribavirin at doses approved for adults (400 mg and 15 mg/kg in two divided doses daily) was tested among adolescents with chronic HCV genotype 2, receiving 12 weeks of treatment, or genotype 3, receiving 24 weeks of treatment. Sustained viral response rates were 100% (13 of 13) and 97% (38 of 39) in genotype 2 and 3 infections, respectively.

This regimen was safe and well tolerated, and the pharmacokinetic properties of sofosbuvir were equivalent to those among adults. The United States Food and Drug Administration and European Medicines Agency therefore approved

sofosbuvir for adolescents 12 years of age and older or weighing at least 35 kg with genotype 2 or 3 chronic HCV infection without cirrhosis or with compensated cirrhosis in combination with ribavirin, including adolescents coinfecting with HIV and HCV.

At this point, the American Association for the Study of Liver Diseases and Infectious Diseases Society of America guidelines and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines recommend that treatment of children 3–11 years old with chronic hepatitis C be deferred until interferon-free regimens are available (33,34).

Sofosbuvir + ledipasvir can be used with most ARV drugs. Because this therapy increases tenofovir levels when given as TDF, concomitant use requires considering renal function. The absolute tenofovir levels are highest, and may exceed exposure with established renal safety data. There is also insufficient data on safety for TDF co-administration with ritonavir- or cobicistat-containing regimens. If these drugs are being evaluated, consideration should therefore be given to changing the ARV drug regimen. If the combined use is unavoidable, renal monitoring is recommended during the treatment.

TAF may be an alternative to TDF during sofosbuvir + ledipasvir treatment for people receiving cobicistat or ritonavir as part of their ART. Ribavirin should not be used with zidovudine because the combination has been reported to increase the rates of anaemia. Before starting treatment, people should be evaluated for potential drug–drug interactions with selected antiviral medications by consulting the prescribing information and using other resources (such as <http://www.hep-druginteractions.org>).

Most of the recent or ongoing studies on HCV infection among children still follow a staggered approach. That approach delays the inclusion of younger children and therefore the approval for their weight or age band.

## 4.2 Proposed solutions

### **Include adolescents older than 12 years coinfecting with HIV and HCV in adult trials**

Adolescents older than 12 years and weighing more than 35 kg can be usually treated with adult formulations. Adolescents should therefore be included in trials involving adults coinfecting with HIV and HCV to speed up the availability of HCV drugs in that age group.

### **A staggered approach is not needed in clinical trials involving children older than three years with HCV infection**

A recent expert recommendation on how to speed up research on ARV drugs among children has envisioned the possibility of simultaneously enrolling different age cohorts by recommending that children other than infants (<2 years) should be recruited without a staggered approach if no specific concerns are present (35). This could also apply to HCV infection and HCV antiviral drugs.

### **Indication of new drugs for adolescents coinfecting with HIV and HCV**

Indication of new drugs for adolescents coinfecting with HIV and HCV should be granted if the drug has been approved in HCV-monoinfected adolescents and there is enough evidence on safety in adults coinfecting with HIV and HCV.

## 4.3 Case study

### **Example of an adult trial that includes adolescents**

There are some examples of randomized controlled trials that include adolescents older than 12 years at the same time as adults and with the same formulation. For example, an ongoing clinical trial of adults living with HIV also includes adolescents older than 12 years. The ADVANCE trial (ClinicalTrials.gov identifier: NCT03122262) intends to demonstrate that DTG + TAF + FTC is



equivalent to or better than DTG + TDF + FTC or EFV + TDF + FTC in first-line HIV treatment of adolescents 12 years or older.

#### 4.4 Useful resources

- Guidelines for the screening, care and treatment of persons with hepatitis C infection. Updated version, April 2016. Geneva: World Health Organization; 2016 (<http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en>, accessed 22 May 2018)
- Chapter 5. Consolidated guidelines on the use of antiretroviral drugs for treating and prevention HIV infection: recommendations for a public health approach. 2nd ed. Geneva: World Health Organization; 2016 (<http://www.who.int/hiv/pub/arv/arv-2016/en>, accessed 22 May 2018).
- Recommendations for testing, managing, and treating hepatitis C. Arlington (VA): American Association for the Study of Liver Diseases and Infectious Diseases Society of America; 2017 (<http://www.hcvguidelines.org>, accessed 22 May 2018).



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## 5. SUMMARY

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- Coinfections should be considered in developing ARV drugs and formulations for children, especially those that have a substantial epidemiological overlap with HIV, those that cause substantial morbidity and mortality among children living with HIV or those that are likely to have overlapping toxicity or clinically significant drug–drug interactions.
- Key coinfections to be considered in the process of developing ARV drugs and formulations for children include TB, HBV and HCV.
- Overarching major challenges introduced by coinfections include lack of appropriate formulations for children to treat coinfecting children, delays in initiating studies involving children and challenges with recruiting coinfecting children for these studies. This results in delayed or absent data with which to inform treatment.

## 6. KEY CONSIDERATIONS

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- To ensure equitable and evidence-informed treatment of coinfecting children, the development of appropriate formulations and initiation of trials of ARV drugs among co-treated children must start much earlier than they do currently.
- Innovative strategies to retain coinfecting children in ARV drug studies should be incorporated into study designs.
- Other key solutions include facilitating more rapid recruitment for studies through specific resource investment in sites with a high burden of coinfecting children, pooling data from smaller studies when appropriate and using innovative analytical methods such as pharmacometrics.
- Close collaboration and improved coordination between disease areas are critical to addressing these challenges.

## 7. ACKNOWLEDGEMENTS

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# MODULE 5: ACCEPTABILITY

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# 1. INTRODUCTION

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In all disease areas, despite the availability of effective molecules, formulations adapted for children are still lacking and their development falls behind that of formulations for adults. Children are often either not treated or, based on anecdotal paediatric evidence, treated off label or off licence with formulations for adults (1–5).

During the past two decades, new legislation and regulation-related guidance from the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are progressively changing this situation with the mandated concurrent development of formulations for adults and for children (6–11).

Other countries have introduced policies to enhance the labelling of products for children (12): in Japan, by extending a product's re-examination period; in Canada, through a six-month extension of data protection providing acceptability and efficacy data for children; and, in Switzerland, through the obligation to submit paediatric plans and incentives for including data in the medicine label in accordance with the agreed plans. India and China are becoming important pharmaceutical industry actors, and their legislation is being revised to include specific provisions for developing drugs for children.

Pharmaceutical companies are now required to consider very early in a new drug's development the specific needs of children (13) in terms of therapeutic indication and the appropriateness of the envisioned drug formulations for the relevant target populations.

In parallel with regulations mandating the development of formulations for children for new or innovative medicines, the EMA paediatric-use marketing authorization is a dedicated marketing authorization covering indications and appropriate formulations for medicines that are developed exclusively for children, for products

already authorized that are no longer covered by patents. This includes over-the-counter products for which safety and acceptability may be problematic. With the incentive of additional data and marketing protection, the paediatric-use marketing authorization aims at transforming off-label use of drugs into safer and better circumscribed authorized use. Similarly, the Best Pharmaceuticals for Children Act in the United States provides incentives to encourage the performance of studies involving children that provide data on the effectiveness, safety and appropriateness of medicines already on the market for same or expanded indications.

Although determining the formulation type, dose and intake frequency that provide adequate drug exposure across all age or weight bands is an essential component of developing drugs for children, the acceptability of the formulation itself also needs to be maximized, since it partly conditions adherence and ultimately treatment effectiveness and safety (14).

The objective of this module is to discuss issues around formulation acceptability and to assist scientists and organizations confronted with the development of age-appropriate medicines for children. The module focuses on product development strategies for oral dosage forms – solid and liquid – although other forms, such as long-acting injectables or inhalants, may play an increasing role in therapy for children. Importantly, although the theme of this initiative is developing better antiretroviral (ARV) formulations for children living with HIV, the scope of the discussion extends to other therapeutic fields, such as antibiotics and antituberculosis drugs, medicines for diseases of the blood and blood-forming organs and cancer and malaria therapy, where acceptability may be key, as well as medications for chronic conditions.

## 2. BACKGROUND

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The EMA defines acceptability as “the overall ability and willingness of the patient to use and its caregiver to administer the medicine as intended” (11). The word “medicine” refers here to the therapeutic entity as it is to be delivered to the end user. This includes the type of dosage form, its formulation: composition and appearance (tablet size, shape and colour), the dose of its specific active substance, dosing frequency, packaging, medical device, dosing devices, container closure system together with written user’s instructions (product label and package leaflet) (15)

Acceptability, in this context, is essentially a characteristic of the product and of how it is delivered. Acceptability may significantly affect adherence – behaviour rather than a characteristic of the patient or caregiver – and may secondarily affect efficacy and safety. However, the precise contribution of acceptability to adherence is difficult to establish (16,17). However, from an ethical viewpoint that considers the inherent vulnerability of children and adolescents, acceptability needs to be maximized regardless of how it affects clinical outcomes.

Clinical appropriateness is a somewhat broader concept than acceptability, referring to the medicine characteristics that determine whether, in their personal environment and life situation, children and/or their caregivers can use the medicine as intended. For example, the need for refrigeration is a major economic and practical obstacle to the use of some liquid formulations in tropical climates. Appropriateness for children is discussed in detail in several reflection papers by WHO, the EMA and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (10,18–20). The FDA and the EMA (11,18) have also issued various recommendations on designing age-appropriate medicines for children (21).

In commentary on the EMA guidelines (11), Piotr Kosarevitz (22) states:

As a general rule, acceptability aspects should be embedded in the development programme and evaluated, (preferably) during the clinical study (preferably) with patients from all target age group(s). ...The choice of the acceptability testing method and acceptance criteria (to determine whether the medicine dosage form is considered acceptable or not), should be described and justified, taking into account the characteristics of the target age group, the condition relevant to the medicine, incidental and multiple use, co-medication and differences between countries

In compliance with regulators’ requirements, pharmaceutical companies must submit their initial paediatric investigation plans (for the EMA) or paediatric study plans (for the FDA) early in the drug development process. Paediatric investigation plans are submitted slightly earlier than paediatric study plans, and both need to be agreed on with regulators before approval of products for adults. Plans describe and justify the age appropriateness of the formulations envisioned for the relevant children (and justify waivers for specific groups of children).

Although they may be modified during drug development, paediatric investigation plans (and paediatric study plans) should provide sufficient data to enable the assessment of the medicinal product quality (including acceptability), safety and efficacy in children and thus its benefit–risk profile for children (23).

Moreover, if formulations already exist for the subsets of the children in question, their suitability should be discussed.

In its published scientific document template for a paediatric investigation plan application, the EMA specifies further its expectations for formulations adapted for children.



The section of the paediatric investigation plans and paediatric study plans on developing formulations for children should address critical issues, such as:

- the need for a specific formulation, pharmaceutical form, strength or route of administration in relation to the chosen subsets or age groups of children and the benefit of the chosen formulation, pharmaceutical form, strength or route of administration;
- potential issues related to excipients and children's (anticipated) exposure levels;
- the administration of the medicine to subsets of children, including acceptability, use of specific administration devices, ability to mix with food and possible use with a nasogastric tube; and
- the precision of dose delivery and/or dose accuracy for any pharmaceutical form for the anticipated dose for children and indicated age range.

If, based on scientific justifications, a formulation or pharmaceutical form relevant and acceptable for children cannot be developed on an industrial scale, the applicant should state how it intends to facilitate the industry-verified or extemporaneous preparation of an individual ready-for-use formulation for children.

Despite little empirical evidence, it is generally accepted that the availability of better age-adapted formulations would reduce the risk of medication and dosing errors and increase the overall safety and effectiveness of treatment (14). Although they may still play an important role in the drug development approaches, traditional liquid formulations present important limitations in terms of stability, palatability and costs. For children, the development of liquids has shifted to solid formulations in the past two decades (24,25). Children and caregivers prefer solid oral dosage forms, including tablets, capsules, mini-tablets or pellets and chewable, dispersible and multi-particulate dosage forms

(15), which tend to replace liquid dosage forms: syrups, solutions, emulsions and suspensions (Table 5.1) (26).

To achieve the targeted drug exposure, more than one dosage form and/or strength may be needed to cover the range of ages and weight bands as children grow and mature. Alternative administration strategies with flexible formulations may be considered for children who cannot be accommodated by a specific dosage form: such as segmenting or crushing tablets, co-administration with food or liquids or multi-use formulations such as dispersible chewable tablets (11).

Although children and caregivers have an opinion about what are the most desirable types of formulations, preference does not equal acceptability (27). For older children and adolescents, for example, lifestyle and peer pressure greatly influence medication preferences.

**Table 5.1.** Advantages and disadvantages of various oral formulations for children

Oral dosage forms	Dose flexibility	Dose preparation	Ease of ingestion	Tolerability and safety
<b>Syrup, solution, drops</b>	High (with limits for drops)	Need for measuring device	Easy to swallow; palatability and volume are possible issues	May require buffers, co-solvents, flavours, sweeteners; multidose containers may need preservatives
<b>Emulsion</b>	High	Requires measuring device and shaking for homogeneity	Easy to swallow; palatability and volume are possible issues	May require flavours, sweeteners; multidose containers require preservatives and surfactants
<b>Suspension</b>	High	Requires measuring device and shaking for homogeneity	Easy to swallow, uncertain palatability, consider volume, gritty sensation possible	Multidose containers require preservatives and may require buffers, surfactants, flavours or sweeteners
<b>Effervescent or dispersible tablet</b>	Low	Suitable volume and quality of water for dissolution and dispersion	Easy to swallow; palatability and volume are possible issues	May require flavours, sweeteners; consider sodium, potassium and bicarbonate content
<b>Multi-particulates, granules, powders</b>	Medium to high	Appropriate use of measuring device or packaging; may need food or liquid vehicle	Easy to swallow; from birth on if dispersed in liquid, from six months on with semi-solid food; dose, volume, texture and palatability require consideration	Risk of aspiration or choking when not dispersed
<b>Tablets</b>	Low	No preparation	Difficult to swallow for younger children, depending on size and shape; limited organoleptic issues	Risk of aspiration or choking; ability to swallow limited for younger children; lack of data on age versus suitable size
<b>Hard gelatin capsules</b>	Low	May need preparation if administered with food or liquid	Difficult to swallow for younger children, depending on size; limited organoleptic issues	Risk of aspiration or choking; risk of gelatin shell sticking to gastrointestinal mucosa; gelatin may not be acceptable in some cultures – alternatives exist
<b>Soft gelatin capsules</b>	Low	No preparation	Difficult to swallow for younger children, depending on size; limited organoleptic issues	Like hard gelatin capsules; potential risk of chewing
<b>Mini-tablets (1–4 mm)</b>	Medium	Multiple mini-tabs may require counting; device or packaging – manual dexterity	Easier to swallow than conventional tablets; limited organoleptic issues	Risk of aspiration or choking, especially for children younger than two years if coated
<b>Oro-dispersible tablet or melt</b>	Low	No preparation; water not necessary	Easier to swallow than conventional tablets; taste and grittiness are the main considerations	Risk of aspiration or choking; may require flavouring or sweeteners
<b>Chewable dosage forms</b>	Low	No preparation	Should be chewed and not swallowed; palatability may be an issue	Risk of aspiration or choking; may require flavouring or sweeteners; risk of intestinal obstruction if swallowed whole
<b>Oral films (dispersible)</b>	Low	No preparation, water not necessary – manual dexterity	Easy to swallow	May require plasticizers, flavours or sweeteners

Source: reprinted from Int J Pharm., 536, Walsh J, Ranmal SR, Ernest TB, Liu F, Patient acceptability, safety and access: a balancing act for selecting

	<b>Risk of incorrect dosing</b>	<b>Stability – shelf life in use</b>	<b>Development and manufacturing complexity</b>	<b>Supply chain</b>	<b>Relative cost</b>
	Incorrect use of measuring device	Less stable than solids; microbiological contamination in use; compatibility with primary packaging	Simple development, routine manufacturing and packaging	Bulky and heavy for transport and storage; may need refrigeration	Low
	Incorrect use of measuring device; shaking for homogeneity and dose uniformity	Less stable than solids; microbiological contamination; thermodynamic instability	Development can be complex; routine manufacturing and packaging	Bulky and heavy for transport and storage; may need refrigeration	Medium to high
	Incorrect use of measuring device; shaking for homogeneity and dose uniformity	Less stable than solids; microbiological contamination; physical instability	Development can be complex; routine manufacturing and packaging	Bulky and heavy for transport and storage; may need refrigeration	Medium
	Need to absorb full dispersion volume and residue	Moisture sensitivity; solution or dispersion of limited stability	Simple development; routine manufacturing and packaging; low-humidity conditions and modified tooling	Easier transport and storage	Low to medium
	Risk of incorrect dosing for products requiring dose measurement; incomplete dosing if the food or beverage vehicle is incompletely consumed; reconstitution errors for powder for suspensions	Good stability; compatibility with food or beverage vehicle to be verified	Complexity depends on technology; routine packaging with standard equipment; can serve as intermediate for other dosage forms	Easier transport and storage	Low to medium
	Low risk of incorrect dosing, except if tablet manipulated	Good stability	Not complex; routine packaging with standard equipment	Easier transport and storage	Low
	Low risk of incorrect dosing and incorrect use	Good stability	Non-complex development process; routine manufacturing and packaging process	Easier transport and storage	Low
	Low risk of incorrect dosing and incorrect use	Potentially less stable than tablets; may be sensitive to high temperature and humidity	Requires specialist development and manufacturing processes; routine packaging with standard equipment	Easier transport and storage; may be sensitive to high temperatures and humidity	High
	Risk of incorrect dosing if multiple mini-tablets required per dose	Good stability	Non-complex development process; routine manufacturing and packaging process; content uniformity a challenge	Easier transport and storage	Low
	Low risk of incorrect dosing and incorrect use	Good stability; may require moisture protective packaging	Complexity depends on technology; routine packaging with standard equipment; or specialist process and equipment (lyophilizates)	Easier transport and storage	Low to high
	Low risk of incorrect dosing and incorrect use	Good stability; may require moisture protective packaging	Complexity depends on technology; routine packaging with standard equipment; or specialist process and equipment (deposited formulations and softgels)	Easier transport and storage	Low to medium
	Low risk of incorrect dosing	Good stability; requires moisture-protective packaging	Requires specialist development, manufacturing and packaging processes	Easier transport and storage	Medium to high

## 3. CHALLENGES

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There are multiple challenges in developing better acceptable formulations for children. Most obvious is the lack of consensus around what acceptability means and consequently the lack of guidance from regulators on how it should be evaluated. Another difficulty arises from the fact that acceptability is only one attribute of formulations appropriate for children. Other considerations include stability, absorption, disease, safety and cost. Formulations for children are often considered late in development, when efficacy and safety for adults begins to be known and when stability and pharmacokinetic data have already started to be accumulated. Another difficulty is that acceptability is not an inherent property of the product; it is also defined by the end-users: the children and their caregivers. Finally, standardized methods and quality assurance are lacking for assessing the acceptability of formulations ranging from solid oral dosage forms such as tablets, capsules, mini-tablets and pellets, to chewable, dispersible, multi-particulate dosage forms and liquid dosage forms such as syrups, solutions, emulsions and suspensions. The following sections describe these difficulties in greater depth and explore what solutions can be found.

### 3.1 Lack of guidance from regulators and varying definitions of acceptability

European and United States regulators require that pharmaceutical companies describe and justify in their development plans the choice of their formulations for all target populations and require that they document and report the acceptability of their formulations, but they offer little guidance on what studies should be performed and reported to comply with this requirement.

How acceptability is understood and defined obviously depends on the question asked. Here the essential question is to determine whether a formulation proposed for registration is acceptable for the relevant target populations of children: can the claim for age-appropriate medicines for children be effectively substantiated? However, published studies show extreme variation in how acceptability is defined and assessed.

In the most recent reviews examining various aspects of acceptability of pharmaceutical dosage forms, the multiplicity of keywords used to identify relevant literature confirms this variation and confusion around the concept of acceptability. Published literature searches most often include such words as acceptance, adherence, tolerability, satisfaction, preference, palatability, taste and swallowability (28).

Because paediatric investigation plans and paediatric study plans must be submitted at the very beginning of clinical development of the medication (for adults: Phase I in Europe and Phase II in the United States), at the time of these first trials, the real constraints of the formulations for children are not yet known. Pharmaceutical companies may therefore not want to or be able to describe the envisioned dosage form for children in a detailed manner.

Following the submission of the paediatric investigation plans and paediatric study plans, regulators may request clarification about the target group or the choice of formulation. Although interactions between regulatory agencies and pharmaceutical companies are not public, a review by the EMA of the paediatric investigation plans submitted to the Paediatric Committee during the first years of implementation of the paediatric regulations indicated that in 82% of the cases, the excipients were questioned (their justification, dosage

and the possibility of avoiding them through alternative formulations); in half the cases, testing for palatability and acceptability was discussed; and in 23% of cases, formulations and practical issues related to manipulations or small volumes were considered problematic (13).

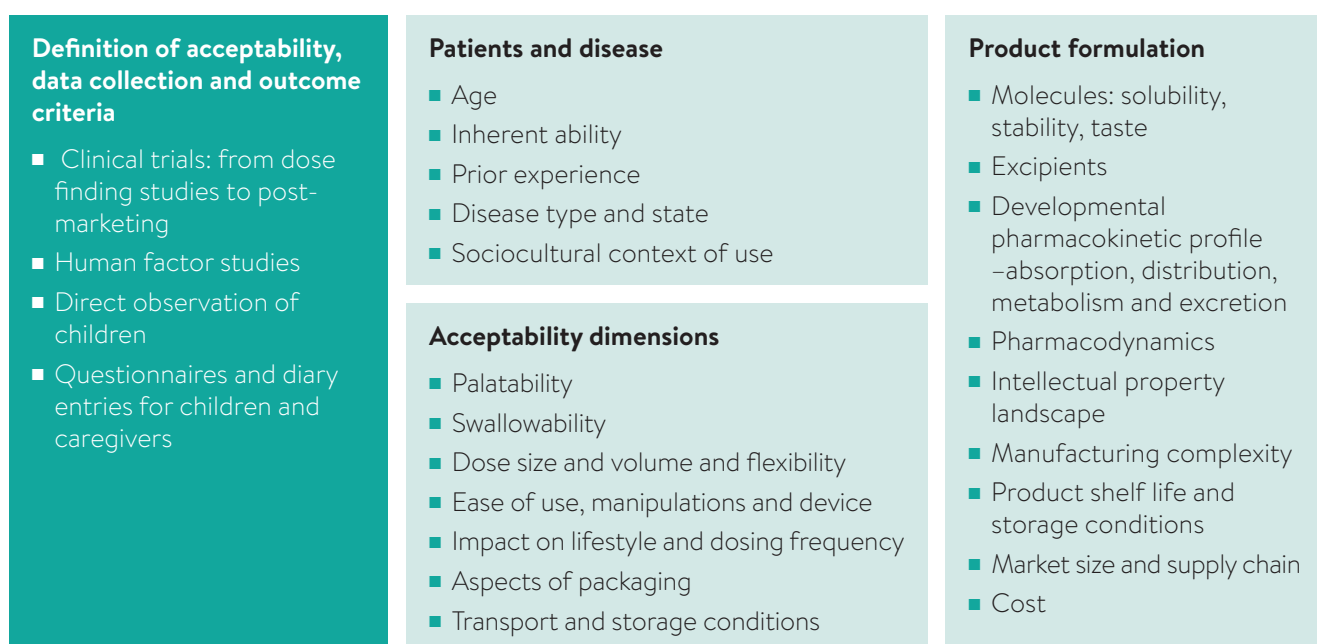
In another review covering 2007– 2011 (29), 150 paediatric investigation plans were examined (16 therapeutic areas and 220 oral dosage forms in 431 strengths and compositions). One third of the paediatric investigation plans involved tablets, 20% liquids and 16% dosage forms stored as a solid but swallowed as a liquid, such as dispersible tablets. According to this report, the Paediatric Committee review and interactions with pharmaceutical companies resulted in an increase in the number of oral dosage forms or a modification of their specific composition or strength. For many paediatric investigation plans, the target age range was widened and the excipient composition and usability aspects modified (30,31).

### 3.2 Dosage forms for children are a necessary compromise between stability, absorption, disease, safety, cost and acceptability

The ideal formulation should have flexible dosage increments and minimal excipients, be palatable, safe and easy to administer and be stable with regard to light, humidity and heat (Fig. 5.1) (32). However, as stated by Walsh et al. (26), “a single ideal dosage form does not exist”.

The development of age-appropriate medicines for children is constrained (33) by the characteristics of the target population of children (age group) and by the characteristics of the molecules (solubility, stability and taste), their age- and development-dependent pharmacokinetic profiles (absorption, distribution, metabolism and excretion), their pharmacodynamic profiles (therapeutic window, mode of action and toxicity), the disease and the disease stage

**Fig. 5.1.** Medicine formulations: a compromise between stability, absorption, disease characteristics, safety and cost



(forgiveness and acute versus chronic condition), the circumstances of use (clinic, home, nursery, school or other), the intellectual property landscape, the manufacturing and packaging complexity, the product shelf life and storage conditions, the market size and the supply chain and cost, which ultimately determines access.

The characteristics of the final product therefore represent a compromise between multiple constraints (Fig. 5.1). When suboptimal formulations are finally obtained, mitigation strategies can be developed to minimize the impact on acceptability. Risk-based strategic approaches to innovation could guide the selection of formulations (27,34), but within this process, acceptability has often been considered an adjustment variable resulting in pharmaceutical products that remain poorly adapted to children.

### **3.3 The influence of the user and the medicinal product cannot be studied separately**

The characteristics of the user and those of the medicinal product drive acceptability (35,36). Although distinguishing what relates to the user and what relates to the dosage form is useful, they cannot be disentangled since acceptability is precisely what links formulation characteristics with specific target groups.

### **3.4 Acceptability studies are often carried out late**

Although the development of formulations for children can still continue after products for adults have been registered along a timeline based on agreed commitment to the EMA and FDA, and acceptability questions can be addressed during the whole duration of development, in practice the window of opportunity during which acceptability can be assessed and the formulation modified is short (37). As explained above, the characteristics of the product only begin to be known when

the paediatric investigation plan or paediatric study plan is submitted, and it is only when the first formulation prototype is available that acceptability can be truly evaluated in the target population and the formulation possibly modified. The prototype formulation can be intermediate of the intended final formulation for children or derived from the existing formulation for adults. Using such a prototype often requires performing a bioavailability study to ensure that it leads to the same active ingredient exposure as the final commercial formulation (unless a biowaiver is granted based on the solubility and permeability properties of the active ingredient). Produced under good manufacturing practice standards that ensure reproducible bioavailability, it can later be bridged to the final commercial preparation (38,39).

### **3.5 Standardized methods and quality assurance for assessing acceptability are lacking**

After almost 10 years of implementation of the paediatric regulations, both in the United States and in Europe, many experts have investigated how the acceptability of formulations for children is assessed and reported. All reviews stressed the lack of standardized methods for assessment and of quality assurance (13,14,28,36,40–45).

In the studies that are published, the domains of acceptability explored vary considerably, with palatability being, by far, the most common attribute measured. Little to no information is provided about how data capture tools are developed and validated or the precautions taken to avoid interviewer bias. Hypotheses tested and criteria for acceptability are rarely clearly stated.

Research reports hardly ever define what is considered “acceptable”. Although the acceptability threshold used in veterinary research (44) is relatively unambiguous, no such criteria are available for humans. Percentages or scores based on ad hoc summarized or regrouped direct or proxy measurements of

acceptability reported in published studies cannot be readily interpreted.

However, most of the acceptability studies for product registration have not been published. In a review of the studies involving children listed in the clinicaltrials.gov database in preparation for a symposium, Pinto & Selen (46) note that the results of palatability and swallowability studies are simply not communicated. Of 7259 studies listed, 874 provide study results, but none on swallowability and only two on palatability (46).

Published articles report few aspects of acceptability, with limited evaluation of acceptability dimensions, limited categories of information providers and large variation in assessment approaches and tools (42).

As explained above, as a result of the incentives and mandatory requirements from stringent regulatory agencies, the development of drugs for children is systematically initiated in parallel to the development of drugs for adults, and more formulations for children will become available, although their acceptability does not or perhaps cannot take precedence over other key attributes such as efficacy, pharmacokinetics or stability.

ARV medicines clearly exemplify this situation. The first anti-HIV molecules marketed in the early 1990s had severe toxicity and limited efficacy and formulations for children comprised at best liquid forms that were difficult to procure, store and administer. In many low- and middle-income countries where the HIV epidemic was most severe, the only way to keep children with HIV alive was to treat them with a mix of syrups and solutions and fractions of adult tablets.

The first palatable, easy-to-take fixed-dose combination became available in 2007. Triomune Baby® (6 mg stavudine + 30 mg lamivudine + 50 mg nevirapine) and Triomune Junior® (double these concentrations) were the first fixed-dose combinations licensed for children younger than 12 years. They were scored so that they could easily be broken in half, allowing use within a simple weight-band dosing table.

However, the more potent option for newborn infants, lopinavir/ritonavir solution, was a heat-unstable, foul-tasting solution with 45% alcohol and 17% propylene glycol. It was only in 2015 that a better adapted multi-particulate lopinavir/ritonavir solid-pellet formulation received regulatory approval. Nevertheless, this formulation cannot be given safely to newborns, is difficult to administer by caregivers and is poorly accepted by children because of its remaining bitter taste.

In a report of the M-CERSI paediatric formulation development workshop in 2016 through the University of Maryland's Center of Excellence in Regulatory Science and Innovation, Robert Ternik and colleagues have compiled the various approaches used to assess and document palatability and swallowability (34).

### Palatability

Many approaches have been used to assess palatability in children (47–49).

With the rank order or preferential method, the subject is asked to place products in order of preference or choose the one they prefer. Evaluation is brief and does not involve sustained attention and is therefore suitable for young children.

With the facial action coding system, children are exposed to stimuli and the facial expressions are videotaped; however, this approach is time consuming and costly (50).

With scaling methods, subjects older than five years are presented samples and asked to select the likeness of sensation on a scale (51,52).

Scaling methods include:

- facial hedonic scales: these are a scale from 2 to 10 with pictorial descriptors (43) that can be used with children as young as three years old, but cognitive maturity may influence the results (52,53);
- visual analogue scale: a scale from 10 to 100 points on a horizontal 10-cm line, anchored with word descriptors at each end (43,52)

- Likert scale: it assigns 5–11 points to verbal descriptors, ranging from “extremely weak” to “extremely strong”; and
- labelled magnitude scale (54), a hybrid scale with verbal descriptors on a quasi-logarithmic vertical scale, suitable for describing the taste intensity of highly divergent samples because of its broad scaling (54)

Finally, with verbal response (descriptive methods), children are asked to rate preference using verbal descriptors such as “no taste” to “very strong taste”. This method is more discriminating than scaling methods (34) but is not suitable for younger children who cannot visualize and accurately use the descriptors.

### Swallowability

Palatability is subjective, but swallowability is more objective since it describes an ability of children rather than an appreciation. Most studies used direct observation, investigating children’s mouths after administration. Few studies used questionnaires or diary entries to provide parents’ reports of the outcomes of swallowing or whether or not a problem in swallowing the product occurred (28,29,55,56). The difficulty lies in defining the outcome: “everything swallowed”, “smooth swallowing”, “swallowing with a choking reflex or cough” and “biting or chewing followed by swallowing” (34). For palatability, children’s cooperation highly influences the assessment.

### Ease of use

Ease of use is a third major component of the acceptability of a medicine. Human factor studies are designed to evaluate the user interface of a product (57). Drug development should consider the user interface and factors that can reduce the risk of medication errors. Since children are often dependent on a caregiver for preparing and taking the drug, such studies may not involve young children. Human factor studies are typically conducted with representative users to evaluate the ability of the user to perform critical tasks to

understand the information in the packaging and labelling. Formative studies may be conducted during the iterative product development process to assess user interaction with the product and identify potential difficulties or errors in use. They are followed by human factor (simulated or actual-use) validation studies to demonstrate that the intended users can use the final product without serious errors or problems under the expected use conditions. In situations when understanding the information provided in the labelling of a combination product is critical to using a product safely and effectively, a study to assess the user’s understanding of such information is appropriate. Knowledge task studies may be carried out as part of the formative or validation process. Use-related risk analysis helps to identify the critical tasks to be evaluated in a human factor study, inform the priority for testing the tasks and determine whether specific use scenarios should be included in testing. The analysis should consider all the intended uses, users and use environments; therapeutic or diagnostic procedures associated with the use of the product; similar products used within the environments; and any associated medical factors that may affect the safe and appropriate use of the product.

There is considerable need for developing an operational and pragmatic definition of swallowability and palatability and for establishing a simple, standardized method for evaluating all dimensions of acceptability, swallowability, palatability and ease of use. Researchers in the field stress the need to bridge in vitro and in vivo data and to develop new technologies for assessing palatability and caution about using adult panels to predict palatability among children.

Alignment between stakeholders in defining acceptability, assessment methods and criteria would clearly foster much better understanding of the relationships between acceptability, swallowability and adherence to therapy. This relationship is essential to understand risks and develop appropriate mitigation strategies to achieving the desired therapeutic outcome.



## 4. SOLUTIONS

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This section outlines some potential solutions for addressing the challenges described.

### 4.1 Seek advice from regulators as early as possible in the process of developing formulations

Building the much-needed consensus between regulators and the pharmaceutical industry around what is meant by age-appropriate medicines for children, what acceptability is and how acceptability should be assessed and reported will likely take considerable time. Nevertheless, before and during a marketing authorization procedure for a medicinal product, pharmaceutical companies have various opportunities to discuss critical issues in the drug development process with regulators.

Part of this dialogue is scientific advice, an opportunity for (early) communication between a company and a regulatory authority (the EMA and/or national competent authorities) on quality and both clinical and nonclinical aspects of drug development, such as study design, choice of endpoint and indication (see [http://www.ema.europa.eu/ema: Scientific advice and protocol assistance](http://www.ema.europa.eu/ema:Scientific%20advice%20and%20protocol%20assistance)).

The EMA scientific advice is open to pharmaceutical companies, academia and other parties developing medicines and is free of charge for questions related to children. The number of companies requesting scientific advice related to medicines for children has increased every year. In 2007, only 7.6% of scientific advice was related to children versus 24.4% in 2016. Companies conducting clinical development in accordance with scientific advice recommendations are more likely to be granted marketing authorization (58).

Opportunities for scientific advice from the FDA are similar. Most importantly, a parallel mechanism has been put in place for EMA and FDA reviewers to concurrently exchange with pharmaceutical companies their views on scientific issues during the development phase of new medicinal products. This increases the dialogue between agencies and pharmaceutical companies from the beginning of the life cycle of a new product, provides a deeper understanding of the basis of regulatory decisions, optimizes product development and avoids unnecessary testing replication or unnecessary diverse testing methods. Parallel EMA and FDA advice can be obtained at the request of the developer.

### 4.2 Clearly define the characteristics of users and products

As explained above, the final formulation is necessarily a compromise between the constraints of the molecules and the specific needs of children. Although at the planning stage of developing formulations for children, when early clinical studies involving adults have just been completed, little is known of what these constraints are. Carefully considering the characteristics of the target populations of children and caregivers in their environment as well as those of the medicinal product is very important when establishing the target product profile (59).

The following characteristics of the user should be considered:

- age: relative arbitrary characteristic of the classically defined age groups given the variability and non-linearity of body composition and physiological maturation;
- inherent ability: neurocognitive development and dependence on the caregiver;

- previous experience of the child with the formulation, ability to learn how to take a given product (60) specifically, immunologic functioning (CD4+ T-cell%and/or the ability of the caregiver to prepare the product or use a device (short- versus long-term acceptability);
- disease type and state: acute versus chronic, disease type and state that may affect the ability to take the product; need for multiple active pharmaceutical ingredients or co-treatments, such as for HIV, tuberculosis (TB) or malaria therapy and previous knowledge of the dosage form; and
- the sociocultural context of medicine use (40,61).

The following characteristics of a medicinal product should be considered:

- palatability: the most frequently measured attribute of acceptability;
- appearance: for example, colour, shape, embossing etc.;
- swallowability: size, shape and integrity of the dosage form, such as film coating;
- the complexity of modification before administration if required: determining the dose, weight band width and frequency of dose adjustment; over time, shift of responsibility from caregiver to children;
- fixed-dose combinations;
- the required dose: for example, the dosing volume, number of tablets, break marks etc.;
- the need for a vehicle: soft food or liquid, culturally and financially determined;
- the required dosing frequency and duration of treatment;
- the selected administration device (62), if any;
- the primary and secondary container closure system; weight and bulkiness; need for refrigeration and physical, chemical and microbial stability; specific storage requirements;

- the actual mode of administration that reflects understanding user instructions and the feasibility of following them and the device–user interface, such as dial, touch screen, indicators, operating instructions, packaging etc.; and
- associated adverse reactions, tolerability and risk of misdosing.

### 4.3 Consider all acceptability attributes simultaneously and study them systematically

All the elements of acceptability should be systematically explored among children of the relevant age groups and appropriately reported. This applies to questions of taste, smell and texture but also the swallowability of less traditional solid forms, such as pellets of different sizes with or without coating, granules and mini-tablets (dispersible or not).

In terms of palatability, it is important to determine to what extent the results obtained in the laboratory (such as electronic taste sensing systems and cell models), in animal models and through adult taste panels or evaluations by healthy adult volunteers can be extrapolated to children (17).

It is also necessary to determine whether the results of acceptability studies among children can be extrapolated to children in different age groups, or for different types of diseases, considering the volume of liquid to be administered or the size of multi-particulate granules, for example (42). The research carried out in recent years around the acceptability of mini-tablets or pellets is an example of this approach (63–70).

Box 5.1 lists acceptability domains, providers of information and data capture tools, with selected articles and reports to which the reader can refer.

**Box 5.1.** Acceptability domains, providers of information and data capture tools

**What aspects and dimensions of acceptability are measured?**

- Taste, swallowability, other (34,71–74)
- Ease of use, need for device or for vehicle (62,75–79)
- Accuracy of the dose administered and completeness of dose intake (5,80)

**Who is providing the information on acceptability?**

- Health-care professionals (80,81)
- Educated panels of adult testers or evaluators (82)
- Caregivers: observational versus proxy measures (27,61,83,84)
- Children: issue of outcomes reported by children (85)

**What tools are used to capture and report acceptability?**

- Hedonic scales, Likert scales or visual-analogue scales: the complexity must be age appropriate (41,53,86–89)
- Direct observation or recorded reaction: closing mouth, pushing the product or vehicle away, crying or spitting out; refusal to take the medicine; inability to swallow (41,85)
- Time taken by the nurse or caregiver to administer the medicine
- Other tools, such as electronic tongue, animal models, etc.

**Adherence and effectiveness as indicators of acceptability (60,81,89,90)**

## 4.4 Plan acceptability studies as early as possible

At the earliest conception of the strategy for developing formulations for children, all the dimensions of acceptability listed above must be considered. The need for data to inform the biopharmaceutical risk assessment should be identified early so its collection can be synchronized with the programme for developing formulations for adults. For example, these may include evaluating potential taste issues using animal models and trained adult taste panels.

When the adult dosage is being developed, an exploratory formulation is usually used for the Phase I and IIa studies. Based on these, a commercial formulation for adults may be developed. The development of a formulation for children starts much later (Fig. 5.2). When the paediatric investigation plan is submitted to regulators, the formulation for children can only be broadly described based on the exploratory formulation for adults used at the time.

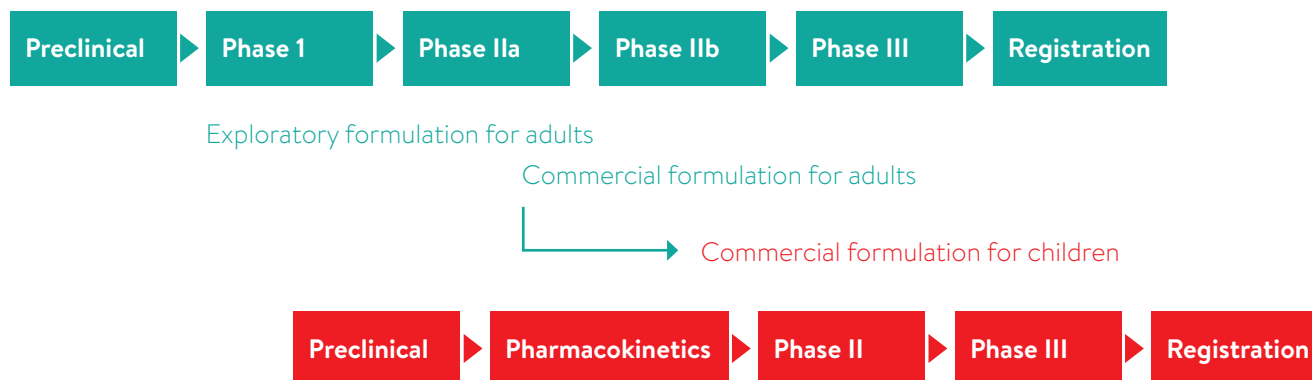
Acceptability for children can first be assessed during the initial dose-finding or population pharmacokinetic studies. All components of acceptability in the target populations must be evaluated to minimize the risk of delays in developing the final commercial formulation for children.

Acceptability in the target populations can thus be directly assessed and documented early when the formulation is being developed at the time of the initial dose-finding pharmacokinetic studies involving children. Using prototype formulations may limit the delays incurred if the formulation design needs to be modified based on the evaluation of acceptability.

Acceptability can still be further assessed in pre-registration or in post-marketing studies, but this would likely be too late to effectively inform the development of formulations for children. The data generated may only lead to modifying the product labelling or to amending the dosing instructions.

**Fig. 5.2.** Evaluating all aspects of acceptability in the first pharmacokinetic studies involving children

**Developing formulations for adults**



**Developing formulations for children**

**4.5 Capitalize on existing scientific networks**

If several hundred paediatric investigation plans or paediatric study plans have been submitted, it is only now that they start to result in registered products. It is therefore too early to draw the lessons learned from the first decade of implementation of the regulation of the development of formulations for children. Issues of stability, bioavailability and dose determination and the safety of excipients have largely dominated the scene and taken precedence over the question of acceptability. Nevertheless, the regulation of the development of formulations for children has set in motion considerable interest and debate around acceptability, as shown by the work of scientific networks regrouping academics and formulation scientists such as the European Paediatric Formulations Initiative and the IQ Consortium Drug Product Pediatric Working Group. All stakeholders agree on the need to systematically incorporate acceptability considerations within drug development without delaying the availability of therapies for children.

**4.6 Harvest what is already available**

Regulators, in collaboration with both the innovator and generic pharmaceutical companies, should work to identify opportunities to share key lessons learned and best practices based on their interactions. The types of information most valuable to developers should be reviewed and discussed, with agreement on the types of information that could be shared without disclosing the confidential proprietary data. Routinely making this information available to companies throughout the course of developing a paediatric investigation plan or paediatric study plan would facilitate the efficient development of a formulation for children.

The publication of best practices for evaluating acceptability by regulators would be helpful in planning and implementing the development of tailored formulations. The publication of best practices has been applied for Phase I studies, population pharmacology, efficacy and safety, extrapolation of data collected for adults and post-registration studies. Similar to the above, if alignment can be reached on what constitutes precompetitive sharing of best practices, this would greatly facilitate formulation assessments.

Although regulators should require that the essential elements that constitute the acceptability of a product in the various target groups be evaluated clinically in children, the pharmaceutical industry should re-evaluate their publication strategies with respect to the clinical results related to assessing the acceptability of drug products and devices in these trials. A strategy that mirrors the publication of clinical safety and efficacy endpoints could serve this purpose (25). This will progress biopharmaceutical science and minimize registration delays.

Regulatory agencies provide the opportunity for free scientific advice; pharmaceutical companies are therefore strongly advised to consult with regulators periodically or as needed to ensure strategic and technical alignment. This is especially true for the generic pharmaceutical industry, since it is playing an increasingly important role in providing medicines for children. The creation of fixed-dose combinations of several molecules poses problems that transcend the already complex issues of stability, compatibility and bioequivalence. Scientific advice and early interactions with regulators can help to minimize biopharmaceutical risks and speed up product registration.

#### 4.7 Start to collect data systematically

Without unnecessarily increasing the complexity and duration of developing formulations for children, all the components of acceptability should be evaluated among the relevant users for all paediatric subsets of interest. This requires that the team in charge of interacting with the regulators, the scientists responsible for developing formulations and the clinical teams within a company work in close collaboration from the onset of the programme for developing formulations for children.

Paediatricians and paediatric research networks should systematically include in research protocols a module for assessing the acceptability of formulations for children in any clinical trial

involving children, in pharmacological studies to determine the dose that ensures optimal exposure across all age and weight bands and in the subsequent efficacy and safety studies. These evaluations are essential to better understand the longer-term acceptability of the drugs developed as well as the impact of acceptability on adherence and the outcomes of major interest: effectiveness and safety (15,91).

Children and their caregivers must be involved as early as possible in developing the medicines that are safe and designed for them. The participation of children and caregivers in clinical trials can contribute in a meaningful way. In many instances, the lack of children to participate in trials can slow recruitment and hinder the completion of clinical studies. This reality is a meaningful obstacle to developing products for children. This same reality makes it even more important that drug product and formulation elements are considered from the earliest stages of developing formulations for children to avoid changes late in development that further slow the registration of medicines for children.

#### 4.8 Broaden acceptability studies to include cultural elements and involve social scientists

Not only children and their parents, but families and the broader community, health professionals, public health stakeholders and civil society organizations should be more involved in studying the acceptability of formulations (see the module on community engagement). Geographical and cultural environment should be considered, especially in countries in which patients have limited access to health care (15,40). Parents are often not frontline caregivers, either because they have health problems themselves or because they are absent. The extended family of brothers and sisters or grandparents are in turn responsible for ensuring that children receive the medications they need. The conditions for delivering and storing drugs and the availability of foods and vehicle types

vary considerably from place to place. The design of formulations, packaging and instructions to users must take these circumstances into account (57,92).

Social scientists must be involved in this research to better understand the use of drugs in the economic, geographical and cultural context of their use. This goes beyond the supposed but very poorly documented variation in taste preferences across cultures. For example, the ability of parents or caregivers and children to use a drug depends in part on the community's perception of the disease in question and the expected role of the therapy and of the health-care system that makes it available (90). The stigmatization of HIV infection has raised public awareness of these issues, but the same considerations apply to managing other diseases, whether TB, malaria or chronic diseases among children.

#### **4.9 Encourage methodological and translational research**

Academia and formulation scientists must undertake more primary fundamental and translational research, with the support of government organizations such as the United States National Institutes of Health or philanthropic organizations such as the Bill & Melinda Gates Foundation, in addition to or even in collaboration with the work being done in the pharmaceutical industry.

Methodological research is needed. It should cover the study designs (validated scales for endpoint assessment, children versus adults as assessors, power analyses and sample sizes, use of controls and need for randomization and single-dose versus

multi-dose studies) and their standardization, the evaluation of the reliability and reproducibility of the results and the analysis of the data. The tools for collecting acceptability data need to be validated according to age groups, the greater or lesser involvement of parents or guardians and the economic and cultural context in which children live. The methods, strengths and limitations of patient-reported outcome studies that collect data to support claims in medical product labels need to be assessed. Standardized methods would enable comparisons across studies and define which products are better accepted in which populations.

Standardized, universal, objective, simple metrics must be developed and validated to evaluate the acceptability of existing formulations for children and optimize that of formulations under development. This research must necessarily involve the concerned populations, researchers and regulators. Multicomponent referential models to assess acceptability are currently being evaluated (mapping and clustering models) (80).

This research must also be translated to enrich decision-making models that would allow, at the planning stage of the development of formulations for children, the best options for dose forms for children to be determined with the best degree of reliability. These models should accelerate the development of appropriate formulations for children with the effect of increasing efficiency for all stakeholders and delivering optimized medical outcomes to children.

## 5. CASE STUDIES

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This section describes two examples of situations where acceptability was considered in developing pharmaceutical products.

### 5.1 Developing ritonavir and lopinavir/ritonavir for treating children with HIV

Ritonavir and lopinavir (LPV) are very potent ARV drugs that have been widely used in combination with various nucleoside reverse-transcriptase inhibitors for treating people living with HIV since the early 2000s. One important characteristic is that they present a solid barrier to the emergence to resistance mutations. They have therefore been extensively used as a second-line regimen for adults and as first- and second-line regimens for children whose initial viral load is very high compared with that of adults. However, both drugs are insoluble and poorly absorbed. The initial formulations developed by the innovator pharmaceutical company AbbVie were complex solutions presented in soft-gel capsules for both adults and children or as liquid formulations for children with excipients, which made their taste difficult to bear. In the late 2000s, AbbVie subsequently developed a solid formulation using the melt-extrusion technology that resolved taste and excipient issues, presented in the form of tablets for adults and smaller tablets for older children.

The generic company Cipla has more recently developed a pellet formulation of the LPV/ritonavir (LPV/r) combination for infants and young children in resource-limited settings (with tentative approval by the FDA), but as shown in the study summarized below, taste remains a significant challenge for younger children, and swallowability creates difficulty in using this formulation for infants younger than three months of age. Cipla in collaboration with the Drugs for Neglected Diseases initiative is further

developing a taste-masked formulation with solid granules that associates four drugs LPV, ritonavir, abacavir and lamivudine, a 4-in-1 with the aim of resolving the limitations of the pellets and simplifying therapy for infants (93).

Finally, AbbVie has successfully developed and commercialized a solid powder formulation of ritonavir to replace the liquid formulation, which needs refrigeration for storage and is therefore difficult to use in the tropical climates of Africa, where more than 95% of children living with HIV reside. Ritonavir is used as a booster for other protease inhibitors.

The publication of this development by AbbVie is forthcoming. Indeed, the case of LPV and ritonavir exemplifies the complexities of developing age-appropriate medicines for children when the chemistry of the active ingredients severely limits formulation options.

### 5.2 Example of acceptability evaluation embedded in a Phase II comparative bioavailability study of a generic versus an innovator product

WHO and national guidelines recommend LPV/r for children younger than three years initiating first-line antiretroviral therapy (ART) and older ones requiring second-line ART. Whereas older children (older than five years) who can swallow tablets may have minimal problems taking their medications, the younger ones would need a syrup, pellet or mini-tablet or dispersible formulation. Although currently licensed formulations of LPV/r syrup and pellets taste bitter, in the CHAPAS-2 trial in Uganda comparing solid and liquid formulations, the pellets were more acceptable than syrup largely because they were easier to store and transport, since they are heat stable and hence

do not require refrigeration. However, the acceptability of the pellets waned over time, with the reported challenges being the need to mask the bitter taste with food, increasingly refused by the children, and the caregivers worrying about ensuring that the child is taking the whole dose. The requirement that the LPV/r syrup be refrigerated makes the formulation less acceptable than heat-stable pellets in low- and middle-income countries, although the pellet

formulation remains less than ideal because it tastes bitter. In CHAPAS-2, the older children preferred LPV/r tablets to pellets, and taste was the main factor. An LPV/r formulation suitable for younger children with improved taste masking therefore still needs to be developed. In the meantime, ongoing caregiver support needs to be embedded in national programmes in the countries in which the LPV/r pellets have been rolled out (94–96).

## 6. SUMMARY

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The acceptability of a drug formulation to the intended users may have a significant impact on treatment adherence and ultimately safety and efficacy. As a result of recent paediatric regulations in the United States and the European Union, considerable effort has been made to improve the acceptability of drug formulations for children. However, acceptability studies are often carried out late

in the drug development timeline, and there is little consensus about how acceptability should be defined, measured and reported. This may contribute to unnecessary delays in making new medicines available to children. The considerations below aim to promote clearer and more systematic evaluation of the acceptability of new formulations for children to facilitate their development.

## 7. KEY CONSIDERATIONS

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- Consensus around assessing the acceptability of formulations for children should be established among key experts.
- Standard criteria for measuring acceptability should be developed.
- Risk-based strategic approaches should be used to guide the selection of formulations.
- The characteristics of users and products should be clearly defined and considered simultaneously.
- Acceptability studies should be planned early in the process of drug development.
- Regulators should make available existing non-proprietary data on acceptability.
- Acceptability data should be collected systematically.
- Acceptability studies should be broadened to include cultural elements, and social scientists should be involved.
- Methodological and translational research relating to the acceptability of formulations should be encouraged.



## 8. USEFUL RESOURCES

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- European Paediatric Formulations Initiative: [www.eupfi.org](http://www.eupfi.org)
- IQ Consortium Drug Product Pediatric Working Group: [www.iqconsortium.org](http://www.iqconsortium.org)
- United States Pediatric Formulations Initiative: [www.bpca.nichd.nih.gov/prioritization/researchandcollaborations/Pages/pediatric-formulations-initiative](http://www.bpca.nichd.nih.gov/prioritization/researchandcollaborations/Pages/pediatric-formulations-initiative)
- Global Research in Paediatrics (GRIP) work package 5: Paediatric Formulations: [www.grip-network.org](http://www.grip-network.org)
- Pediatric Formulations Task Force (American Association of Pharmaceutical Scientists)

## 9. ACKNOWLEDGEMENTS

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The authors are grateful for the input received from the European Paediatric Formulations Initiative and the IQ Consortium Drug Product Pediatric Working Group, especially Catherine Tuleu (University College London, Chair, European Paediatric Formulations Initiative) and David Cheng Thiam Tan (AbbVie, Co-Chair, IQ Consortium) as well as Trupti Dixit (independent), Eleni Dokou (Vertex), Elizabeth Galella (Bristol-Myers Squibb, Co-Chair, IQ Consortium Drug Product Pediatric Working Group), Melissa Keeney (Eli Lilly), John Morris (AbbVie), Yogesh Patil (Amgen), Fabrice Ruiz (Clinsearch), Smita Salunke (University College London), Daniel Schaufelberger (Janssen), Julia Schiele (AbbVie) and Robert L. Ternik (Eli Lilly).

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# MODULE 6: COMMUNITY ENGAGEMENT



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# 1. INTRODUCTION

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Since the beginning of the HIV epidemic, community engagement has played an important part in clinical research and drug development. This is particularly true for adults living with HIV, in which activists are strongly involved in clinical trials and policy decisions – notably through community advisory boards. In addition, countries in Europe and the United States of America are starting to include patient perspectives in their health-care systems and decision processes, using value frameworks (1).

Although community involvement in biomedical research is not only expected but an essential requirement for funding (2), the involvement of children (or their caregivers) and adolescents lags behind that of adults.

This module describes the issues and complexity associated with engaging the paediatric community in the process of HIV drug research and development. It also provides solutions as to how best to involve the community. It aims to help researchers, drug manufacturers and regulatory authorities strengthen existing partnerships and develop new ones.

Despite limited evidence, the recommendations should facilitate effective engagement of the paediatric HIV community, taking into account consent procedures, legal and policy frameworks as well as the geographical and cultural context of the research.

## 1.1 Definition

This section aims to explain what “community” and “community engagement” mean in clinical research involving children and adolescents and in the context of this toolkit.

### 1.1.1. Community

Community is a broad and fluid concept. Individuals are always members of multiple communities, with views and perspectives that may have competing interests, potentially shifting over time with changing priorities.

#### Box 6.1. Definitions used in paediatrics

**Trial participant** (also called a human subject) – a person who participates in research and is observed by researchers

**Paediatrics** – the management of medical conditions affecting babies, children and young people

**Minor** – a minor is a person below a certain age (usually the age of majority) that legally separates a child from an adult; the age varies between countries and settings but is generally 18 years

**Legal guardian** – a person who acts as the primary caretaker and makes decisions on behalf of a child or minor

**Infant** – a child younger than one year of age

**Child** – a person 19 years or younger unless national law defines a person to be an adult at an earlier age. WHO defines a child as a person 1–9 years of age

**Adolescent** – a person from puberty to legal adulthood. WHO defines an adolescent as a person 10–19 years of age

**Vulnerable groups** – groups of people who are particularly vulnerable to HIV infection in certain situations or contexts. These include: adolescents (particularly adolescent girls), orphans, street children, people in closed settings (such as prisons or detention centres), people with disabilities and migrant and mobile populations.

The United States National Institutes of Health defines community as the population in and for which the research is being conducted (3). For the purpose of this toolkit, community refers to trial participants (children and adolescents living with HIV), their caregivers and advocates as well as others who may be affected by HIV and/or the research being conducted (see the module on trial design). Box 6.1 shows other definitions.

### 1.1.2 Community engagement

Community engagement in research is a complex, dynamic and interactive relationship between researchers, policy-makers and the community (3). The aim is to involve participants and their advocates as partners in research rather than merely trial subjects or eventual users of the drug or intervention.

Effective community engagement should result in the community becoming increasingly critically aware of and involved in research activities, processes and decision-making.

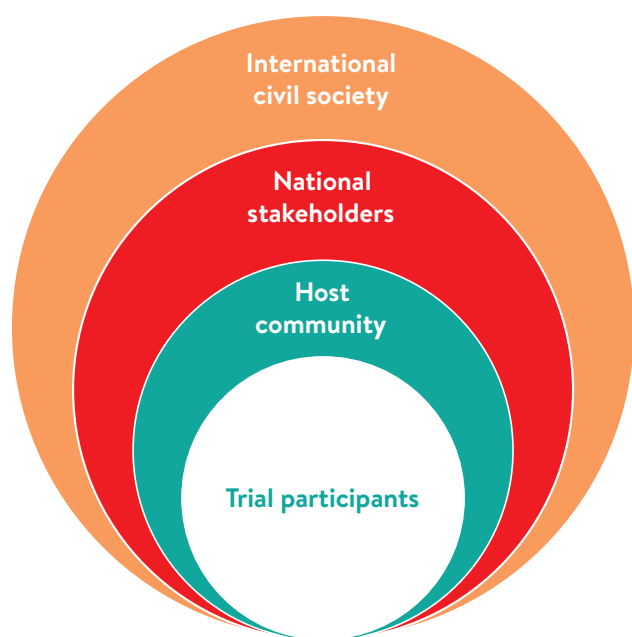
The balance of power between researchers and participants can affect how communities engage, who represents the different communities and what type and level of interaction exists between the different stakeholders and at what stage of the research process. Successful engagement that considers the research priorities alongside the needs of the community improves the quality and outcomes of research (4).

### 1.1.3 Levels of community engagement

Fig. 6.1 illustrates everyone who represents the different communities and their level of engagement in research.

Scientists, researchers and other stakeholders involved in clinical trials have a critical role to play in how they engage and interact with the paediatric community. Even where the selection of community and community representatives is clear, the way they communicate, the language and scientific terms they use, how they perceive community involvement and their level of understanding can influence how the community engages in the research process (4).

**Fig. 6.1.** Levels of community engagement



- **Trial participants** – neonates, infants, children and adolescents directly involved in the trial
- **Host community** – children living with and affected by HIV, adolescents and their caregivers, advocates and community-based and nongovernmental organizations (such as community advisory boards) that represent the paediatric HIV community directly
- **National stakeholders** – anyone who has a role in the political, scientific, social enterprise of developing drugs at the national level, including political decision-makers, regulatory authorities, ethical review committees, health ministry, national nongovernmental organizations, civil society advocates, donors and funders
- **International civil society** – non-profit, organized, citizen-led groups interested in the goals, processes and outcomes of paediatric HIV research and drug development and/or in the rights of communities and research participants (such as WHO and UNAIDS) networks or the media

Source: Slevin et al. (2). Reproduced from the PATH website at [www.path.org](http://www.path.org), 14 June 2018.

## 1.2 The need to engage the community in research and drug development

Once communities have been identified, knowing why they should be involved in the research process is important. This section examines the rationale, principles and ethical considerations for engaging the community in the research process and drug development.

### 1.2.1. Rationale behind community engagement in the research process

Engaging the paediatric community in the clinical research process may require different approaches because of regulatory, cultural, political, traditional, religious or socioeconomic factors prevailing in the communities and countries of interest.

Community engagement can provide valuable input in identifying ways to improve clinical study outcomes, for instance, through helping to facilitate recruitment and participant retention (5). Community members are frequently highly motivated and invested in support of the planned and ongoing research. One of the benefits of community engagement can be increased support and investment in the research, and this can improve study success by helping to identify and address potential issues.

A collaborative approach and effective communication between researchers and the community are paramount to ensure that those representing the paediatric community truly understand the purpose and procedures of research. Such an approach can also help enhance mutual trust and create a sense of collective ownership.

### 1.2.2. Principles of community engagement in research

To support researchers in involving communities in the research process, the United States National Institutes of Health developed a set of principles (Table 6.1) (3).

### 1.2.3. Ethical considerations

Guidelines on ethics in clinical research are well established with the Nuremberg Code and the Declaration of Helsinki as the core foundation. The purpose of ethical conduct in research is both to protect trial participants and to preserve the integrity of the science (6). Nevertheless, ethical considerations in community-engaged research raise additional questions when community representatives and trial participants may take part in relationships among or between communities, the researchers and research institutions as well as other stakeholders, with principles and codes that are not as well defined (5,6). This is especially true in research involving children and adolescents, a population dependent on their adult caregivers.

The Nuffield Council on Bioethics (7) recently published a report focusing on the ethical aspects of involving children and young people in research, providing recommendations about the roles and responsibilities of children, their parents or guardians, researchers and others.

The United Kingdom Medical Research Council (8) and the European Commission (9) have also produced extensive guidance on the ethics of conducting medical research among children, though these documents tend to refer to children and adolescents as trial participants and less about considering their role as collaborators in the research process.

Researchers must pay particular attention to their role and responsibilities related to child protection and safety when dealing with vulnerable groups. Caregivers have an important duty as gatekeepers whose informed consent must always be sought when involving minors as participants or collaborators in research. In addition, children younger than the age of consent should be able to provide their assent within a safe and non-coercive environment when working under supervision with adult researchers.

**Table 6.1.** Principles of community engagement in research

<b>Set clear goals</b>	Community engagement must meet the needs of the populations and/or communities affected by the research, strengthening the community's role and capacity to actively address research priorities and helping to ensure the development and implementation of relevant, feasible and ethical research.
<b>Learn about the community</b>	It is important to become knowledgeable about the social and cultural context of the community in terms of its economic conditions, political leadership, demographic trends, history (overall and regarding research) as well as its perceptions of and experience with engagement activities.
<b>Develop cultural competence</b>	Knowledge and understanding of the community's predominant attitudes, perceptions and practices will help ensure more effective and respectful communication and interactions, leading to culturally responsive engagement activities.
<b>Foster transparency</b>	The community should be encouraged to express itself independently during the community engagement process.
<b>Build partnerships and trust</b>	Partnering with community stakeholders is necessary to create change, build mutual trust and improve health. Toward that end, it is important to seek commitments from community-based organizations and to identify formal and informal leaders in the community.
<b>Provide and promote capacity-building</b>	Sustainable community engagement can only be achieved by identifying and mobilizing the community and by developing the capacities and resources within the community.
<b>Maintain a long-term commitment</b>	Community collaboration requires an ongoing, long-term commitment by the research organization, its partners and the community.

Source: adapted from *Recommendations for community engagement in HIV/AIDS research: a guide for communities and researchers, version 2.0* (3).



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## 2. CHALLENGES

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The research community can often perceive community engagement in research as demanding and time-consuming. This section highlights some challenges researchers might consider when engaging the paediatric HIV community in the research process and drug development.

### 2.1 The paediatric community

#### ***Working with children and adolescents***

Children and adolescents are not “miniature adults” but a heterogeneous group with unique and complex characteristics, marked by different physical and cognitive developmental stages that not only affect the pharmacokinetics and pharmacodynamics of medicines (see the module on pharmacokinetics) on the body but also the way adults interact and collaborate with them.

Although personal motivation and commitment is key, it is important to recognize that children and adolescents require age-appropriate information and support from adults as well as time, flexibility, patience and additional resources from the research community to improve their collaboration in the research process.

#### ***Identifying representatives of the paediatric community***

Another challenge with engaging the paediatric community in research is identifying those who best represent children, from neonates to adolescents, alongside their caregivers.

With power inequity (especially for young girls) compared with adults, children and adolescents are usually underestimated in their capacity to experience life and make meaningful decisions for themselves. Their lack of experience and knowledge of research alongside the ethical issues

of working with children and adolescents, as well as vulnerable groups, can affect researchers’ willingness to engage with this community.

The research community should take on board the voices of children and young people that have already been captured, such as those published in the Nuffield Council on Bioethics report (7). Asked what qualities they thought were important for clinical researchers, young people themselves included “courageous” alongside the more expected descriptors such as “trustworthy” and “openness”.

### 2.2 Stigma, disclosure, confidentiality and fear

HIV continues to be stigmatizing beyond children’s ability to understand the root of such behaviour. Confidentiality and the parents’ fear of disclosing their own status to their extended community, and to their children, can be challenging. Sometimes the children participating in clinical trials have not yet been told their HIV status by their caregivers. The risk that children living with HIV could be hurt, misjudged or poorly treated because of their health condition causes great anxiety for parents.

Research can also raise parental concern when it investigates HIV drugs using data extrapolated from adult clinical studies and for which safety and efficacy needs to be proven among children. The feeling of personal risk related to treatment side-effects and associated interventions as well as stringent trial design may deter trial participation (10). Children and young people participating in research on drug development may worry about their ability to manage their new treatment or the possible disruption hospital appointments and treatment side-effects might have on their daily routine and lifestyle.

Further, misconceptions, rumours and suspicions can potentially arise about specific research projects and hinder research progress and drug development (5,11). Particular attention should be brought to those who might

not directly be included in the community of interest (such as extended family members and religious leaders) but who have considerable power and influence over and above local beliefs and cultural practices.

**Table 6.2.** Requirements to support children’s participation in the reporting process

<b>Transparent and informative</b>	Children must receive full, accessible, diversity-sensitive and age-appropriate information about their right to express their views freely and to have their views given due weight and about how this participation will take place, its scope, purpose and potential impact
<b>Voluntary</b>	Children should not be coerced into expressing views against their wishes and must be informed that they can cease involvement at any stage
<b>Respectful</b>	Children’s views have to be treated with respect, and children should be provided with opportunities to initiate ideas and activities
<b>Relevant</b>	Children should draw on their knowledge, skills and abilities to express their views on relevant issues. Space needs to be created to enable children to highlight and address issues they have identified as relevant and important
<b>Child-friendly environment</b>	Environments and working methods should be adapted to children’s capacity (time and resources)
<b>Inclusive</b>	Participation needs to provide for equality of opportunity for everyone, including marginalized children, without discrimination on any grounds, including age, and be culturally sensitive to children from all communities. Special measures should be taken to include very young children and other children from marginalized communities
<b>Capacity-building</b>	Adults need preparation, skills and support to facilitate children’s participation effectively. Children also require capacity-building to strengthen their skills relevant to the process
<b>Safe and sensitive to risk</b>	Adults have a responsibility towards the children with whom they work and must take every precaution to minimize the risk of violence, exploitation or any other negative consequences of their participation.
<b>Accountable</b>	Child-led organizations, children’s groups and nongovernmental organizations should ensure that children have a clear understanding of their role and how their views will be interpreted and used.

Source: adapted from *Working methods for the participation of children in the reporting process of the Committee on the Rights of the Child* (13).

## 3. SOLUTIONS

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Although challenges may arise while engaging with the paediatric community, as with any other stakeholders, effective communication and trusting relationships are key to successful collaboration. The following section proposes several ways to improve how scientists and researchers engage with the community in the research process.

### 3.1 Involving children and adolescents in research

According to the United Nations Convention on the Rights of the Child (12), children should be taken seriously and given every opportunity to express their views and concerns on matters that affect their lives. Every effort should be made to provide children and adolescents a safe environment to encourage and enable them to participate in identifying research priorities and decision-making. Researchers need to ensure that “an invitation to participate in research constitutes a ‘fair offer’ to children, young people and their parents” (7).

Recent years have witnessed a shift in how scientists and researchers view the paediatric community. Children and adolescents are starting to be recognized as being extremely resourceful and committed to dealing with their own health issues. It is also being recognized that their input is essential to understanding how to get it right, as evidenced by data showing that the HIV response is failing children and adolescents.

The United Nations established a set of requirements to support children’s participation in the reporting process (Table 6.2) (13). These requirements can also be applied to the participation of children and adolescents in the scientific HIV research process.

### 3.2 Community advisory boards

A community advisory board engages in a two-way relationship between researchers and the targeted community (3,14). Community advisory board members commonly include volunteers from activist and patient groups as well as nongovernmental and sometimes government organizations that best represent the community affected by the research. The involvement of community advisory boards in the research process can:

- improve communication and cooperation between community representatives and researchers;
- develop the treatment and research literacy of community representatives;
- give community participants the opportunity to provide input on and help to resolve challenges for the trial; and
- advocate for implementing the trial results in national plans and guidelines.

A community advisory board aims to ensure community engagement, ensure that the research is conducted in the best interests of the community, develop mutual trust between the researchers and the community and dispel any myths and rumours that might arise because of lack of information and understanding fuelled by local beliefs (3,14). Such considerations tend to foster transparency and the implementation of culturally sensitive strategies that are best suited to the setting, local practices and the targeted population.

Community advisory board activities can also help stimulate the participation of the community at various stages of the research process, including providing input on trial design, informed consent forms and other community materials and participating in study implementation, expanded access programmes and pharmacovigilance.

In addition, community advisory boards can support partnerships between researchers and the community and the dissemination of research results. This model has also proven to be effective in recruiting and retaining study participants, since it promotes collaboration that leads to practical advice and constructive feedback (3,14).

Although community advisory boards have played an important role in HIV research and drug development, questions are starting to emerge about the limitations of their approach, which may not be entirely independent and representative of the overall HIV community (2). Community advisory boards increasingly include young people as established board members. However, younger children remain underrepresented, which constitutes an important gap in research.

### **3.2.1 Children and adolescent advisory groups or networks**

In recent years, children and adolescent advisory groups or networks have started to arise because of increasing demand and are being solicited to provide valuable input to the research process. It is therefore essential to provide those representing the community with age-appropriate information and the opportunity to develop this.

With support, their active community participation and collaboration in clinical trial discussions can enrich the process. Enabling children and adolescents to share their views on protocol design and ethical issues and welcoming their input in developing age-appropriate treatment literacy materials and consent forms can help trial participants to be better informed when enrolling in drug trials (15).

Several paediatric community networks have recently emerged at the national and international levels, giving children and adolescents a safe space to voice their views and concerns on matters that are relevant to them. A non-exhaustive list can be found in the section on resources of this module.

### **3.2.2 Community empowerment**

WHO refers to community empowerment as “the process of enabling communities to increase control over their lives. It assumes that people are their own assets, and the role of the external agent is to catalyse, facilitate or “accompany” the community in acquiring power” (16).

Scientists and researchers have a responsibility to help to empower those directly affected by the research being conducted. This can mean: shared ownership on defining priorities, supporting the process of community–researcher partnership and addressing the social, cultural, economic and political aspects of research.

Children and adolescents can be supported to take a leadership role in engaging in every step of the research process: for instance, by ensuring adequate information-sharing, ensuring transparency and allowing sufficient time for critical-thinking. Valuing the voices of children and adolescents in research and understanding their lives from their own perspective is an important contribution to paediatric studies.

### **3.2.3 Capacity-building**

Capacity-building is an important part of responsible engagement of the paediatric community. Children and adolescents may be from different socioeconomic and cultural backgrounds and at different stages of development, with different skills and knowledge. With an emphasis on their existing talents, researchers should invest time, resources and logistical support in training children and adolescents representing their community who are committed to becoming collaborators in the research. Their ability to develop confidence and treatment knowledge will be of immense value to community engagement and research involving children.

Capacity-building should be tailored and appropriate to the age and developmental stage and stage of life of the community being engaged. This will be very different for young children than for adolescents.



Adolescents are transitioning into adulthood, and capacity-building should also provide them with transversal skills that will help them in their personal and professional development.

The following list is intended to provide examples of training topics that can support the involvement of children and adolescents as research participants and can develop important research and social skills:

- communication;
- presentation and public speaking;
- listening abilities;
- information and technology training;
- introduction to HIV, treatment and prevention;
- ethics and human rights in clinical research;
- advocacy and peer representation;
- introduction to research and clinical trials;
- confidentiality; and
- understanding committees and related expectations.

### 3.2.4 Confidentiality

Ethical considerations and principles related to confidentiality, anonymity and data protection are the same whether researchers are working with adults or with children and adolescents. Age-appropriate information on confidentiality and data protection must be provided to those involved in research either as trial participants or community representatives. This should be agreed at the start of the collaboration and reiterated when necessary.

### 3.2.5 Community engagement models and frameworks

Community engagement in research and drug development means that innovator manufacturers – and researchers – should acquire better understanding of the health needs and challenges patients experience in their daily lives, beyond seeking the opinion of advocacy and market

research groups after the drug has been developed (17). With limited evidence on the benefits of engaging the community (adults) in health care and the research process, which is often inconsistent, recommendations on best practice are lacking.

Nevertheless, such patient groups as #PatientsIncluded and PatientsLikeMe are increasingly being invited to share their views and opinions during decision-making. In addition, regulatory authorities are proactively taking on patient-centred activities in drug development to gather patients' perspectives on various aspects of health. For instance, the United States Food and Drug Administration started the Patient-Focused Drug Development Initiative that helps evaluate the advantages and disadvantages of new therapies (17).

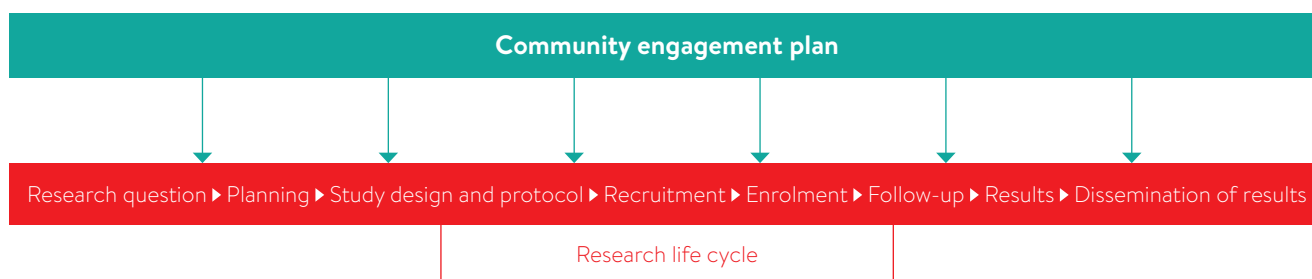
Pharmaceutical companies are encouraged to engage with the community, including the paediatric community, in a true partnership during the research and drug development process, if they want to better understand the needs and concerns of their customers. Community engagement models and frameworks should be developed with the community, alongside recommendations based on evidence, to strengthen present and future collaboration and community engagement.

### 3.2.6 Community engagement plan

Based on the stakeholder engagement plan developed by UNAIDS and the AIDS Vaccine Advocacy Coalition (18), a community engagement plan (Fig. 6.2) provides a structured approach for researchers to engage with the paediatric HIV community in every aspect of the research process, including planning, designing, implementing, reviewing and disseminating the results of the research being conducted.

Researchers must identify relevant community stakeholders and representatives in a broad, multifaceted, inclusive way and develop partnerships that support effective and locally acceptable research. This process should consider the trial population to be studied

**Fig. 6.2.** Community engagement plan



and known stakeholders and understand the differences and power relations of potential and known stakeholders.

Involving the community in developing the plan will ensure that research priorities and community needs are included, help determine the frequency and methods of engagement and inform the process of reviewing and adopting community engagement plans.

### 3.3 A child- and adolescent-friendly approach to research

Children and adolescents must feel welcomed and valued if researchers want them to actively engage in clinical trials. Whether as trial participants or collaborators working with researchers, children and adolescents are not only sensitive to their environment but also to the approach adults use to communicate with them. Ensuring a child- and adolescent-friendly and safe environment in which they feel comfortable expressing their views and ideas is one of the many requirements researchers must consider when working with the paediatric community.

Children and adolescents should also be presented with information adapted to their age and in a friendly manner. A family-centred approach and age-appropriate communication methods are preferred to encourage their involvement while providing a positive and meaningful experience. Seeking children's and adolescents' contribution to clinical research in an innovative and creative way, for instance by

using illustrations and cartoons in the design of information sheets and consent forms, is likely to boost interest and encourage participation.

### 3.4 Compensation

Compensating children and adolescents for participating in clinical research and those representing the paediatric community remains controversial. Although the financial coverage of direct trial-related expenses including transport, meal allowance, accommodation and access to health care is commonly accepted in biomedical research in some countries, the payment of children's and adolescents' participation as a token of appreciation for their time and inconvenience is far from straightforward (19–21).

Compensation for minors to participate in clinical research may influence the decision-making of the child and/or caregiver, leading to increased acceptance of risk. This could also influence the decisions made by adolescents who are adults legally (19).

Nevertheless, the absence of reimbursement for direct trial-related expenses, as well as time and inconvenience, may interfere with the opportunity for study participation and enrolment, hindering significant advances in paediatric research (19).

Researchers must recognize the complexity behind compensating trial participation, considering not only the ethical but also the contextual and individual decisions related to trial participation during the entire research process.

## 4. CASE STUDIES

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### ***Meaningful participation in dissemination***

Clinical trials involving children significantly emphasize informed consent. This occurs at the opening stages of the trial. A critical element in ensuring young people's meaningful participation in the research process is dissemination towards the end of the trial, which tends to receive far less attention.

We held a dissemination event for participants (10–21 years old) and their caregivers in a clinical trial in Uganda to explain the findings. The investigators explained the trial findings and their implications, answering all the questions posed by the young people and their caregivers. We then held focus groups with the young people a few weeks later to explore their experiences in the trial.

Those involved highly valued this rare event: by being informed appropriately, they better understood what they had been part of and why. Many described understanding for the first time why blood tests had been taken so frequently. This shows the importance of treating informed consent as a process, rather than a single event, and providing regular opportunities to revisit young people's understanding of the trial to ensure and develop their understanding.

Having learned of the potential significance of the trial findings, the participants described pride in their participation because they considered it to have contributed to the more effective treatment and that their fidelity to their assigned trial arm had been worthwhile.

Many had participated in previous trials, but because they were not told about the trial findings appropriately, some had assumed the trial had been a failure. Understanding the results of this trial made them feel it was a success, and this gave them hope for their future health.

Now hearing that the results were successful gave me a lot of hope that, in future, someone can have a break

for more than one day or it could even be a month without taking drugs. (20-year-old man)

You may have something that you do, but when you do not know what you are doing, the progress of something that you are doing. We get to know that this happens and to know the progress of the study we are participating in rather than just coming to have your blood tested then you go back. You go without getting to know anything. (21-year-old man)

Yes, it is good to inform us because we are able to answer some questions: "you are in the study but how is it helping?" If you ask me how it has helped me I can respond that the results were positive. It was important and it also helped us. (20-year-old man)

Why I clapped my hands is because I saw a great achievement because I saw a great achievement in fighting HIV through this research done upon or reducing or ending HIV. (16-year-old woman)

This dissemination was useful. In what way? Okay, let us assume it is like a journey. If you are on a journey and you see where you are heading. When you start seeing there you get the courage to continue walking. But when you are travelling and you do not know where you are heading and you do not see where you have reached, you get discouraged. So, this thing gave us strength. It gave us courage in that when I heard the results, it gave me more courage to adhere to the drugs and I saw that already we have reached somewhere. We are on track. And it gave me more strength and I got to know that, if this was possible, then other things are coming. But if they had not told us about it, we would be there, taking drugs, on the study, not knowing how far it has reached, where it is, you just see, they tell us that we are in the study and we do not know. So it was vital. (18-year-old man)

### ***A young person's experience as a trial participant***

A 16-year-old was questioned on his experience as a participant in a clinical trial. Asked about the enrolment process and information received, he experienced some difficulties: "the information was clear, but I did not understand some of the words, as they were a bit complicated and for grown-ups and I was given a month to think about getting enrolled". He shared that research staff members were available to answer any questions,

although he described the process as being “a bit over the top”. He felt very comfortable giving consent: “I did not feel under pressure. I felt like I could say no if I didn’t want to do it” though “there were too many words and it was hard to read”.

Confidentiality about his HIV status was not an issue, since he clearly said “No, never, I trust them 100%”, referring to the clinical and research staff. Overall, his experience as a trial participant was good:

“there was an appointment every month for three months, and then the appointments were three times monthly. It was fine because I understood why this was and that they had to check I was okay. For me, everything is really good, it’s going really well”. Although the department was not adolescent-friendly, “No I never got that feeling, it was a very adult environment”, he was motivated and keen to be involved: “I felt good about myself because, if it goes well, I’ll be helping people.”

## 5. SUMMARY

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- Community engagement plays an important role in the development of antiretroviral drugs to treat adults living with HIV, but such engagement has lagged behind for children living with HIV.
- Innovator manufacturers, researchers and other stakeholders involved in clinical trials play a critical role in how they engage with the paediatric community.
- There are legal and ethical frameworks within which the involvement of children and adolescents in clinical research must be conducted.
- Engaging the paediatric community presents many challenges and requires different approaches in different age groups and settings.
- Community advisory boards and children and adolescent advisory groups or networks can provide valuable input to the research process.
- A community engagement plan provides a structured approach for researchers to engage with the paediatric HIV community.
- Children and adolescents can contribute to protocol design and ethical issues and the development of age-appropriate treatment literacy materials and informed consent documents.
- Child- and adolescent-friendly environments are critical to their successful engagement.

## 6. KEY CONSIDERATIONS

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- **Engage community members early in designing the study.** This might mean working with existing national or regional community advisory boards or youth boards or setting up an appropriate advisory board for the study. For infants and other young children, involving parents and caregivers is critical; for older children and adolescents, this should mean engaging those from the relevant age groups.
- **Provide treatment and prevention literacy training.** To contribute in a meaningful way, trial participants and their advocates need to understand the science of HIV and the research interventions.
- **Produce informed consent forms in collaboration with the community.** Giving truly informed consent on behalf of a child or yourself requires that protocols be explained in plain language.

- **Produce age-appropriate, study-related materials in collaboration with the community.** Ensure that information is shared in a way that is acceptable to those who need it. This could mean using illustrations, photographs or videos.
- **Ensure a child- and adolescent-friendly clinic environment with continuity of care.** It is important that families have a research nurse or other relevant health worker that they can rely

on and trust to discuss any concerns or questions that they have over the duration of the trial.

- **Communicate results in a timely and accessible manner.** Participants and/or their caregivers need to receive results, explained in an accessible way, before they are widely disseminated.
- **Consider appropriate, non-coercive forms of compensation.** This could take the form of vouchers for clothes, telephone airtime etc.

## 7. USEFUL RESOURCES

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### Community advisory boards

- European Community Advisory Boards: <http://www.eatg.org/ecab>
- African Community Advisory Boards: <http://www.afrocab.info>
- United Kingdom Community Advisory Boards: <http://www.ukcab.net>

### Children and adolescent advisory groups and networks

- Children's HIV Association Youth Committee: <https://chiva.org.uk/our-work/youth-committee>
- Adolescent HIV Treatment Coalition: <http://www.iasociety.org/HIV-Programmes/Programmes/Adolescent-HIV-Treatment-Coalition>
- International Children Advisory Network: [www.icanresearch.org](http://www.icanresearch.org)
- Youth Trial Board: [www.youthtrialsboard.org](http://www.youthtrialsboard.org)
- Children and Young People Network: <https://www.ncb.org.uk/children-and-young-people-hiv-network>
- HIV/AIDS Network Coordination: <https://www.hanc.info/Pages/default.aspx>
- Adolescent Medicine Trials Network for HIV/AIDS Interventions: <https://atnweb.org/atnweb>
- Global Network of Young People Living with HIV: <http://www.yplusleadership.org>

### Other community engagement networks

- Patients like me: <https://www.patientslikeme.com>
- Patients included: <https://patientsincluded.org>

### Community engagement projects

- National Institute for Health Research: INVOLVE: <http://www.invo.org.uk/about-involve>
- Patient-focused drug development initiative of the United States Food and Drug Administration: <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>
- Patient-Centered Outcomes Research Institute: <https://www.pcori.org/engagement/influencing-culture-research>

### National Health Council

- <http://www.nationalhealthcouncil.org>
- <http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA-Patient-Engagement.pdf>

## 8. ACKNOWLEDGEMENTS

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*Special thanks to Sarah Bernays, Abi Carter and Djamel Hamadache for sharing case studies and young people's experiences as trial participants.*

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# MODULE 7: TARGET PRODUCT PROFILES



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# 1. INTRODUCTION

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Target product profiles are key strategic documents used to communicate summary requirements for new products that fulfil a priority need. The purpose of target product profiles is to guide industry during the drug development process and serve as a planning tool that can facilitate discussions with regulatory agencies and be updated as new information becomes available.

The importance of target product profiles resides in their role in identifying the critical attributes of a product before development begins, to ensure that the final product is adapted and responds to the needs of the end-users (Fig. 7.1). Target product profiles can help address issues early in the product development process and prevent late-stage development failures.

**Fig. 7.1.** A target product profile as a strategic planning tool



The global community, including WHO, UNAIDS, the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), the United States President’s Emergency Plan for AIDS Relief (PEPFAR) and the United Nations Children’s Fund (UNICEF), have a responsibility to define the requirements around paediatric medicines and have clear, transparent communication to industry on the products that are required to meet the unique needs of children.

Some organizations, such as WHO, UNICEF and the Drugs for Neglected Diseases initiative, have developed target product profiles for specific desired products such as medicines, diagnostics and vaccines that have served to guide industry in their own product development process.<sup>2</sup> The target product profile describes how the end-user will use the product and is based on such attributes as indications, targeted population, clinical efficacy, safety and tolerability, stability, route of administration, dosing frequency and cost, along with development timelines.

Table 7.1 outlines various properties of target product profiles and the optimum or ideal characteristics and minimum characteristics. Key properties include the ability to use the product across the age spectrum of children and adolescents, ease of administration, heat stability, palatability and swallowability and acceptable production costs.

<sup>2</sup> <https://www.dndi.org/diseases-projects/paediatric-hiv/paedhiv-target-product-profile/>; [https://www.unicef.org/supply/index\\_91816.html](https://www.unicef.org/supply/index_91816.html); [http://apps.who.int/iris/bitstream/handle/10665/135617/WHO\\_HTM\\_TB\\_2014.18\\_eng.pdf;jsessionid=6D9A30EDDBCC978978CF9928FAB921AE?sequence=1](http://apps.who.int/iris/bitstream/handle/10665/135617/WHO_HTM_TB_2014.18_eng.pdf;jsessionid=6D9A30EDDBCC978978CF9928FAB921AE?sequence=1)

**Table 7.1.** Properties of target product profiles

Property	Optimum or ideal target product profile	Minimum target product profile
Target population	One dosage form for ages 0–6 years >6 years: adult	Ages 0–2, 2–6 and >6 years
Safety, tolerability	Excipients selected from already used excipients in the new drug application or abbreviated new drug application and in accordance with the Inactive Ingredients Guide of the United States Food and Drug Administration Limited use of excipients, minimum toxicity and drug interactions	Excipients selected in accordance with regulatory guidelines on inactive ingredients
Drug attributes	Accommodates a wide range of doses and drug properties (such as solubility) Durability – high barrier to resistance	A set of 3–5 technologies that accommodate 80% or a majority of drug types and doses and fixed-dose combinations
Weight based dosing	Possible to administer the same dosage form across multiple weight bands 1 formulation for children age <6 years; 1 formulation for age >6 years: adult (or half a dose)	Possible to administer the same dosage form across multiple weight bands
Administration considerations	Easy to administer – minimum manipulation by the caregiver Minimal opportunity for child to reject medication Easy to apply with no irritation (non-oral) Fixed-dose combination, dispersible or small tablet size	Solid oral dosage forms preferred If bottle pack, then it should have a child-resistant cap
Administration device consideration	Product does not need device or appropriate device supplied if needed Intuitive – no use instructions necessary	Minimum instructions necessary to use device if needed
Taste and texture (oral dosage)	Palatable, child-friendly flavour, good mouth feel	Palatable, acceptable taste and mouth feel
Manufacturing	Accessible development and manufacturing capability in low- and middle-income countries Robust and able to deliver medicines of adequate quality at an affordable price Feasibility for technology transfer	Low technology – easy to manufacture in resource-limited settings
Cost	Acceptable cost to caregivers and funders	Low-cost (total cost of goods and landed costs) options
Preparation before administration	Should not require complex preparation by the end-user before administration Include recommendations for extemporaneous compounding in the summary of product characteristics	Easy to prepare and administer, such as with water, milk or food Suitable for low-literacy settings
Heat stable, longer shelf life	Suitable for all climatic zones, including International Council for Harmonisation Zone IVb (30°C and 75% relative humidity) and ≥24 month total shelf life See Annex 2, <i>Stability conditions for WHO Member States by region (5)</i> . No special transport and storage handling requirements	Suitable for the supply chain and end-user No special transport and storage handling requirements or Easy to transport and store

Property	Optimum or ideal target product profile	Minimum target product profile
Packaging	Compact, light weight, easy to open and administer, inexpensive, easy and low cost to transport, sustainable packaging	Same
Disability	For example, Braille labelling or “talking patient information”	Due consideration for end-user disabilities
Regulatory approval	Clear regulatory approval pathways considered up front both in source and end-user countries	Regulatory pathways in end-user countries considered up front
Patents	Full geographical access, open licences, no data exclusivity Feasible to have product monographs in official pharmacopoeia as soon as possible to produce generics	Equitable geographical access

Sources: Special Programme for Research and Training in Tropical Diseases (1), WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report (2), Target product profile – paediatric HIV (3), Lopez et al. (4) and Annex 2, Stability testing of active pharmaceutical ingredients and finished pharmaceutical products (5).

Additional considerations in the drug formulation development process include target candidate profiles and critical quality attributes. These include various drug characteristics that impact what type of formulations can be manufactured and include: solubility and permeability of the active pharmaceutical ingredients (Biopharmaceutical Classification System classification); bioavailability + food effects of the active pharmaceutical ingredients; polymorphism; particle size; stability of the active pharmaceutical ingredients; taste and potential to “mask” taste during manufacture; content of active pharmaceutical ingredients per dosage form; dose variability versus age; dose accuracy requirements; manufacturability; good technology fit to manufacture the active pharmaceutical ingredients into a finished pharmaceutical product; possibility to combine several active pharmaceutical ingredients into fixed-dose combinations (pharmacokinetics, pharmacodynamics and drug–drug interactions); active pharmaceutical ingredients amenable to age-appropriate simple dosage forms; and environmental pollution with active pharmaceutical ingredients during production (6).

Table 7.2 outlines the advantages and disadvantages of various formulations. Oral liquid preparations and oral solid preparations are the most common formulations used for antiretroviral (ARV) drugs. In general, oral solid preparations are preferred to liquids since they require less space and are easier to procure and store. Nevertheless, young children may not be able to swallow solid dosage forms. Depending on the active pharmaceutical ingredients, granules, pellets or chewable tablets may be difficult to taste mask, and children may refuse these products because of poor taste (7–13). Liquid formulations allow better accuracy in dosing but may be less palatable. Refrigeration may be required for some liquid formulations, which will increase the difficulty of storage, both during transport and for the end-user. For specialized products, more expensive production costs or equipment may be required.

**Table 7.2.** Advantages and disadvantages of various formulations

		Target age	Formulation	Active pharmaceutical ingredients	Procurement
<b>Oral liquid preparations</b>	Oral solution	Younger age group (unable to swallow)	In principle, easy to manufacture	Soluble, chemically stable	Difficult
	Oral suspension	Younger age group (unable to swallow)	Other particles can be suspended, like coated pellets...	Non-soluble, chemically stable. Better than solutions for active pharmaceutical ingredients that do not taste good	Difficult
	Syrups	Younger age group (unable to swallow)	In principle, easy to manufacture	Soluble, chemically stable	Difficult
	Emulsions	Younger age group (unable to swallow)	In principle, easy to manufacture	Non-soluble, chemically stable	Difficult
	Effervescent tablets	All ages	Difficult technology available	Soluble, non-chemically stable	Difficult
<b>Oral solid preparations</b>	Oral powder, granules and multiparticulate systems	Better suited for young age	Can contain beads or mini-tablets Technology readily available	Palatable and unpalatable active pharmaceutical ingredients	Easy
	Tablets	Older children (able to swallow)	In principle, easy to manufacture	Soluble, non-chemically stable	Easy
	Chewable tablets	Older children	Easy to manufacture. Technology readily available	Soluble, non-chemically stable, palatable active pharmaceutical ingredients	Easy
	Oro-dispersible tablets	All ages	In principle, easy to manufacture	Soluble, non-chemically stable, palatable active pharmaceutical ingredients	Easy
	Splitting tablets	Older children (able to swallow)	In principle, easy to manufacture	Soluble, non-chemically stable, palatable active pharmaceutical ingredients	Difficult (big size)
	Solids for reconstitution	Younger age group (unable to swallow)	In principle, easy to manufacture	Soluble and non-soluble, non-chemically stable	Easy
	Oral lyophilizates	All ages	Requires specific equipment	Palatable active pharmaceutical ingredients	Easy
	Oral films	Limitation with high doses	Limited quantity of ingredients	Palatable active pharmaceutical ingredients	Easy

Source: adapted from: Penazzato et al. (14). © 2015 Penazzato M et al.; licensee International AIDS Society.

Storage	Palatability	Acceptability	Administration	Special precautions
Difficult	Only for acceptable taste or easy-to-mask active pharmaceutical ingredients	Volumes >5 ml problematic for children <5 years	Solvents Measuring device Only low doses	Quality of water Measurement problems
Difficult	Suspensions allow better taste-masking than solutions	Volumes >5 ml problematic for children <5 years	Clear information on shaking before use Measuring device Only low doses	
Difficult	Only for acceptable taste or easy-to-mask active pharmaceutical ingredients	Volumes >5 ml problematic for children <5 years	Problems measuring Only low doses	Alcohol, sugar content
Difficult	Only for acceptable taste or easy-to-mask active pharmaceutical ingredients	Volumes >5 ml problematic for children <5 years	Clear information on shaking before use Measuring device Only low doses	
Difficult	Only for acceptable taste or easy to mask active pharmaceutical ingredients			Effervescent technology required
Easy	Taste can be an issue if administered directly or mixed	Can be administered directly in the mouth	Information on food, liquids restrictions Allows dosing flexibility Various strengths needed	Risk of aspiration or choking
Easy	Palatable and unpalatable active pharmaceutical ingredients	Well accepted	May be difficult to swallow depending on size	
Easy	Only for acceptable taste or easy to mask active pharmaceutical ingredients	Well accepted	Various strengths may be needed	
Easy	Taste needs to be acceptable or easy to mask	Well accepted	Various strengths may be needed	
Difficult (size)		Well accepted	Dosing instructions may be difficult	
Easy	Taste needs to be acceptable or easy to mask	Volumes >5 ml problematic for children <5 years	Problems measuring Only low doses	Quality of water
Easy				Lyophilization required
Easy	Taste needs to be acceptable or easy to mask			Equipment required

## 2. CHALLENGES

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The development of pharmaceutical products for children presents additional challenges. These products need to be adapted to a population that is growing, gaining weight and undergoing neurodevelopmental changes, has changing elimination pathways (see the module on pharmacokinetic modelling), relies on caregivers to administer medications and requires special characteristics such as palatability, swallowability and dosing flexibility. Lack of stable electricity supply, difficulty in supplying and storing medications and additional logistical issues in low- and middle-income countries contribute to the challenges in designing medicines for children, especially those more commonly used in low- and middle-income countries. These requirements and challenges should begin to be considered several years before the process of product development.

### 2.1 Target population: developing formulations across the weight and age spectrum

There is a critical need to develop appropriate formulations of medications suitable for use across the weight bands and age groups of children and adolescents (15,16). Pharmacokinetic and safety information as well as appropriate dosing information lags far behind for children, especially neonates (see the modules on pharmacokinetic modelling and trial design) (17).

Key questions include:

- How will the limited number of formulations and dosage strengths available provide the flexibility required for adjusting the dose for growing neonates, infants, other children and adolescents while drug metabolism and elimination are changing rapidly?

- Since the acceptability of various dosage forms varies widely with the age of the child (see the module on acceptability), how can it be ensured that caregivers will administer the correct dose and that the child will receive the appropriate dose?

Although information is limited on the safe and appropriate use of ARV drugs for neonates, even less information is available for low-birth-weight and preterm neonates (18). About 20% of infants born to women living with HIV have low birth weight or are preterm, and there is very little pharmacokinetic and safety information on ARV drugs for such neonates. Once a suitable drug formulation is licensed for use for full-term neonates, the drug is often used for low-birth-weight or preterm neonates, for whom there are no safety or pharmacokinetic data (see the module on pharmacokinetic modelling). Questions remain about how appropriate research should be supported for such vulnerable populations.

### 2.2 Adherence: developing formulations to which people will adhere

Adherence to chronic medications is challenging for most people, but especially adolescents (19). Factors that may influence adherence include the following: pill size, pill number, frequency of dosing, volume of solution, palatability, food requirement and side-effects attributed to medications. Although multiclass fixed-dose combination single-dosage formulations have greatly simplified treatment regimens, the actual size of the combination tablet may be an obstacle to adherence. Many people, including adults, have pill aversion and have difficulty swallowing pills.

There are limited data on the acceptability of different dosage forms for younger children and adolescents (see the module on acceptability), but

dispersible tablets, mini-tablets, scored tablets, granules and other flexible dosage forms have been promoted as preferred by many people.

The physicochemical properties of the active pharmaceutical ingredients determine the range of formulations that can be selected. For instance, not all active pharmaceutical ingredients can be formulated into all dosage forms. Pharmaceutical excipients may be needed to mask bitter taste and/or to increase solubility, which may also affect the decision on which formulation is the most appropriate. The quantity of active pharmaceutical ingredients is also an important factor, since it determines the size and volume of the finished dosage form. The condition to be treated determines the duration of treatment and the dosage requirements. For ARV drugs used for treating people living with HIV, the decision on the most appropriate dosage form needs to consider the importance of good adherence and need for lifelong treatment, and acceptability is therefore an important consideration.

Factors related to administration are key when deciding on the most appropriate dosage form. Drugs for children need to be formulated in a dosage form that is easy to administer and that minimizes potential dosing errors. If measuring administration devices are required, these have to be adapted and easy to use.

### **2.3 Costs: development and manufacturing costs for novel medications and formulations**

Some medications needed for older children and for drugs that have no palatability issues can be produced using conventional formulations such as tablets and capsules. However, alternative pharmaceutical formulations may be required to successfully deliver drugs to children in an acceptable, palatable and easy-to-use manner, but these are more expensive than conventional formulations. They may require specific equipment to manufacture, the addition of specific excipients or the use of measuring devices.

For example, oral liquids, tablets and capsules are easier to manufacture and relatively inexpensive. Other more specific formulations such as granules, mini-tablets or oral lyophilizates, and 3D printed tablets require dedicated manufacturing equipment and may be more expensive to produce. Even manufacturing dispersible tablets, which are produced using a well established and frequently used technology, is slightly more expensive than producing conventional tablets.

All these factors increase the manufacturing costs for products that offer less market return in principle (see the module on product commercialization). Further, the potentially smaller market for children means that the economies of scale needed to mitigate the additional costs are difficult to achieve.

### **2.4 Supply chain issues**

Medicines for children may need to be shipped to and stored in low- and middle-income countries, where climatic conditions can be hot and dry or hot and humid (5,20). They should be easily transported, not require refrigeration and be readily available to the people who need them. Medicines formulated to comply with regulatory jurisdictions such as the European Medicines Agency (EMA) or United States Food and Drug Administration (FDA) may not have been subjected to stability studies for climatic conditions in countries where they are most needed: hot and humid tropical zones (International Council on Harmonisation Zone IVa and Zone IVb stability conditions). This should be considered when formulating medicines for children.

Factors that are more relevant in low- and middle-income countries than in high-income countries can affect the procurement and storage of medicines, such as the need for cold-chain transport and storage. Transporting and storing conventional medicines for children formulated as oral liquids that may require refrigeration can also be challenging; instead, one could consider

developing a tablet for oral solution or suspension or a dispersible tablet. Bulky products, such as oral liquids, increase shipment costs since they take up more space, and the cold chain cannot always be maintained during transport and storage. The existence of multiple dosage forms for different age groups also affects procurement and makes quantifying needs more difficult.

## 2.5 Harmonizing regulatory requirements: regulatory issues

The lack of harmonization of regulatory requirements and pathways across regulators is a challenge for drug development. In some countries, such as India, the national regulator requires clinical trials in their populations even if a product has already been approved in Europe, Japan and the United States of America. This can affect access to medicines for children worldwide since Indian generic manufacturers, who supply medicines to most low- and middle-income countries, have greater difficulty obtaining local approval, which then affects price and development timelines. This not only affects India, since most countries require registration in the country of origin before the product is authorized for use elsewhere. Regulatory issues can also affect supply and logistics. Differences between regulatory requirements for labelling may lead to a lack of harmonization. Labels with text differing from that required by local authorities may be blocked in customs.

Some regulatory authorities ask for local clinical trials when they consider that existing ones may not demonstrate safety and efficacy specifically in their population. This was the case for India, and although the authorities agreed to grant a waiver for products for children WHO identified as a priority, this may still be problematic for drug development (21).

## 2.6 Product development challenges: formulation development issues

Formulation issues innovators encounter during drug development may not be communicated to the generic manufacturers. The factors that help define the dosage form can be grouped into four categories: (1) factors related to the physicochemical properties of the active pharmaceutical ingredients and excipients used in the formulations, (2) factors related to the condition, dosing and medical need, (3) factors related to transport and procurement and (4) cost factors.

The ideal formulations that consider these factors and better respond to these challenges are characterized in the target product profile but may be difficult to develop for cost or feasibility reasons. The innovator or generic pharmaceutical company may develop the target product profile as the starting-point of product development, but a supplier may also develop this. Lack of proper communication between companies and suppliers to better understand the needs, feasibility and costs, as well as the stages of the development process, may cause delays or even failure when developing formulations for children.



## 3. SOLUTIONS

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This section outlines several solutions and ideas for addressing these challenges. Further references and cross-references to other modules enable more in-depth analysis.

### 3.1 Target population: developing formulations across the age spectrum

To ensure that formulations for children and adolescents are developed so that these medications can be used across the age spectrum, additional planning and investigation should be undertaken.

- Plan early in the drug development process the potential need for smaller doses for infants and other young children. The ideal formulation should be heat stable, convenient to use, require simple instructions for use and minimal manipulation to prepare, allow for flexible dosing and not contain potentially toxic excipients such as ethanol or propylene glycol in high concentrations. Excipients should be selected based on the most recently approved excipient guidelines published by the FDA and EMA (22,23).
- Neonates are very difficult to study, especially low-birth-weight or preterm infants. A mechanism should be developed and encouraged so that this information becomes available as more infants receive empiric therapy, enhanced prophylaxis and early treatment for HIV infection. Pharmacokinetic modelling and simulations combined with data from older infants and other children can provide an initial potential dose for medications with good safety profiles that can be studied in low-birth-weight or preterm infants (see the module on pharmacokinetic modelling). The following are suggested as potential solutions for obtaining pharmacokinetic and safety data for ARV drugs for low-birth-weight or preterm infants:

1. regulatory requirement for safety, pharmacokinetic and dosing information for life-saving drugs;
  2. incentives for pharmaceutical companies and research networks to collaborate on the research needed to obtain this information;
  3. flexible dosage forms that can be safely administered to low-birth-weight or preterm infants; and
  4. pressure from organizations and guideline committees to obtain this information.
- Investigation of drug stability in breast-milk and other solutions and foods should be encouraged as part of formulation development (see the modules on pharmacokinetic modelling and pregnant and breastfeeding women).

### 3.2 Adherence: developing formulations to which people will adhere

In developing formulations for children, factors that relate to people's preferences should be considered.

- Pill size is important, and manufacturers need to consider acceptability when developing formulations. This is even more important when formulating fixed-dose combinations that combine several active ingredients.
- Before deciding on the formulation and the devices or instructions that it may require, research should be conducted on what are acceptable formulations in various age groups, both for the patients and caregivers (see the modules on acceptability and community engagement).

Innovative alternatives, such as long-acting formulations, could be considered and developed as alternatives to daily oral medications.

### 3.3 Costs: development and manufacturing costs of novel medications and formulations

The smaller market for drugs for children and the higher manufacturing costs of many formulations for children highlight the importance of limiting the number of formulations. It is important to avoid further reducing the market size, to correctly quantify the costs in advance and to increase opportunities for leverage incentives, such as funding for research and development and advance market commitments.

The following actions could help in identifying manufacturing costs and limiting the impact of unplanned additional expenditure.

- Each specific target product profile should set a target indicative price.
- Accurately quantifying and estimating the size of the market may help in planning the investment needed to develop formulations for children and ensure financial sustainability (see the module on product commercialization).
- If a supplier, buyer or other stakeholder develops the target product profile, sharing this information with the pharmaceutical companies is important to understand potential obstacles to product development that may increase cost. Input from manufacturers needs to be considered in the final target product profile. This can be done through an open consultation process to develop the target product profile, online publication of a draft for comment, industry and stakeholder consultations and, if needed, face-to-face meetings. The target product profile and all product information, including timelines, should be shared in advance with teams and organizations in charge of procurement, to accelerate product introduction. Procurement of drugs should be based on identifying the desired drugs and dosage forms, estimating the requirements for each drug product for a given period and determining what resources are available (24).
- Rapid product uptake helps in mitigating financial risk and recovering investment. For ARV drugs, this can be done through the Antiretroviral Procurement Working Group, which coordinates the demand of major purchasers such as the Global Fund, UNICEF and the Partnership for Supply Chain Management.
- Developing a business case for the product needed and characterized in the target product profile permits measurement of the financial risk. Information sharing between manufacturers and suppliers is also key in this step, since it enables investment to be adapted to the expected return.

### 3.4 Supply chain issues

The following actions could avoid supply-related problems for formulations for children.

- Stability studies must demonstrate the stability of the medicinal product throughout its intended shelf life under the climatic conditions prevalent in the target countries. For global supply, product stability should be systematically conducted in the most stringent conditions (climatic zone IVa, 30±2°C and 65±5% relative humidity or IVb, 30±2°C and 75±5% relative humidity) unless the characteristics of the active pharmaceutical ingredient typically do not support such conditions (5,20).
- Products should be labelled with actual storage temperatures. Stating that a product does not require special storage conditions is unacceptable for use in countries where these products are most needed.
- Heat-stable products that do not require cold chain or end-user refrigeration are ideal.
- Age-appropriate solid oral dosage forms or medicines in appropriate packaging greatly reduce weights and volumes and thereby shipping and storage costs.

### 3.5 Harmonizing regulatory requirements: regulatory issues that affect supply and logistics

- Efforts to ensure harmonized regulatory requirements should be increased. These efforts include the following.
- Efficient collaboration between regulatory agencies and manufacturers would greatly reduce the costs and delays involved in both drug development and supply and logistics.
- Improving the harmonization of regulatory requirements and pathways and regulatory interpretation of stability studies across regulators can positively affect drug development and supply and logistics.
- Specific country regulatory requirements need to be considered early in the drug development process to avoid additional hurdles and obstacles to importation and in-country approvals.
- WHO and other global health agencies should consider how to leverage influence to encourage the regulatory agencies to better harmonize their requirements.

### 3.6 Product development challenges

The following product development challenges should be considered.

- Regardless of whether a manufacturer or a supplier develops the target product profile, communication between the parties involved is important, to understand whether the proposed target product profile covers the requirements and whether it is feasible industrially. Precise knowledge of the costs associated with product development enables proper planning.
- Planning properly, establishing timelines and outlining product development benchmarks are also key. Face-to-face meetings, mainly when the process starts and the target product profile is established, are needed for this purpose. The target product profile can be adapted over time to incorporate new information or to reflect important changes in product development.



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## 4. CASE STUDIES

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This section provides examples of products developed by adopting some of the solutions outlined in this module.

### 4.1 Lopinavir/ritonavir 40 mg/10 mg pellets

Based on the results of IMPAACT (International Maternal Paediatric Adolescent AIDS Clinical Trials) P1060, WHO recommended lopinavir/ritonavir as the preferred treatment for infants newly diagnosed with HIV (25). Lopinavir/ritonavir 40 mg/10 mg pellets were launched in 2015 and have been rolled out in several countries in Africa, where acceptability studies are underway. Cipla developed these heat-stable pellets to avoid problems with the oral solution, which requires refrigeration and does not taste good, thus helping to increase uptake and implement WHO treatment guidelines. Cipla designed and developed the formulation following recommendations from organizations working in the field and in close communication with suppliers. The product characteristics were discussed in advance, which contributed to its acceptability (see the module on acceptability).

The Drugs for Neglected Diseases initiative is working with Cipla to develop a 4-in-1 fixed-dose combination product including abacavir + lamivudine + lopinavir/ritonavir that will be easier to administer to young children who cannot swallow pills. Taste masking has been a major challenge in developing the 4-in-1 product.

### 4.2 Raltegravir

Many national and international guidelines now prefer the integrase inhibitors as first-line agents in combination with other ARV drugs. Raltegravir is the first in this class the FDA has approved for use for infants and other children starting

from birth and weighing  $\geq 2$  kg. Raltegravir is available for use for children as oral granules for suspension, chewable tablets and film-coated tablets (18,26,27). The bioavailability of raltegravir varies by formulation, and the dosing recommendations for the solid tablets are different and not interchangeable from those for the chewable tablets or oral granules for suspension. Preparing the oral granules for suspension requires that caregivers receive proper training, since several steps are involved in reconstituting the granules and measuring the appropriate dose. A study is currently underway to assess the acceptability and feasibility of the raltegravir oral granules for suspension in low- and middle-income countries.

The use of raltegravir chewable tablets, although not yet approved for children younger than two years, has been recently investigated to determine whether these may be dispersed and administered to infants and other young children (27). In vitro evaluation was conducted demonstrating stability in various liquids, including breast-milk. Several studies using chewable tablets as dispersible tablets are planned among young children, since the chewable tablets are anticipated to be easier to use in low- and middle-income countries.

### 4.3 Excipients in neonatal formulations

Unanticipated toxicity has been observed when drugs licensed for older children are used for neonates and low-birth-weight or preterm infants. Experience with lopinavir/ritonavir has taught the need for extreme caution among these vulnerable children. FDA labelling includes a black-box warning that lopinavir/ritonavir should not be used in the immediate postnatal period for premature infants because an increased risk of toxicity has been reported.

This toxicity includes: transient symptomatic adrenal insufficiency (28); life-threatening bradyarrhythmia and cardiac dysfunction, including complete atrioventricular block, bradycardia and cardiomyopathy (29); and lactic acidosis, acute renal failure, central nervous system depression and respiratory depression. This may be caused by the drug itself and/or by the inactive ingredients in the oral solution. Transient asymptomatic elevation in 17-hydroxyprogesterone levels has been reported among term newborns treated at birth with lopinavir/ritonavir (28).

Extreme caution must be used when including excipients in formulations designed for neonates and other young children.

#### 4.4 Long-acting formulations

There is considerable interest in developing long-acting formulations for both prophylaxis and treatment of HIV and other infectious diseases. However, no information is currently available as to what types of long-acting formulations (injectable, patch or implants) are acceptable to different age groups or caregivers.

## 5. SUMMARY

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Target product profiles are key strategic documents used to communicate summary requirements for new products that fulfil the priority needs of children and adolescents. The purpose of the target product profiles is to guide industry during the drug development process and serve as a planning tool that can facilitate discussions between regulatory agencies, manufacturers, suppliers and global health organizations.

A target product profile should consider: target population, safety and tolerability, drug attributes, weight-based dosing, ease of administration, need for administration devices, taste and texture of oral dosage forms, manufacturing capability and technology, cost, drug preparation before administration, heat stability and shelf life, packaging, adaptations for end-user disabilities, regulatory approval and patent issues.

## 6. KEY CONSIDERATIONS

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- The target product profile should capture key attributes so that the end product meets the needs of the target population (including neonates and other young children), facilitates good adherence and avoids supply chain issues and regulatory challenges.
- Additional considerations, including physicochemical characteristics and bioavailability, are part of the target candidate profiles and critical quality attributes.
- Potential challenges in product development and manufacturing costs need to be addressed early, and strategies need to be in place to address these issues.
- Several formulations respond better to children's needs, such as dispersible tablets. However, all properties need to be properly assessed through the target product profile to ensure that the final formulation is appropriate.
- The decision on the type of formulation for children affects the development process.
- The formulation developed needs to be adapted to the age for which it is intended and to be usable across weight bands for this target population; small-size tablets, fixed-dose combinations and any other dosage forms developed need to maximize adherence; development costs that may negatively affect the final price need to be minimized when possible; the final product should be stable in the most stringent climatic conditions; specific country regulatory requirements need to be addressed; and strict and clear timelines and suggestions from suppliers in the development plan and the target product profile need to be incorporated.

## 7. USEFUL RESOURCES

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- Reflection paper: formulations of choice for the paediatric population. London: European Medicines Agency, Committee for Medicinal Products for Human Use; 2006 ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003782.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf), accessed 22 May 2018).
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# ACKNOWLEDGEMENTS

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# MODULE 8: PRODUCT COMMERCIALIZATION

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# 1. INTRODUCTION

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Successful product development and securing of regulatory approval does not guarantee that a product will be commercialized and available to the people who need it. The successful development of a new drug for children must also consider its commercial viability to ensure that it reaches the populations for which it is intended.

The impact of new products on the lives of children living with HIV relies on upstream activities related to drug development and regulatory approval to bring a new product to market, but downstream activities are just as important to ensure that the market for antiretroviral (ARV) drugs for children is sustainable and products are accessible in the settings in which they are most needed. Both supply and demand considerations must be considered beginning early in the process of drug development.

The majority of ARV drugs, including those used in infants and other children, are used in low- and middle-income countries, and cost is therefore a significant consideration. Generic manufacturing, which relies on economies of scale to achieve affordable pricing, has been critical for scaling up antiretroviral therapy

(ART) in low- and middle-income countries. However, the market for many drugs for children is much smaller than that for adults and as a result, developing a clear business case for industry to develop, manufacture and supply medicines for children at an affordable cost can be challenging. In the absence of consolidated global forecasts and demand planning, there may be no clear incentive or indication for manufacturers to initiate the development of formulations for children.

Careful procurement planning and clear communication between procurers, national programmes and suppliers can ease the launch of a new formulation for children. In the absence of this, suppliers can be hesitant to take on inventory risk and commit production resources to the new products until larger orders are received. Thus, lead times may become very long, risking loss of interest from programmes to adopt new products, shortages of ARV drugs or even stock-outs, which may result in treatment interruption.

## 2. CHALLENGES

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The market for ARV drugs for children is relatively small and fragmented across multiple formulations, and the uptake of new formulations in countries can be slow. These factors make the commercialization of new ARV drug formulations for children much more challenging than for ARV drug formulations for adults.

### 2.1 Small market size

The market for many medications for children is typically much smaller than that for adults; this is particularly true for ARV drugs, since children make up only 5% of the people receiving ART (1). A clear business case must be available to give incentives to industry to develop, manufacture and supply medicines for children.

A first step in developing a business case for developing a new ARV product for children is to anticipate the number of children who will benefit (the market size). There are many variables to consider when estimating the market size for a new ARV drug for children. First, ART coverage among children is growing – ambitious targets set by the Start Free, Stay Free, AIDS Free initiative are expected to continue to increase the number of children living with HIV receiving ART (2). At the same time, with the success of campaigns for preventing the vertical transmission of HIV, fewer infants are newly infected with HIV each year, leading to a relatively smaller population of infants and other young children requiring ART.

Another key dynamic is that the increasing success of ART for children means that infants and other young children are more likely to survive long term on treatment, which means more children and adolescents will need ART

in the higher weight bands before eventually transitioning into adult cohorts. In addition, since ART is a lifelong need and previously used regimens were often suboptimal, it is important to consider the sequencing of new drugs, since an increasing proportion of children receiving ART will eventually require second- or even third-line ART. Finally, the increasing use of more potent ARV drugs in first-line ART, which have a higher genetic barrier to resistance, could result, over time, in more durable first-line regimens and lower demand for products needed for future lines of ART for children.

### 2.2 Fragmentation across duplicative products

Despite the relatively small size of the market for ARV drugs for children, there are multiple dosage forms for the limited number of ARV drugs that have been approved for children. However, generic manufacturers rely on accumulating order volumes that achieve a minimum production batch size as a threshold to determine when production should be initiated.

The minimum batch sizes may be on the order of thousands or even tens of thousands of packs, but when procurement orders are divided across small volumes of duplicative drug dosage forms, consistently reaching the threshold necessary to maintain a reliable supply of products may be challenging. Too many ARV drug choices produce a limited demand for each and decrease the likelihood of sustained supplies and adequate access to care for children.

## 2.3 Slow uptake at the country level

Even after the product is developed, delays in introducing new products for children may occur for several reasons, including but not limited to:

- lack of awareness from global buyers and/or in-country decision-makers of the availability and benefits of the new drug;
- limited visibility into development and filing timelines may discourage programmes from incorporating new products into national policies and programme plans;
- uncertainty about how a new product aligns with or replaces other products for children that are already being procured and are widely used;
- delays in commercialization by suppliers because the product for children has low priority and/or low volume for them relative to other new products in their portfolio; and
- limited production capacity and/or uncertainty about supply security that may diminish demand-side enthusiasm for the new product.

# 3. SOLUTIONS

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Partner coordination, rationalization of paediatric formularies and proactive scaling up of production capacity are strategies to stabilize the market for ARV drugs for children and to facilitate the entry of newer products.

## 3.1 Coordination

Although early efforts such as the Unitaid–Clinton Health Access Initiative Paediatric HIV/AIDS Treatment Project (3) supported the scaling up of ART for children, ongoing efforts to improve supply security through a process of coordinating procurement and strategically managing demand have reduced the risks of supply disruption.

The Antiretroviral Procurement Working Group (formerly known as the Paediatric ARV Procurement Working Group) brings together major buyers of ARV drugs for children, including donors, funders, country programmes and implementing partners. It was established in 2011 to support coordination at the global level to improve the supply security of ARV products

for children by sharing market intelligence and coordinating the procurement of ARV drugs for children and other low-volume ARV products (4).

The Antiretroviral Procurement Working Group serves as an excellent resource for both programmes and manufacturers for clear, consistent and reliable market intelligence about new and existing products. This allows the global community to better anticipate and mitigate potential supply issues. In addition, placing orders according to timelines recommended by the Antiretroviral Procurement Working Group can minimize lead times when low-volume individual orders may not meet a supplier's minimum batch size.

In collaboration with Unitaid and other key partners, WHO has established a forecasting working group with the objective of consolidating criteria and different models used by various organizations<sup>2</sup> to estimate future needs. The work of this group, which is expected to deliver prototype forecasting tools by the end of 2018, will also help better quantify the size of the market.

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<sup>2</sup> The group consists of Avenir Health, the Clinton Health Access Initiative (CHAI); the Global Fund to Fight AIDS, TB and Malaria; the Medicines Patent Pool (MPP); the Partnership for Supply Chain Management (PFSCM); PEPFAR; UNICEF; USAID and its Global Health Supply Chain-Procurement and Supply Management (GHSC-PSM) project, and several others.

### 3.2 Rationalization of formularies for children

The WHO essential medicines group developed optimizing formularies for essential medicines as an approach to facilitate the rational usage of drugs and promote equitable access to critical drugs. Optimizing formularies is especially critical for relatively fragmented markets such as that for ARV drugs for children, since the inherent small volumes make drug companies less likely to invest, making the market vulnerable and highly cost sensitive.

The optimal and limited-use paediatric ARV formularies, established in 2011, took this approach to develop a focused list of products for children that are needed to deliver ART across all age groups and weight bands of children using a set of criteria to identify dosage forms that most closely align to the

target product profile and simplify supply chain management (Table 8.1).

The optimal paediatric ARV formulary includes the minimum number of dosage forms for children necessary to enable all WHO-recommended preferred first- and second-line regimens and neonatal prophylaxis for preventing vertical transmission of HIV to be administered across all appropriate weight bands for children. In addition, the limited-use list provides for dosage forms of drugs that may be needed for special circumstances, such as third-line ART, neonatal treatment and drugs that are being phased in or out of use.

Since new ARV products enter the market and guideline recommendations are updated, the optimal paediatric ARV formulary and limited-use lists are revised to ensure that they remain current, with updates released in 2013 (6), 2015 (7) and 2016 (8); an updated version is

**Table 8.1.** Criteria for selection of optimal ARV drug dosage forms for children

Criterion	Definition
Meets WHO requirements	Included in the latest WHO guidelines for treating children
Enables the widest range of dosing options	Enables flexible dosing across multiple weight bands and ages
Approved by the stringent regulatory authority or WHO prequalification	Availability of at least one product approved by the stringent regulatory authority
User-friendly	Easy for health-care workers to prescribe Easy for caregivers to administer Supports adherence
Optimizes supply chain management	Easy to transport Easy to store Easy to distribute
Available for low- and middle-income countries	Product is licensed or registered for use in low- and middle-income countries Reliable supply of product
Comparative cost	Cost should not be a deciding factor, but the comparative cost of formulations of the same combination of drugs should be considered

Source: adapted from: Penazzato et al. (5). © 2015 Penazzato M et al; licensee International AIDS Society

anticipated in mid-2018. Programmes have been encouraged to refer to this list to guide the selection and procurement of ARV products for children.

A focused list of products increases the volume orders of particular products, thus providing incentives for production on a regular basis, which stabilizes supply. This also makes the overall market more attractive to manufacturers and encourages continued investment in developing new products. Procurement and implementation are also easier at the programme level if a limited number of formulations are available for use across weight and age bands.

### 3.3 Scale-up planning

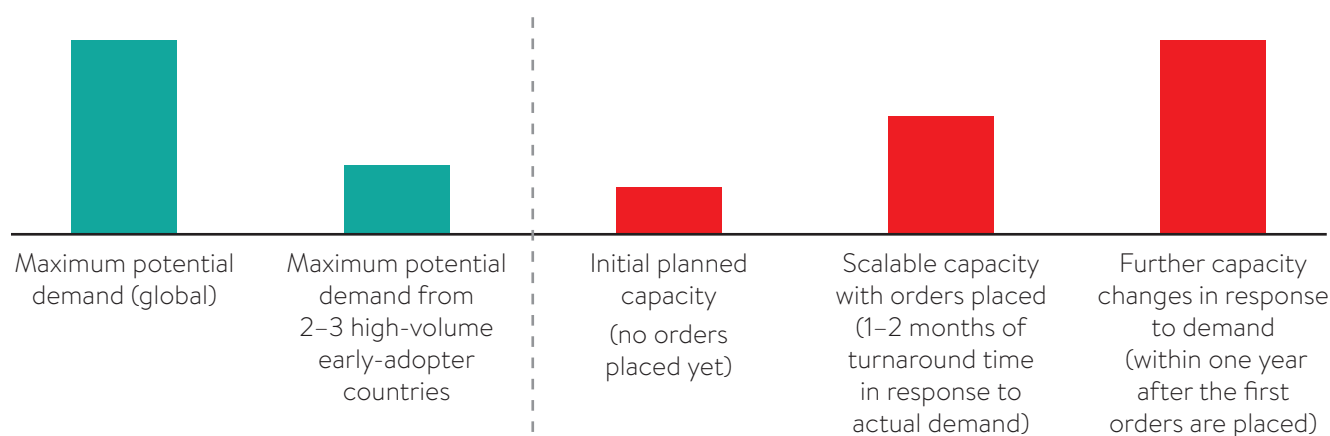
From the early stages of development of ARV drugs for children, it is critical to consider the settings in which the finished drug product will be used. This includes supply chain considerations for the finished dosage form to ensure successful implementation in low- and middle-income countries, where most children living with HIV receive treatment, in addition to the characteristics of the finished dosage form (see the module on target product profiles).

Some of the dynamics described earlier around preventing vertical transmission and improving formulations are compounded by limited reliable data available from countries about true breakdowns of children receiving ART by age, weight and line of ART. All this, with different appetites for change or early adoption across country programmes, makes creating accurate global demand forecasts several years out difficult if not impossible.

However, based on the intended use (such as children younger than three years), the relative scale and ranges of possible demand can be determined using modelled epidemiological data from UNAIDS (9). One can get a sense of the maximum potential market size (assuming every eligible child is receiving treatment with the product in question) and work backwards from that to real-world scenarios of demand over time.

Whereas suppliers generally initiate actual production only on receiving confirmed orders, with a sense of the maximum potential market size, suppliers can and should have proactive plans and commitments in place to increase production capacity concomitant with various scenarios for scaling up demand (Fig. 8.1).

**Fig. 8.1.** Illustrative proactive (pre-launch) production scale-up planning



Such a proactive plan can help suppliers in balancing capital investment risk, inventory risk and production line opportunity costs while minimizing delays in access to drugs should a scenario with rapidly scaled up demand materialize. Otherwise, suppliers will simply hedge their risk with lower capacity and only increase it reactively, leading to long delays in product availability. This is especially important when additional regulatory approval may be needed to be able to increase commercial

production capacity (such as process variation and additional manufacturing sites) that may become bottlenecks in product availability if pursued in a reactive manner.

For such an exercise to be useful, suppliers have to be forthcoming about what relative ranges are relevant for their production planning based on the product in question (such as material differences in demand being 10 000 versus 100 000 packs per month or 10 000 versus 15 000 packs per month).

## 4. CASE STUDY

### **Abacavir + lamivudine 120 mg/60 mg**

Since 2013, the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (10) have recommended using abacavir (ABC) and lamivudine (3TC) as a preferred nucleoside reverse-transcriptase inhibitor backbone for children three years and older and as one of two preferred options for children younger than three years. At the time it was included in the guidelines, a fixed-dose

combination tablet of ABC + 3TC 60 mg/30 mg was available to dose across all weight bands. However, the pill burden for older children was of concern, since they would require up to six tablets of ABC + 3TC 60 mg/30 mg daily, with additional tablets needed to complete a three-drug regimen. In response to the need for a stronger tablet for children, generic manufacturers developed an ABC + 3TC 120 mg/60 mg scored tablet that could still be used across all weight bands but had a far lower pill burden (Table 8.2).

**Table 8.2.** Dosing of ABC + 3TC 60 mg/30 mg for weight bands for children

Weight band (kg)	Daily dosing of ABC + 3TC 60 mg/30 mg	Daily dosing of ABC + 3TC 120 mg/60 mg scored
3–5.9	2	1
6–9.9	3	1.5
10–13.9	4	2
14–19.9	5	2.5
20–24.9	6	3
25–34.9	1 adult tablet (600 mg/300 mg)	1 adult tablet (600 mg/300 mg)

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and prevention HIV infection. Recommendations for a public health approach – second edition (10).



The United States Food and Drug Administration tentatively approved the new ABC + 3TC 120 mg/60 mg tablet in October 2014 (11) and subsequently added it to the 2015 optimal paediatric ARV formulary (7). However, despite the increased uptake of ABC + 3TC-containing regimens for children, the first order for ABC + 3TC 120 mg/60 mg was not placed until October 2016, two years after approval. Several factors contributed to the delay between stringent regulatory approval and commercialization, including issues related to national registration and country concerns about supply security, since the product was only initially available from a single supplier.

In addition, the availability of the product may not have been communicated to programmes in time to be included in procurement plans. Although

programmes expressed interest, it was not until a country with a high burden of HIV infection placed a large order for the product that ABC + 3TC 120 mg/60 mg was commercialized. Since then, uptake has been rapid, with the forecast for ABC + 3TC 120 mg/60 mg now outstripping that for 60 mg/30 mg (12).

The example of ABC + 3TC 120 mg/60 mg demonstrates that, even when a more optimal dosage form that is in high demand is developed and receives approval by a stringent regulatory authority, additional steps are needed to ensure successful commercialization and uptake. This includes consideration for national drug registration, ensuring communication of availability of the product to buyers and inclusion in procurement plans.

## SUMMARY

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Significant strides have been made in consolidating and stabilizing the ARV drug market for children through such efforts as those of the ARV Procurement Working Group. Careful procurement planning and clear communication between procurers, national programmes and suppliers can ease the launch of a new formulation for children.

A high level of coordination is already occurring between various stakeholders across the upstream and downstream components of new product introduction through various initiatives such as the Unitaid-funded Paediatric HIV Treatment Initiative and the Global Accelerator for Paediatric Formulations (13).

## KEY CONSIDERATIONS

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- National programmes should rationalize their formularies to the most optimal formulations as much as possible while proactively transitioning children to WHO-recommended and age-appropriate regimens and formulations.
- Global partners should collaborate to ensure that clear and consistent messages about new products are being sent to national programmes and suppliers.
- Suppliers should have a proactive and transparent production capacity scale-up plan before filing their dossier to be able to react quickly to demand.

# ACKNOWLEDGEMENTS

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Generous support from Unitaid enables the work of the Clinton Health Access Initiative on optimal ARV drugs for children.

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A close-up photograph of a woman with dark skin and a black headscarf with white floral patterns. She is smiling gently and holding a young child with dark skin and curly hair. The child is looking directly at the camera with a neutral expression. The background is softly blurred, showing what appears to be an outdoor setting with some foliage.

# MODULE 9: REGULATORY FILING

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# 1. INTRODUCTION

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Although the end result is almost always similar, the approaches for new antiretroviral (ARV) drug approvals and the development of ARV drugs for children differ somewhat between the European Union (EU) and the United States of America. This module describes the approval processes in the EU and United States and regulatory steps toward approving drugs for children on a more expedited timeline. It also describes procedures specific to the product quality reviews conducted by WHO.

In the United States, new drugs, including ARV drugs, are approved after a new drug application dossier is submitted and the United States Food and Drug Administration (FDA) reviews it. The time frame for reviewing new drug applications is established in United States law and allows for either “standard” or “priority” review. Each new drug application must contain sufficient information to demonstrate that the drug is safe and effective when used as indicated and to describe the processes for manufacture, and each must contain either a paediatric assessment or a request for deferring or waiving the requirement for studies involving children.

The paediatric assessment summarizes the basis for evaluating the drug among children of all ages and any clinical data on children submitted in the new drug application; a waiver or deferral of studies involving children may be requested if these studies have not been completed at the time the new drug application is filed. Of note, the United States laws and regulations relevant to developing drugs for children refer to age groups and not weight bands.

In Europe, new ARV drugs placed on the market have to be authorized according to centralized marketing authorization procedure, for which manufacturers submit the dossier with the evaluation of quality, safety and efficacy of the drug to the European Medicines Agency

(EMA). The centralized procedure foresees a single marketing authorization application (marketing authorization application). The EMA is responsible for scientific review through its Committee for Medicinal Products for Human Use. If the Committee comes to a positive opinion following the assessment, the proposal to grant a marketing authorization for the concerned medicines is sent to the European Commission, which grants the marketing authorization for the EU as a whole.

Afterwards, the launch for individual European national markets must be applied to the corresponding national authorities. A central marketing authorization is automatically valid in all 28 EU countries plus the three EEA-EFTA countries (Iceland, Liechtenstein and Norway). Applications for marketing authorization of new ARV drugs must include the results of studies carried out as part of a paediatric investigation plan agreed by the EMA Paediatric Committee or information on a paediatric investigation plan deferral or waiver. ARV drugs authorized across the EU based on the results of studies complying with a completed paediatric investigation plan are eligible for an extension of their supplementary protection certificate by six months.

Through specific laws, both the FDA and the EMA require pharmaceutical innovators to study drugs among children whenever a new drug is likely to be needed for children. As part of this requirement, innovators are required to submit a paediatric study plan to the FDA (1) and a paediatric investigation plan to the EMA (2–4). The EMA requires submission of the paediatric investigation plan at the end of Phase I drug development (after initial dose finding and safety); the FDA mandates submission of the paediatric study plan at the end of Phase II drug development (after preliminary evidence of efficacy).

Both paediatric investigation plans and paediatric study plans must provide a summary of the nonclinical and clinical evidence available to support the study of the drug among children, an outline of the proposed studies among children, including the expected population (such as the ages and weights to be studied and key enrolment criteria), a rationale for any request to waive studies in specific subgroups and a timeline for completing the proposed studies.

Despite submitting these plans for developing drugs for children, studies involving children may take up to 8–10 years to complete after the drug has been approved for adults. These regulatory processes apply to all drugs, and extended lag times are not unique to ARV drugs but can be identified in many programmes for developing drugs for children. Expediting the regulatory processes could improve access to products for children for other diseases of public health importance such as tuberculosis (TB), malaria and viral hepatitis.

To address the lag in approvals of drugs for children, collaboration between the FDA and EMA, with the participation of Health Canada, Japan's Pharmaceuticals and Medical Devices Agency and Australia's Department of Health, was established to help support global development plans for medicinal products for children and to exchange information on applications and topics related to development. These regular meetings by phone or videoconference among regulators in clusters or areas of cooperation focus on special topics, such as developing medicinal products for children (5).

These meetings can result in issuing a non-binding common commentary to inform the sponsor of the discussion of their product at the meeting. The cluster teleconferences can be used to align the requirements in paediatric investigation plans and paediatric study plans and in overall paediatric development plans. However, they do not guarantee, even if an early dialogue between regulators is established, that the assessment of the same set of data by the

EMA and FDA will lead to the same conclusions or that it will lead to similar labelling of the drug.

Regulatory approval of novel formulations of approved drugs (without a reference product), especially fixed-dose combination products specifically intended for use in low- and middle-income countries, was previously outside the scope of stringent regulatory authorities. To address this gap, the WHO Prequalification Programme was formed in 2001 to assess the quality of products and inspect manufacturing plants for HIV drugs in low- and middle-income countries. The WHO Prequalification Programme has subsequently expanded their assessments; they not only assess a range of finished pharmaceutical products in several therapeutic areas but also assess active pharmaceutical ingredients and quality control laboratories. It also provides technical assistance and conducts extensive training activities.

In 2006, as part of the United States President's Emergency Plan for AIDS Relief (PEPFAR), the FDA described a regulatory path to receive tentative approval specifically for ARV products intended for use in low- and middle-income countries while maintaining patent protection within the United States (6). This process followed the review model used by the FDA Office of Generic Drugs but added in components of the 505(b)2 new drug application process of the FDA Office of New Drugs for novel products that relies on information owned by other sponsors, previously reviewed by the FDA or in the public domain (Table 9.1).

New products for which there is a marketed reference product use the standard generic drug abbreviated new drug application filing and review process (such as a generic Truvada, emtricitabine + tenofovir disoproxil fumarate tablet) through the FDA Office of Generic Drugs. New products for which no reference listed product exists (such as lamivudine + tenofovir disoproxil fumarate) are submitted to the FDA Division of Antiviral Products of the Office of New Drugs for review. Should there be questions regarding a product's dossier or

the appropriate filing approach, the Division of Antiviral Products offers pre-submission advice through an active programme available before filing an investigational new drug application (the pre-investigational new drug programme) (7,8).

The PEPFAR review team has committed to completing their reviews on a priority review schedule for the first three manufacturers for each PEPFAR product, but successful review depends on the FDA receiving a complete application at the time of submission and the manufacturers passing the required inspections. Products approved or tentatively approved by the FDA are co-listed on the WHO Prequalification Programme product list but may not be eligible for the Collaborative Registration Procedure.

The EMA, in collaboration with WHO, can give an opinion to manufacturers for products intended for non-EU markets through the mechanism of EUM4All (Article 58 of Regulation (EC) No. 726/2004 procedure) (9). The European Commission established the Article 58 mechanism in 2004 to facilitate registration by low- and middle-income countries of medicines to prevent or treat diseases of major public health interest, including neglected infectious diseases, such as HIV infection. This procedure was intended to assist regulators in low- and middle-income countries by providing a scientific assessment of a dossier for a medicinal product for use outside the EU. This assessment is intended to provide national regulatory authorities in low- and middle-income countries

with analysis and information to support their own registration decisions rather than making this decision for them.

Under Article 58, the Committee for Medicinal Products for Human Use conducts a regulatory review that is identical in all aspects to standard EMA regulatory review and requires submitting a full regulatory dossier. Article 58 enables participation by WHO experts and the national regulatory authorities of target countries in the review process. This includes advice on the risk and benefit in low- and middle-income countries and on whether the drug is needed and appropriate for these settings. Importantly, the Article 58 process does not culminate in regulatory approval but in the scientific opinion by the Committee for Medicinal Products for Human Use on the product. Article 58 has the strength to offer a superior standard to most regulatory alternatives in low- and middle-income countries since it not only provides a regulatory assessment at the same level afforded to any product for use in the EU but also incorporates an informed assessment of risk and benefit from experts in endemic countries.

Nevertheless, alternative pathways and incentives have been developed, and some core barriers remain to Article 58 realizing its full potential. Manufacturers are unclear about or unconvinced of its benefits and are reluctant to use it because successful precedents are lacking. The fees are considered burdensome or prohibitive (especially the annual maintenance fees).

**Table 9.1.** Recognized FDA regulatory pathways

FDA pathway	Filings acceptable for using the pathway	Typical sponsor of the filing
New drug application	New molecular entities	Innovators
New drug application 505(b)2	New formulations, fixed-dose combinations and new product strengths under PEPFAR	Innovators and generics
Abbreviated new drug application	Generic drugs	Generics
Pre-investigational new drug or investigational new drug	First in human studies, new clinical or modelling data to support additional dosage forms or strengths	Innovators, generics, third party for ease of reference

Many national regulatory authorities are unaware of Article 58 or consider it a lower-grade review, since it does not confer EU marketing approval. Poor coordination between the EMA and WHO, both in terms of general logistics and the management of variation and pharmacovigilance, limits the potential impact of their collaboration for both national regulatory authorities and manufacturers.

In addition, since the FDA PEPFAR route typically confers some procurement eligibility using donor funds, manufacturers more commonly use the FDA route. Products that have been positively assessed through the Article 58 procedure are co-listed on the WHO Prequalification Programme product list. Manufacturers can also request participation in the Collaborative Registration Procedure based on the EMA or WHO Prequalification Programme reviews.

Only 10 product applications have completed the Article 58 process since 2004, all from multinational pharmaceutical companies. Three of these were label extensions or new formulations of existing HIV drugs: Aluvia® (lopinavir/ritonavir) has a public assessment report, whereas Lamivudine ViiV® (lamivudine) and Lamivudine/Zidovudine ViiV® (lamivudine + zidovudine) were withdrawn (10).

WHO has implemented a Collaborative Registration Procedure: a collaborative procedure between the WHO Prequalification of Medicines Programme and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products (11). This addresses the issues of significant delays in national registration in low- and middle-income countries. Finished pharmaceutical products reviewed by the WHO Prequalification Programme team have been evaluated and inspected according to international standards. However, the national regulatory authorities of the countries for which market entry is sought must still approve them for use. Repeating assessment and inspection of these finished pharmaceutical products not only

consumes scarce regulatory resources but also extends the time needed to make them available.

WHO has therefore designed a collaborative procedure that enables national regulatory authorities to use work already carried out by WHO and to strengthen their own regulatory oversight processes, in accordance with international best practices. Of greatest interest to manufacturers is that application of the procedure enables faster registration. The Collaborative Registration Procedure is open to national regulatory authorities in all WHO Member States and holders of prequalified finished pharmaceutical products, on a voluntary basis, and its principles are a model for other regulatory collaborative initiatives.

In addition to the Collaborative Registration Procedure, WHO has implemented a collaborative registration pilot for medicines approved by a stringent regulatory authority. This pilot was initiated in 2012 as an extension of the WHO Collaborative Registration Procedure and aims at facilitating the registration of essential medicines approved by a stringent regulatory authority in countries that may have limited regulatory resources. Since November 2014, the EMA has participated in developing and implementing the pilot (five products related to HIV, TB and malaria), resulting in more rapid approval by national regulatory authorities in participating countries.

In this context, EMA's scientific assessment reports are shared with regulators in other countries by companies holding EU marketing authorizations that want to market their products in these countries. Unfortunately, the FDA does not yet have a corresponding review-sharing mechanism and does not participate in the Collaborative Registration Procedure, although efforts are underway to determine whether there may be a viable pathway for data sharing. WHO Prequalification is not required to use the stringent regulatory authority Collaborative Registration Procedure route for filing.



For in-country registration in low- and middle-income countries through national regulatory authorities, each manufacturer must submit a dossier and any associated fees for each country in which they would like to register for marketing approval. Although some of the pathways (primarily the WHO Collaborative Registration Procedure) are designed to allow manufacturers to obtain more rapid registration in multiple countries at the same time, not all countries participate in these processes.

Applying for a registration waiver for new products of public health interest is therefore common practice. Nevertheless, applying for and obtaining a waiver is a short-term solution to access to medicines and, ultimately, manufacturers must obtain registration in all countries in which they intend to market. More information on the waiver process is available (12). It is beyond the scope of this document to describe the regulatory procedures of all national regulatory authorities approving ARV drugs.

## 2. CHALLENGES

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The regulatory reasons drug developers most often cite for delay in approving initial (innovator) drugs for children include:

- lack of alignment of requirements in paediatric investigation plans and paediatric study plans;
- different processes and processes perceived to be cumbersome to revise paediatric investigation plans and paediatric study plans;
- difficulties in designing and conducting clinical trials across the age range of children (see the module on trial design);
- difficulties in developing suitable age-appropriate formulations for younger children (see the module on acceptability); and
- the desire of drug developers for additional safety data in adults before initiating trials involving children.

After the first few ARV drug approvals in the 1990s, clinical trials involving children have begun well after the clinical trials involving adults and have progressed stepwise from older to younger children, a process that is often unduly conservative and time-consuming.

Following initial approval of an ARV drug for children, the reasons most often expressed for

a lag in developing and approving generic ARV products, including fixed-dose combinations, for use in low- and middle-income countries include:

- uncertainty regarding what specific products are most needed or desired in the market (and for fixed-dose combinations in what ratios);
- uncertainty about converting age- or weight-based dosing approved in markets with stringent regulatory authorities to the simplified public health approach of weight-band dosing endorsed by WHO (13);
- unwillingness to pay recurring regulatory fees; and
- concern regarding the small size and relative instability of the commercial market for drugs for children.

For both innovators and generic suppliers, changes in the knowledge base leading to changes in product labelling post-marketing can slow the development of ARV drugs for children since the new information must be incorporated into studies involving children or labelling of the drugs, often as these studies are in progress. In addition, the FDA has noted significant deficiencies in many dossiers submitted to the PEPFAR review programme.

## 3. SOLUTIONS

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Regulators and other stakeholders have already begun working together to identify solutions to the long timeline typical of most programmes for developing drugs for children. The FDA, EMA and other stringent regulatory authorities have undertaken a series of regular conference calls to discuss and reduce differences in the requirements for studies involving children. The stated goal of these calls is to bring programmes for developing drugs for children reviewed by stringent regulatory authorities into alignment so that a company can focus on a unified global programme of drugs for children.

The following considerations are expected to expedite the development of drugs for children, and many have been accepted in principle by stringent regulatory authorities (14,15).

### 3.1 Giving priority to products for children

In both the United States and the EU, the obligation to develop a product that is expected to be safe and effective for children can only be waived if there is lack of significant benefit over an existing (authorized) product or if good-faith attempts at developing a formulation have failed and not because a potentially better product exists in the developmental pipeline. However, the development of drugs for children may be deferred for a period of years and can be waived at a later time if public health needs change. If the stringent regulatory authorities adopted recommendations of an external priority-setting process that addressed the public health needs of children, it could help shorten the timelines of development for priority ARV drugs, especially fixed-dose combinations, and minimize resources spent on products that do not meet a public health need.

The Paediatric Antiretroviral Drug Optimization group convened by WHO provides this kind

of extensive product review and prioritization. The priority ARV drug recommendations of the Paediatric Antiretroviral Drug Optimization group might need to be provided earlier in drug development if the goal is to influence EMA Paediatric Committee and FDA decisions, since the agencies review products at a very early stage in development. In addition, further staging to identify which of the priority ARV drugs are the most critical might allow better coordination with generic suppliers.

### 3.2 Earlier development of formulations

As soon as Phase II trials involving adults demonstrate evidence of effectiveness and a decision is made to proceed to Phase III trials, development of an age-appropriate formulation should be initiated. Early discussions about the paediatric investigation plan and paediatric study plan between sponsors, regulators and other stakeholders should include discussion of formulation needs in low- and middle-income countries.

### 3.3 Simplifying paediatric investigation plans and paediatric study plans

Both the EMA and FDA agree that paediatric investigation plans and paediatric study plans written early in the product life cycle should be concise and contain less of the technical detail the agencies already know. When applicable, toxicology data and safety and efficacy data for adults that are already filed could be incorporated via references or briefly summarized. However, when the paediatric investigation plan is submitted early in development, few clinical data may be available and the description of nonclinical data may become more important. Descriptions of proposed clinical trials could be

very limited, with caveats that the final study design and the doses to be studied will be agreed on when adequate information is available.

The applicant can always request to modify the paediatric investigation plan and paediatric study plan and the studies included. Using an agreed protocol template (a master protocol) could assure all parties that clinical trials would meet regulatory requirements and public health needs. Keeping the paediatric investigation plan and paediatric study plan concise would allow more flexibility for innovators to incorporate new information, as needed, since previously included details would not become outdated as a programme progressed.

### 3.4 Streamlining clinical trials involving children

Stringent regulatory authorities are moving toward alignment in areas that will improve the efficiency of clinical trials involving children (see the module on trial design).

#### **Simultaneously developing products for adults and adolescents**

The inclusion of adolescents in trials involving adults is considered acceptable, since adolescents generally use the formulation and dose for adults and no major differences in safety and efficacy are generally expected between adults and adolescents. Separate but concurrently conducted studies involving adults and adolescents may be more practical and still provide the necessary data to include adolescents in the initial marketing authorization for adults.

However, not all national regulatory authorities agree with this approach, and the approval of some ARV drugs for adolescents has lagged behind approval for adults in Africa even as concurrent approvals by stringent regulatory authorities have become more common. For example, the FDA approved dolutegravir (Tivicay<sup>®</sup>, ViiV Healthcare) for both adults and adolescents (weighing >40 kg) in 2013 but has not yet approved it in some sub-

Saharan African countries for children younger than 18 years.

#### **Simultaneously enrolling all age and weight cohorts of children instead of sequentially enrolling older then younger children**

Regulatory agencies have agreed, in principle, with the proposal to enrol age groups of children simultaneously, but the rate-limiting step is usually formulation development for younger children who cannot swallow tablets. Acceptance of this proposal assumes there are no safety concerns that might affect the willingness to administer the drug to infants and other children.

#### **Using standardized weight bands for dosing in clinical trials involving children corresponding to WHO recommendations for ARV drug dosing for children**

Stringent regulatory authorities have agreed in principle to this proposal if there are adequate data to support dosing in all age and weight groups. Using standardized weight bands in the original trials involving children precludes the need for retrofitting pharmacokinetic data collected in other cohorts or for additional studies to validate WHO dose recommendations that might differ from approved labelling. In 2015, the EMA convened a meeting to discuss ways to expedite the development of fixed-dose combination drugs for children and endorsed the use of WHO weight bands as part of the solution. In many cases, national regulatory authorities in low- and middle-income countries have embraced this type of dosing, since it is easier for health-care providers to implement in busy clinics than individualized dosing.

#### **Maximizing the use of all available pharmacokinetic data collected through modelling and simulation**

Innovator sponsors can use pharmacokinetic data for adults and their knowledge of physiological changes among infants and other children to perform modelling to select initial doses for study in younger and smaller children. Similar exercises

can be performed to convert age-based dosing to weight-band dosing, if necessary. Both industry and paediatric stakeholders such as the Paediatric Antiretroviral Working Group can use modelling and simulation to predict the optimal ratio of component drugs in fixed-dose combinations for children. The 2015 EMA meeting on fixed-dose combinations for children also endorsed the use of modelling and simulation to support the dosing recommendations submitted to the EMA (see the module on pharmacokinetic modelling).

In some cases, post-approval modelling to support a novel fixed-dose combination for children can be submitted to the FDA for review and agreement through the Division of Antiviral Products pre-investigational new drug programme (7,8). This programme was originally developed to provide advice to pharmaceutical sponsors during early drug development but can also be used by nongovernmental organizations or academic groups seeking regulatory advice.

For example, pharmacokinetic modelling to support proposed dosing for an abacavir + lamivudine + efavirenz fixed-dose combination for children was provided to the FDA pre-investigational new drug programme after collaborative work among paediatric stakeholders led by the Medicines Patent Pool to ask the FDA whether this modelling could be used to support a future paediatric application. The Paediatric Antiretroviral Working Group used innovator pharmacokinetic data to evaluate different component doses for the abacavir + lamivudine + efavirenz fixed-dose combination for children given priority by the Paediatric Antiretroviral Drug Optimization group. The FDA provided a preliminary assessment of the dosing and modelling and indicated that this would be an acceptable approach to justify the dosing for the abacavir + lamivudine + efavirenz fixed-dose combination. FDA acceptance will allow multiple generic suppliers to use the modelling provided by the Medicines Patent Pool to support registration of an abacavir + lamivudine + efavirenz product for children.

### 3.5 Waiving regulatory fees

There are specific circumstances in which an innovator sponsor may request a user fee waiver when submitting a new drug application to the FDA. However, these conditions are unlikely to apply to the innovator sponsors who develop new ARV drugs. In contrast, the PEPFAR review process allows generic suppliers to apply for a user fee waiver, and these are frequently granted. An FDA guidance document (16) outlines the criteria for eligibility and the request process. As of its most recent reauthorization, the FDA no longer charges a fee for submitting supplements to an already approved new drug application (a supplemental new drug application). Data on children submitted for an approved new drug application would therefore incur no user fee.

Drug developers may request scientific advice from the EMA Committee for Medicinal Products for Human Use on the appropriate tests and studies for developing a medicine. This advice will be free of charge for questions related to children. Applicants may choose to request scientific advice first to help in preparing a paediatric investigation plan or may submit a paediatric investigation plan first and follow it up with a request for scientific advice on specific questions, for example, combined development of formulations for adults and for children given the requirements of the paediatric investigation plan.

The Article 58 process through the EMA also has fees associated with it, and this has been noted as a barrier to using this route for filing. The process is perceived to have high costs (up front and annual) that can be prohibitive for small manufacturers, and the possibility and criteria for fee waivers are largely unknown to manufacturers. The EMA has recently clarified these issues and created a range of regulatory tools to support applicants in developing and submitting applications (17).

In 2013, WHO implemented a user fee structure to balance external and internal funding for the WHO Prequalification Programme (18). In 2017, the fee structure changed, and the fee for an

initial application was increased substantially (19). There are, however, options to apply for and receive a waiver based on specific products and product categories in the WHO guidance document annex (20). Pharmaceutical products formulated specifically for children are listed as a product category for which a manufacturer may apply for a waiver. To receive information on the waiver process, manufacturers should contact the Prequalification Programme team for advice.

### 3.6 Submission of complete dossiers with appropriate cross-references

For generic suppliers submitting dossiers for PEPFAR programme review that rely on information in the public domain or previously reviewed by FDA, appropriately referencing that information is critical to a timely review. Abbreviated new drug applications and 505(b) (2) new drug applications must reference the nonclinical and clinical development programme of relevant innovator products. Labelling must match that of the referenced innovator products. In addition, if proposed dosing for children differs from the original approved dosing, the submission must include justification for that dosing.

For example, if the proposed dose leads to higher or lower exposure, rationale and supportive data or a summary must be included outlining why the lower (or higher) exposure would not compromise safety or efficacy. Such justification can include copies of or electronic links to WHO treatment guidelines, pharmacokinetic modelling (as mentioned above), the Paediatric Antiretroviral Drug Optimization group or Paediatric Antiretroviral Working Group reference documents and priority lists and any other relevant clinical information (such as publications, letters of reference to submitted data, etc.).

Additional recommendations to improve the quality of dossiers submitted to the FDA's PEPFAR review programme include:

- ensuring that adequate stability data are included with the application, including stability data collected at 30°C and 75% relative humidity to enable worldwide distribution;
- ensuring that tablet size and scoring correspond to approved dose recommendations;
- ensuring that an approved reference listed drug is used for bioavailability and bioequivalence studies;
- responding to any questions from the FDA promptly and completely; and
- to obtain pre-submission guidance for PEPFAR original new drug applications, use the Division of Antiviral Products' pre-investigational new drug consultation programme; the programme is useful to discuss specific questions on product quality.

## 4. SUMMARY

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In summary, attempts to coordinate innovator companies' required drug development and studies related to children into unified, globally relevant programmes are underway. Regulators are committed to improving communication and harmonization. Paediatric stakeholders and representatives of stringent regulatory authorities have agreed in principle to many

steps that should expedite the development of products for children with the greatest potential for public health benefits. Continued collaboration among innovators, regulators, generic suppliers, and other stakeholders is necessary to eliminate the current delays in the availability of ARV drugs for children.

## 5. KEY CONSIDERATIONS

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- Programmes for developing drugs for children should focus on priority products most likely to be useful in low- and middle-income countries.
- The development of formulations for children should begin early in the product life cycle.
- Clinical trials involving children should be streamlined, and modelling and simulation should be used to identify initial dosing.
- When doubt arises regarding paediatric investigation plans and paediatric study plans, alignment and advice should be sought from regulatory authorities (the FDA and the EMA).
- Manufacturers should enquire as to whether products might be eligible for a fee waiver or reduction.
- For PEPFAR products (especially novel fixed-dose combinations), all information necessary to justify proposed dosing for children should be provided, and manufacturers should ensure that chemistry, manufacturing and control information is complete at the time of submission.



## 6. ACKNOWLEDGEMENTS

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Comments were also provided by the Division of Antiviral Products of the United States Food and Drug Administration and by representatives of the European Medicines Agency and members of the European Medicines Agency Paediatric Committee. Any views expressed in this publication by employees of the United States Food and Drug Administration or the European Medicines Agency, or members of the European Medicines Agency

Paediatric Committee, are their own and may not be understood or quoted as being made on behalf of or reflecting the position of the United States Food and Drug Administration or of the European Medicines Agency or any of its committees or working parties.

Generous support from Unitaid enables the work of the Clinton Health Access Initiative on optimal ARV drugs for children.

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# **MODULE 10: PHARMACOVIGILANCE**

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# 1. INTRODUCTION

This section introduces the concepts of pharmacovigilance and adverse drug reactions, discusses the burden of adverse drug reactions for children and explains the importance of pharmacovigilance in the context of antiretroviral therapy (ART).

## 1.1 Defining pharmacovigilance

WHO defines pharmacovigilance as the “science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem” (1). It focuses on investigating and monitoring adverse drug reactions after medicinal products are licensed (2). Adverse drug reactions are a response that is noxious and unintended and that occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease or for modifying physiological function (2). They may vary in presentation and occurrence and are commonly divided into type A (augmented pharmaceutical response) and type B (bizarre or hypersensitivity) adverse drug reactions (3).

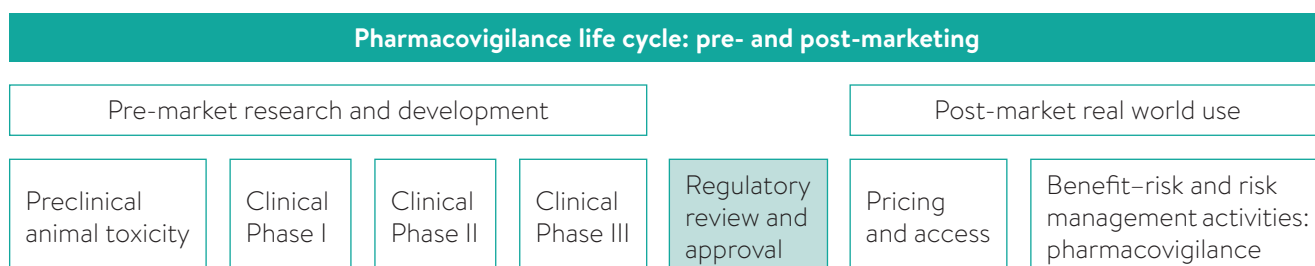
An example of a type A reaction in relation to antiretroviral (ARV) drugs for treating HIV is the negative effect of tenofovir on bone mineral density, which may increase fracture risk (4). An example of a type B reaction is efavirenz-related hypersensitivity in the form of a skin rash with systemic symptoms (5).

The global system of pharmacovigilance was first developed following the thalidomide tragedy in the 1960s, where thalidomide was used to treat nausea in pregnancy, resulting in serious teratogenic events among infants exposed in utero (6). Ideally, pharmacovigilance systems take a life-cycle approach, focusing not only on the properties of the prescribed medicine but also on how it is formulated, dispensed and administered (7,8). This approach is a continuum throughout the process of drug development, from initial research and development activities to final consumer use and is commonly divided into two stages (Fig. 10.1):

- pre-marketing surveillance: adverse drug reactions from preclinical screening and Phase I, II and III clinical trials; and
- post-marketing surveillance: adverse drug reactions from the post-approval stage and throughout a drug’s market life.

Pre-marketing safety assessment is generally limited for children. This commonly results from few children enrolled in paediatric clinical trials and/or the long latency between exposure to the medicinal product and the onset of the reaction, and less common adverse reactions may therefore not be detectable during this phase. The amount of dedicated information on the safety of medicines for neonates, children and adolescents at the time of marketing authorization is therefore very limited, which poses even more reliance on proper pharmacovigilance in the post-marketing stage (9).

**Fig. 10.1.** Timeline of pharmacovigilance for a drug from development (pre-market) to post-marketing use



The module on trial design covers issues concerning efficacy and safety data from Phase I to III studies, including the implications of relatively short follow-up times in drug approval trials and restricted entry criteria into trials.

Post-marketing pharmacovigilance can be conducted through passive and active surveillance systems.

In passive surveillance, health-care professionals or patients send spontaneous reports describing an adverse drug reaction after one or more medicinal products are administered to the marketing authorization holder or regulatory authority. Sometimes such first case reports are published, which may stimulate subsequent reporting. An example is the case report of efavirenz-induced gynaecomastia in a prepubertal girl with HIV, published in 2013 (10). A case series is a series of such reported cases, and these can help to generate hypotheses about an association between drug exposure and an outcome. An example is the case series of gynaecomastia cases reported to the National HIV & Tuberculosis Health Care Worker Hotline in South Africa and published in 2016 (11).

Active surveillance involves enhanced or targeted monitoring for certain events or drugs and seeks to ascertain completely the number of adverse drug reactions through a pre-planned process. Active surveillance is also commonly known as toxicity monitoring (such as the WHO ARV programme) or safety monitoring (12). An example is a cohort study that evaluated the prescribing of, adherence to and adverse drug reactions associated with ART in a large programme in Lagos, Nigeria (13).

Pharmacovigilance (passive or active) was not specific to drugs for children until the beginning of the new millennium, when the Pediatric Rule (United States) and the Paediatric Regulation (European Union) were implemented (14). Aspects related to children are now integrated early in the process of developing a new drug (pre-marketing). Stronger enforcement of requirements to obtain safety information for

children by regulatory agencies in recent years has resulted in an increased number of trials involving children. Following the Paediatric Regulation in Europe, the European Medicines Agency (EMA) issued the Guideline on the Conduct of Pharmacovigilance for Medicines Used in the Paediatric Population, which was recently updated (15).

## 1.2 Burden of adverse drug reactions among children and available studies

Age-specific pharmacovigilance is required among children, since they differ from adults because of ongoing neurobehavioural development and physical growth, including internal organ maturation (9). Further, different maturation milestones are likely to alter the susceptibility of children at different ages to specific adverse reactions and how they react to them, from (pre)term neonates to toddlers at one end of the spectrum to postpubertal adolescents at the other.

Factors influencing the susceptibility of children to adverse reactions for a given medicine include:

- changes in the maturation of organ systems (such as skin, airways, kidney, liver, gastrointestinal system, brain and blood-brain barrier as well as drug transporters) during growth and their development (ontogeny) leading to a different pharmacodynamic and pharmacokinetic profile of a medicine to what is known in adults;
- rapid changes in body mass and shape that can reduce the therapeutic window, leading to increased susceptibility to dose-related adverse drug reactions;
- the immaturity of many organ systems that might lead to different vulnerability to adverse drug reactions in some subpopulations of children, such as preterm neonates;
- the presence of specific pharmaceutically active excipients that may have unintended effects for children (such as alcohol), leading to a risk of adverse reactions; and

- the impact of short- and long-term effects on the developing organs and organ systems, such as the nervous system, skeletal growth and sexual maturation; such effects may only become obvious, visible or identifiable in the long term, with remarkable delay, in adolescence or adulthood.

These considerations highlight the importance of taking into account aspects related to organ maturation and developmental pharmacology when performing pharmacovigilance activities for children and imply that the value of long-term follow-up should be considered systematically (16).

A recent meta-analysis of the incidence of adverse drug reactions in paediatric observational studies demonstrated that the rates of all adverse drug reactions that resulted in hospital admission ranged from 1% to 10% among children (pooled estimate 3%). For hospitalized children, these rates were higher, ranging from 1% to 17% among children exposed to a drug (17). Anti-infective drugs (including ARV drugs) and anticonvulsants were the most frequently reported therapeutic classes associated with adverse drug reactions among hospitalized children.

Although the evidence is limited, the burden of adverse drug reactions among children appears to be similar in high-income countries and low- and middle-income countries (5). Besides the impact of adverse drug reactions on morbidity and mortality and the associated direct costs of managing them, adverse drug reactions also have other significant costs in terms of the loss of confidence in the health system, financial losses of the pharmaceutical industry, increased non-adherence to treatment and the development of drug resistance to anti-infective drugs (18).

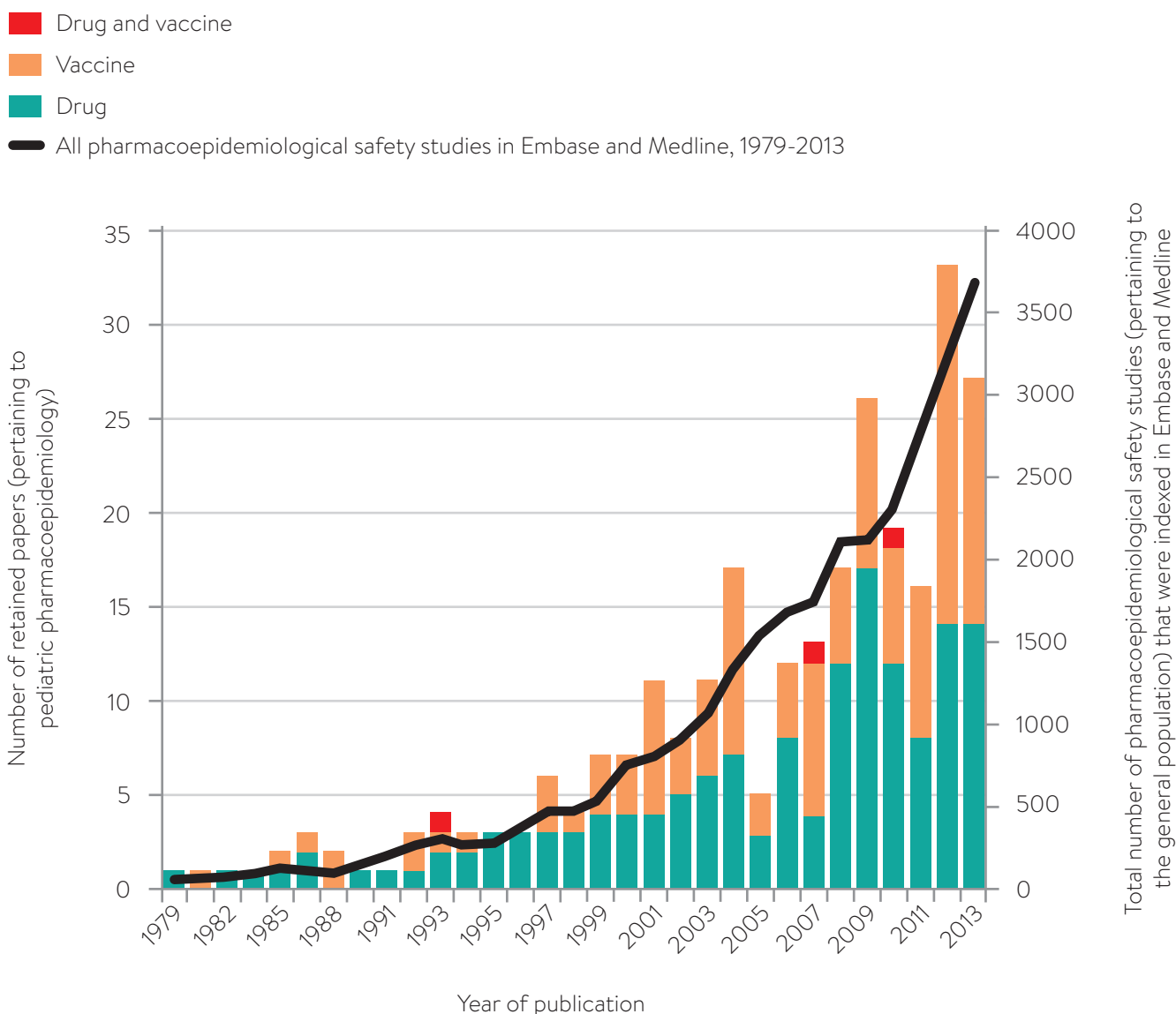
Another systematic review focused on studies quantifying the association between drug exposure and adverse drug reactions among children and adolescents younger than 18 years (19). Surprisingly, only 268 relevant articles were retrieved, with an increase in the number

published over time, as Fig. 10.2 demonstrates. Rather concerning was the great disparity between the number of studies involving children compared with adults, as represented in the right vertical axis of Fig. 10.2, showing about 25–30 published studies involving children versus about 3500 studies involving adults per year in recent years. The following section explores some of the challenges related to conducting pharmacoepidemiological studies involving children exposed to and living with HIV, and this helps to understand the causes of the low level of evidence for adverse drug reactions among children.

For children exposed to HIV and children living with HIV, ART provides enormous benefits, including dramatically reduced mortality risk, improved growth, immune recovery and viral suppression and improved cognitive development (20). However, similar to any drug, ARV drugs have been associated with adverse drug reactions. Short-term adverse drug reactions after initiating ART may include dizziness and gastrointestinal disorders as well as cognitive and sleep disorders. Longer-term adverse drug reactions associated with ARV drugs include changes in body fat distribution (lipodystrophy) and negative effects on bone health (20).

In some studies of ARV drugs, the rates of ART discontinuation have been higher in post-marketing observational studies than in the clinical trials that led to regulatory approval. For example, for dolutegravir (DTG), about 10% of adults in a large cohort study discontinued DTG during the first year of treatment versus only 2–4% of adults in regulatory clinical trials (21). In addition, data on the efficacy of specific combinations of ARV drugs from Phase I to III studies may be limited to specific populations and/or have smaller sample sizes, limiting the ability to evaluate adverse drug reactions. These challenges highlight the ongoing need for long-term pharmacovigilance of ART across different populations of HIV-exposed children and children living with HIV to ensure that the drugs are safe and effective.

**Fig. 10.2.** Number of pharmacoepidemiological safety studies involving children



Source: Osokogu et al. (19). © 2016 The Authors. Pharmacoepidemiology and Drug Safety, published by John Wiley & Sons Ltd.

### 1.3 Importance of pharmacovigilance in the era of expanded access to ART

Post-marketing pharmacovigilance is essential to monitor the longer-term safety of drugs, especially in specific populations and/or situations that are not normally included in pre-marketing studies. Underlying this is the importance of appropriately collecting and reporting safety data to provide information for clinical decision-making. The expansion of

two key public health programmes has resulted in substantial exposure of fetuses in utero and children to ARV drugs: initiatives to prevent the perinatal transmission of HIV and initiatives to improve the survival of children with HIV.

#### Initiatives to prevent the perinatal transmission of HIV

Current WHO and national guidelines recommend that all pregnant women living with HIV receive lifelong ART to prevent the perinatal transmission

of HIV and to improve maternal health. Global coverage of ART for preventing perinatal transmission and maternal HIV treatment is high, with UNAIDS estimating that coverage of ART among pregnant women living with HIV was 76% in 2016 (22). Consequently, HIV transmission rates are now less than 1% in many high-income countries and less than 5% in several low- and middle-income countries (23,24), and estimates suggest that 2 million children avoided acquiring HIV infection globally from 2000 to 2015 because of the roll-out of ART for pregnant women (25).

With the successful scale-up of maternal ART, an estimated more than 1 million infants are exposed to ART in utero and/or in early life through short-term prophylactic ART (26). Although ART is highly effective in reducing perinatal transmission, and preventing children from become newly infected is unquestionably beneficial, there is also global recognition of the potential negative impact of exposure to ART during fetal and postpartum growth and development on the morbidity, mortality and developmental outcomes for millions of children (26,27).

In addition, the roll-out and scaling up of ARV drug pre-exposure prophylaxis to pregnant and breastfeeding HIV-negative women will result in ongoing exposure to these drugs among their offspring, in utero and during breastfeeding, further increasing the number of children exposed to ART globally. The current size of the HIV-uninfected population exposed to pre-exposure prophylaxis is likely to be relatively small, since in many countries pre-exposure prophylaxis is only available to key populations at higher risk such as men who have sex with men and sex workers but this population may be substantially larger in the future.

To sustain the uptake of these programmes and to reduce uncertainty around safety issues related to ARV drugs, post-marketing surveillance of pregnant women exposed to ART is of utmost importance. This is because no ARV drugs have been categorized as United States Food and Drug Administration (FDA) category A in pregnancy, indicating that adequate and

well controlled studies of pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and no evidence exists of risk in later trimesters). This FDA classification system has now been replaced with more informative labelling to enable the health-care provider and patient to better assess risk, although all ARV drugs classified while the system was in use were category B or lower, demonstrating the moral duty to collect adequate safety data (28).

### **Initiatives to improve the survival of children with HIV**

Children living with HIV, who may or may not have been exposed to ART in utero and/or during breastfeeding, and who are prescribed lifelong ART, need proper monitoring to assess the short-term and longer-term effects of ART. ARV drugs have greatly improved the survival of children living with HIV in high-income countries and low- and middle-income countries, even though coverage among children continued to lag behind that among adults, at 43% versus 53%, respectively, in 2016 (29). Children living with HIV are exposed to lifelong ART throughout critical developmental stages of childhood, including the metabolic and hormonal changes of puberty during adolescence. UNAIDS estimates that, in 2016, 2.1 million children younger than 15 years were living with HIV globally, and 160 000 children were newly infected, with projections suggesting that the number of children acquiring HIV will only decline to 100 000 by 2020 (25).

## 2. CHALLENGES

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This section discusses the challenges of conducting pharmacovigilance of ART among children in low- and middle-income countries.

### 2.1 General pharmacovigilance challenges

This subsection describes the challenges relevant to the safety of all medicine, and the next subsection describes those specific to ART.

#### 2.1.1 Regulatory challenges in low- and middle-income countries

There have been significant advances in pharmacovigilance activities in recent decades, and systems are considered well established in most high-income countries. Regulatory developments have supported these advances, and the absolute number of paediatric safety studies has increased since the introduction of the Best Pharmaceuticals for Children Act in the United States in 2002 and the Paediatric Regulation in the European Union in 2007 (19). The implementation of pharmacovigilance in low- and middle-income countries, however, is highly variable. Some countries have no systems at all, whereas a few have more established programmes that are comparable to those in high-income countries, such as South Africa (7). A review of the general pharmacovigilance systems of 46 countries in sub-Saharan Africa in 2010 concluded that the capacity for regulating health products was inadequate in sub-Saharan Africa (30).

Given the importance of pharmacovigilance among children and adults across all settings, WHO has defined the minimum requirements for any routine national pharmacovigilance system, focusing on the least resource-demanding passive surveillance methods that can be implemented without major investment (31). These requirements include:

- a national pharmacovigilance centre with designated staff and at least one full-time staff member;
- the existence of a national spontaneous adverse drug reaction reporting system, incorporating a national individual case safety report form (an adverse drug reaction reporting form);
- a national database or system for collating and managing adverse drug reaction reports; and
- a national pharmacovigilance advisory committee to provide technical assistance on causality assessment, risk assessment and management, case investigation and crisis management, including crisis communication.

Fortunately, the number of low- and middle-income countries conducting passive surveillance and reporting to the WHO Programme for International Drug Monitoring has steadily increased. For example, in a review of pharmacovigilance systems in sub-Saharan Africa, 72% of countries participated as an official or associate member of this Programme (30). However despite a rise in the number of spontaneous adverse drug reaction reports from low- and middle-income countries (7), very few countries have reached the desired target of 100 reports per million inhabitants. Reported challenges to improving the reporting of adverse drug reactions in low- and middle-income countries include (7):

- busy clinics, high patient volumes and few health-care professionals, with no time to focus on reporting suspected adverse drug reactions;
- health-care professionals being uncomfortable reporting adverse drug reactions because they fear perceptions of professional error or culpability, lack of clear legal provisions to guarantee confidentiality of submitted reports, lack of trust in the integrity of authorities and lack of proper training; and



- postal services and Internet being unreliable, complicating reporting to national centres (7).

The review highlighted several gaps in pharmacovigilance in sub-Saharan Africa (30). Although most (74%) of the 46 countries in sub-Saharan Africa had a national medicine regulatory authority and 78% had a national medicine policy, less than half (41%) had a national policy related to pharmacovigilance and medicine safety, and only one third (30%) had a legal mandate to monitor adverse drug reactions. Further, less than one third (28%) of the countries had legal provisions requiring marketing authorization holders to report all serious adverse drug reactions to the national medicine regulatory authority, and only 17% of countries required marketing authorization holders to conduct post-marketing pharmacovigilance.

On the positive side, most (74%) of the countries had a pharmacovigilance centre with a clear mandate and formal organizational structure, 39% had national pharmacovigilance guidelines and a safety advisory committee and 45% had a drug information service providing drug information to health-care professionals and the public.

Coordination among all stakeholders was, however, minimal – only 28% of countries had a platform or strategy to coordinate pharmacovigilance activities at the national level. A pharmacovigilance database existed in half (50%) the countries, but coordination and collation of pharmacovigilance data from all sources was inadequate. The review did not focus on pharmacovigilance involving children, which has only relatively recently gained attention in high-income countries.

### **2.1.2 Competing resource and capacity challenges**

Pharmacovigilance activities involving adults and children have historically been underdeveloped in low- and middle-income countries, partly because of some stakeholders perceive that the cost of pharmacovigilance infrastructure competes with the distribution of scarce resources for direct care delivery (32).

The priority in low- and middle-income countries in recent years has been to establish access to essential medicines to reduce morbidity and mortality. In this light, investing in pharmacovigilance systems was considered an unaffordable luxury (7), thus impeding the allocation of time and resources to developing sustainable global pharmacovigilance. This is especially true for HIV, with the rapid roll-out of ART through the Global Fund to Fight AIDS, Tuberculosis and Malaria and the United States President's Emergency Plan for AIDS Relief (PEPFAR) in early 2000 being aimed primarily at saving millions of lives. Consequently, access to essential medicines for treating such common health conditions as malaria, pneumonia, HIV and diabetes mellitus has increased substantially in low- and middle-income countries, and global coverage of ARV drugs for people living with HIV increased to 53% in 2016 (33).

The consequence of this success is an increasing number of people globally at risk of adverse drug reactions, especially in communities with limited education and fewer trained health-care professionals to guide the safe and appropriate use of medicines. Increased global medicine exposure, lack of information on drug safety and ongoing significant presence of comorbidities emphasize the need for efficient pharmacovigilance systems in low- and middle-income countries, especially for large-scale treatments such as ART and among vulnerable populations such as pregnant women and children.

### **2.2 Specific ART-related pharmacovigilance challenges**

Beyond general challenges to passive and active surveillance in low- and middle-income countries, several specific challenges exist for passive and active surveillance of ARV drugs. We first discuss challenges for case reports and subsequently the challenges for conducting retrospective and prospective epidemiological studies.

### **2.2.1 Challenge in assessing the causality of case reports**

The challenge in assessing causality for suspected adverse drug reactions from case reports is that they are rarely specific to the individual drug, diagnostic tests are usually absent, a re-challenge (such as reintroducing the drug to the patient after an adverse drug reaction) is rarely ethically and clinically justified, and there are frequently no denominators of patients at risk.

Assessing causality for ARV drugs is even more challenging, since multiple drugs are taken together in the form of fixed-dose combinations for ART or HIV prophylaxis, and many may produce similar adverse events. The presence of comorbidities and concomitant treatments (such as for tuberculosis or malaria) further complicate the assessment of causality.

In practice, few adverse drug reactions have a certain or unlikely relationship with a specific drug, and most are somewhere in between these extremes, such as possible or probable. Recognizing the presence of adverse drug reactions may also be more difficult since they may present with a different pattern or severity because of environmental or behavioural factors or comorbid conditions and concomitant medications. Higher incidence rates of drug–drug interactions and adverse drug reactions are therefore naturally expected in low- and middle-income countries (12).

In addition, late initiation of ART, frequently with advanced HIV disease and malnutrition, limited health-care provider expertise and drug stock-outs may result in treatment interruptions and restarts or drug substitutions, both for HIV and comorbidities, that can also contribute to higher rates of adverse drug reactions. Compared with the common comorbidities in low- and middle-income countries, providers in high-income countries face a different array of confounding health conditions and concomitant drugs used, such as illicit drugs, psychotropic drugs and lipid-lowering agents, which can also complicate pharmacovigilance activities.

### **2.2.2 Challenge to distinguish between adverse drug reactions and dosing errors**

The risk of medication dosing errors (under- or overdosing) is high for children and especially among young children receiving ARV drugs, who require frequent dose changes in response to rapidly changing body weight. Use of formulations for children, such as granules and sprinkles, liquids and small tablets, requires proper training and support of the caregiver by the skilled health-care worker and, if not implemented, may result in dosing errors causing adverse drug reactions and drug–drug interactions.

Case reports of medication dosing errors involving infants who received up to 10 times the recommended dose of zidovudine prophylaxis or treatment and the subsequent adverse events (34) highlight the risk for such errors and helped stakeholders advocate for appropriately sized administration vehicles such as syringes for children (35).

### **2.2.3 Challenge in generalizing results from high-income countries**

Currently, pharmacovigilance studies involving children originating from high-income countries dominate the field, but many high-income countries have relatively few children living with HIV compared with low- and middle-income countries. For example, the European Pregnancy and Paediatric HIV Cohort Collaboration has conducted post-authorization safety studies on behalf of pharmaceutical companies for the EMA. These studies involve secondary analyses of prospective cohort data, supplemented by questionnaires on outcomes specific to adverse drug reactions (36). Of the five ARV drugs with findings published to date (36–40), two were for drugs used relatively infrequently in Europe and correspondingly had sample sizes of less than 200 in each study, highlighting the challenges of conducting pharmacovigilance studies with small sample sizes (37,40).

The availability of newer ARV drugs differs by income setting. Children in low- and middle-

income countries are frequently prescribed generic first-generation individual ART drugs and generic fixed-dose combinations, which may no longer be considered preferred regimens in high-income countries. Thus, new evidence for the drug safety of older regimens will no longer be generated from high-income countries with well developed pharmacovigilance systems, leading to an even larger disparity in safety information between low- and middle-income countries and high-income countries.

#### **2.2.4 Challenges based on the quality of source data**

Retrospective epidemiological studies in low- and middle-income countries may rely on extracting data on the outcome and exposure from paper medical records, and the quality of these is likely to vary widely depending on the study context. Treatment records may be incomplete or missing and difficult to retrieve, and a lack of recorded viral load data in many low- and middle-income countries restricts the

ability to investigate the real-world adherence, effectiveness and safety of specific ARV drugs. Adverse drug reactions and medication use are often not documented because of lack of time and lack of awareness of their importance.

#### **2.2.5 Heterogeneity of exposure and populations: effect modification versus power**

Children with ART exposure are not a homogeneous group but comprise distinct populations of HIV-negative children and children living with HIV, all with ART drug exposure differing by duration and the combination of drugs given. These differences may all affect the rates of adverse drug reactions, and studies need to distinguish these factors and study safety by the type of regimen and population. Only if effect modification is absent may exposure be pooled. The need to evaluate effect modification affects the power. ART exposure should be well documented, including maternal and infant exposure, although this proves to be difficult even in high-income countries (41).

A good example is the West Cape Province of South Africa, which has an electronically linked health record system linking maternal and infant records, including pharmacy ART records with a range of health records, including hospital admissions, death and cancer registries. Such surveillance systems may provide a critical foundation for well powered pharmacovigilance systems.

#### **2.2.6 Challenges from selection bias and loss to follow-up**

The surviving and ageing perinatally infected children living with HIV make pharmacovigilance studies difficult to conduct. Challenges include how to select representative samples of children and the appropriate duration of follow-up. Because of dropout or loss to follow-up, the analysable amount of person-time may be low, limiting the power to investigate longer-term safety. This affects the confidence in the findings of different studies.



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### 2.2.7 Multiple outcomes of interest

Paediatric safety outcomes of interest range from prenatal, perinatal and neonatal to longer-term outcomes. Many outcomes may require diagnostics that are not generally available in clinics in low- and middle-income countries, such as dual-energy X-ray absorptiometry and neurological and psychiatric assessment. Longer-term outcomes of short-term and lifelong ART

exposure range from effects on physical growth to rare remote events such as malignancies in adulthood, and all need to be investigated. Studying such a broad range of health outcomes will require varied study design approaches and proper assessment of outcomes over a long lifespan, which is challenging because of the lack of automated and linked health records, migration and loss to follow-up.

## 3. SOLUTIONS

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The safety of ART has improved considerably over time but, similar to any active compounds, vigilance is required, especially in vulnerable populations (such as pregnant women, children and immunocompromised people). Solutions to improve pharmacovigilance in its broader context start with preventing or minimizing risks. Having data available to identify and minimize the risk requires comprehensive signal detection and evaluation studies being in place, to generate actionable information.

### 3.1 Minimizing the risks

Pharmaceutical adverse drug reactions (type A) may be prevented through an array of risk-minimizing activities such as:

- providing access to up-to-date information on the safety of ARV drugs in different populations to health-care providers in high-income countries and low- and middle-income countries so that well informed decisions can be made;
- pretreatment screening to identify people at high risk of specific adverse drug reactions;
- avoiding prescribing concomitant medicines with a shared risk for similar adverse drug reactions, such as multiple nephrotoxic agents;

- implementing medication review into the standard of care to identify the potential for drug–drug interactions; and
- training health-care providers and patients to promptly recognize, treat and document adverse drug reactions.

### 3.2 Improving the regulatory framework to create a safety culture

A key reason for the lack or limited implementation of pharmacovigilance in low- and middle-income countries is a lack of national regulations to enforce the responsibilities of the pharmaceutical industry, including generic drug manufacturers, regarding safety reporting of adverse drug reactions to national pharmacovigilance centres (18). With a pharmaceutical market in sub-Saharan Africa estimated to be worth US\$ 3.8 billion to 4.7 billion, the pharmaceutical industry, both innovator and generic, is a major stakeholder in pharmacovigilance activities. The industry should replicate the standard pharmacovigilance practices they undertake in high-income countries and implement similar activities in low- and middle-income countries to safeguard patients and protect the public health of the communities in which they market their products.

Generic drug manufacturers provide a significant proportion of ARV drugs for low- and middle-income countries, and the lower pricing ensures greater access to drugs among the affected populations. However, historically, generic drug companies may have devoted fewer resources for pharmacovigilance and may perceive that monitoring adverse drug reactions is not relevant for generic drugs with well known safety profiles (18). Generic drug manufacturers may not see it as their responsibility to support pharmacovigilance on market entry even when the innovator company is not marketing the compound. However, in the era when increasingly large proportions of the population living with or exposed to HIV globally are receiving generic ARV drugs, there are increasing calls for regional and national regulations and an increased role for the generic pharmaceutical industry to share the responsibility for pharmacovigilance with other global and national stakeholders.

### 3.3 Strengthening capacity

A 2010 review of existing pharmacovigilance systems in sub-Saharan Africa demonstrated that there was existing capacity in the WHO African Region to conduct medicine safety research that can help identify, evaluate and confirm medicine-related risks (30). Active surveillance, including Phase IV studies to evaluate the safety and effectiveness of medicines, had been or were being conducted by academic institutions, public health programmes, hospitals and international organizations in 22 African countries, although most studies were related to malaria treatment.

To improve the coordination of existing research capacity and resources, regional groups in Africa could be supported to develop networks that link research institutions and regulatory authorities to increase medicine research capacity.

Pharmacovigilance centres in sub-Saharan Africa could also collaborate on a more global level, since many training courses and opportunities for remote collaborations exist and are available remotely (see the section on useful resources).

Building and sustaining the required human capacity to identify adverse drug reaction signals and manage them requires introducing pharmacovigilance in undergraduate- and graduate-level teaching for all health professionals globally. The WHO Collaborating Centre for Pharmaceutical Policy and Regulation in Utrecht, Netherlands, which conducts academic research at the interface of pharmacoepidemiology and policy analysis, has been charged with developing such programmes (42).

The establishment of a WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance in Accra, Ghana has been a major step towards consolidating the establishment of pharmacovigilance in Africa (7). Since 2009, this Centre has been providing pharmacovigilance training, building capacity, promoting advocacy and strengthening adverse drug reaction reporting, with a focus on passive surveillance, in African countries. WHO is also building capacity in sub-Saharan Africa through the Global Training Network on vaccine quality and the through the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, with courses on adverse events following immunization (passive surveillance).

The Pharmaceutical Industry Association of South Africa organized pharmacovigilance training in South Africa with a focus on pre-marketing clinical safety research or post-marketing adverse events following immunizations. Courses and training on pharmacovigilance are also available from other academic institutions and centres of excellence (see the section on useful resources). Teaching institutions with centres of excellence within their own countries also conduct many active surveillance studies, providing the potential for mentorship to non-teaching hospitals to build the capacity of health-care workers in pharmacovigilance at the local level.

In the European Union, the Eu2P programme was developed through funding from the Innovative Medicines Initiative. It is currently offering innovative web-based education and training in

pharmacovigilance and pharmacoepidemiology, including master and PhD programmes that can be conducted alongside day-to-day work and are available for applicants from low-income countries, including regulatory staff and health-care workers. Internships are available in WHO collaborating centres in Uppsala (Sweden), Accra (Ghana), Utrecht (Netherlands) or Rabat (Morocco) (see the section on useful resources).

The pharmaceutical industry can assist national pharmacovigilance programmes by limiting their employment of national qualified personnel from pharmacovigilance centres and investing in pharmacovigilance training. To retain well trained personnel, salaries in the public sector may need to be increased to avoid a drain into the private sector. Joint PhD programmes with high-income countries and private companies may facilitate the retention of personnel in research settings.

### 3.4 Focus on active surveillance

In the presence or absence of functional passive surveillance systems, the primary focus should be on setting up active surveillance. One of the benefits of active surveillance over passive surveillance is the ability to generate information that may inform decision-making, since there is a higher probability of evaluating and quantifying the relationship between the adverse drug reaction and the related drug. Active surveillance may be implemented using existing capacity: for example, through demographic surveillance networks and public health programmes, which exist in many low- and middle-income countries. Collaboration can be initiated between pharmacovigilance experts and public health officials.

### 3.5 Pooling existing data from active surveillance studies

Merging or pooling data from multiple studies increases the statistical power of analysis and can be a relatively cost-efficient approach. Standardized data exchange protocols are available to aid data mergers, including the HIV Cohorts Data Exchange Protocol (43) and the International Epidemiology Databases to Evaluate AIDS Data Exchange Standard.

A recent example of a large-scale data merger is the Collaborative Initiative for Paediatric HIV Education and Research cohort collaboration, which has conducted a data merger on 93 351 children younger than 18 years across 12 HIV observational cohort networks globally to investigate the incidence and predictors of switching to second-line ART (44). Among other findings, children starting ART with non-nucleoside reverse-transcriptase inhibitor-based regimens have been found to have a higher incidence of switching compared with those starting with protease inhibitor-based regimens.

Such collaboration can be a key source of pharmacoepidemiology data, especially in settings with weak underlying pharmacovigilance systems. The existence of electronic health records comprises another available resource for pharmacoepidemiological pharmacovigilance safety studies (19).

### 3.6 Developing standardized methods and protocols

Using standard protocols and definitions for outcomes, exposure and confounders for active surveillance studies may increase validity and ease the pooling of data from disparate settings. Common data models for data collection may be created, facilitating pooling and the use of common analytical data scripts, especially in areas with limited capacity.

### 3.7 Pooling of spontaneous reporting data

A crucial aspect of pharmacovigilance is the ability to easily pool data from disparate sources to inform the global community of emerging trends in adverse drug reactions. National pharmacovigilance systems should establish and maintain adverse drug reaction databases that are compatible with the international standard format for adverse drug reaction reports, known as individual case safety reports. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use developed this international standard, known as the ICH-E2b, which allows easy exchange of adverse drug reaction data between countries, regulatory authorities and the pharmaceutical industry.

Low- and middle-income countries can use the VigiFlow data management system from the WHO Collaborating Centre for International Drug Monitoring at low cost, in which the ICH-E2b is fully integrated. Further, international data sharing is necessary to support global pharmacovigilance, especially given international trade and traffic in pharmaceuticals, and specifically, the small numbers of specific adverse drug reactions involving children.

The power to detect adverse drug reaction signals is greatly enhanced when a data management system can receive and collate pharmacovigilance data from all sources, including routine adverse drug reaction monitoring integrated within public health ART programmes, clinical trials, immunization programmes, active surveillance and periodic safety updates from the pharmaceutical industry.

### 3.8 Harnessing WHO technical support

To support the safe introduction of new ARV drugs for children and address the gaps in safety data within national programmes, WHO provides technical support to countries to implement both routine toxicity monitoring via the HIV patient monitoring system and active adverse drug reaction surveillance for ART. WHO has developed and disseminated patient monitoring tools that capture and enable reporting of treatment limiting adverse drug reactions. WHO also supports the implementation and the strengthening of data quality to encourage the generation of reliable data and maximize the utility of collected data. WHO works with health ministries and technical partners to adapt the minimum datasets, tools and protocols to individual country settings and is supporting the implementation of surveillance of drug safety among pregnant women in Malawi and South Africa.

Moreover, WHO has developed an ARV drug toxicity monitoring tool that provides step by step instructions and reporting tools for countries to implement both routine monitoring of toxicity and active adverse drug reaction monitoring at selected sentinel sites for new ARV drugs among children. WHO aims to produce additional tools and annexes for new ARV drugs, including new ARV drug formulations for children for in-country implementation and adoption. For example, a standardized reporting form is available for countries to report DTG-associated adverse drug reactions, together with training materials and an adaptable data dictionary. WHO is also developing a central database for safety evaluation of DTG to enable pooling of data and inform global guidance. Countries are also being supported with the adaptation of tools, approaches and data analysis, to facilitate the implementation of adverse drug reaction monitoring in their own context.

## 4. CASE STUDIES

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Active surveillance designs typically follow standard epidemiological study designs. In epidemiology, populations are studied and the occurrence of disease is compared between exposure groups. An essential epidemiological concept is that if a drug causes disease, the drug must be administered before the disease developed and must alter the frequency of that disease. Frequency of disease can be measured by risk (cumulative incidence over a specific period) or incidence rates (number of cases for a certain number of people and a certain amount of time). The following are the key observational designs and can be applied for safety and effectiveness studies (Table 10.1).

In cohort studies, the population is divided into exposure groups and the incidence (cumulative or rate) is calculated and compared between the exposure groups. The advantage of cohort studies is that multiple outcomes can be studied at the same time. Cohort studies are usually expensive, since large populations need to be followed over time to monitor the occurrence of disease. For ARV drugs, cohorts may also be complex since treatment may change and many covariates also change over time, all of which need to be measured and considered in any analysis. As an aside, experimental studies (randomized controlled trials) have a cohort design, except that exposure does not follow real-world practice but is randomly assigned by the investigator.

An alternative to cohort studies is case-based studies, which start with the outcome (cases). In case-control studies, the past frequency of exposure to a drug in cases is compared with the frequency of exposure to the drug in controls (people without the outcome). Since the outcome is the entry point into the study and exposure needs to be assessed retrospectively, these designs are efficient but susceptible to selection and information bias, especially if they

rely on consent and self-reported exposure. The advantage is that they cost less and enable multiple exposure patterns to be studied.

In recent years, other case-based studies have been developed that are suitable for brief drug exposure or vaccine safety. They start with the cases with a specific outcome and compare exposure during case occurrence with periods of time for the same person before the case occurred (case crossover) or in unexposed periods (self-controlled case series). These studies inherently control for all confounding factors that are stable (environment and genetics) and are very cost-efficient.

Cross-sectional studies provide a snapshot at one point in time of the co-occurrence of exposure and disease and are suitable for generating hypotheses, but since the temporal association between the exposure and disease is unknown this design cannot be used to evaluate causality.

Case-based studies only provide measures of association (relative risk) between exposure and outcome (odds ratio). Cohort studies do that as well (relative risk) but also provide an absolute measure of risk or incidence.

### 4.1 Tenofovir and renal toxicity

A series of spontaneously reported cases (case series) from passive surveillance often provides the first indication of a safety signal. For example, in the mid-2000s, single case reports and case series highlighted instances of proximal renal tubular dysfunction and other renal toxicity in a few children with HIV taking tenofovir disoproxil fumarate (45,46). This led to the EMA requiring post-authorization safety studies to assess whether the recommended patient monitoring laboratory tests and evaluations are adhered to in routine care (36). Various study designs



**Table 10.1.** Examples of important pharmacovigilance issues in paediatrics and study design approaches

Pharmacovigilance issue in paediatrics	Study design	
	Optimal choices	Less optimal choices
Prenatal exposure to ART and maternal outcomes and birth defects	<p>Cohort of ART-exposed and -unexposed women and specific investigations of maternal health and birth outcomes (provides rates and associations)</p> <p>Case-control study of infants with birth defects (cases) and without (controls) (efficient design; provides a measure of association)</p>	<p>Case series of women receiving a specific ART regimen (no good reference group)</p> <p>Cross-sectional (no temporal association)</p>
Nervous system and mental effects of specific ARV drugs on children	<p>Cohort study of children initiating ARV drugs on various ART regimens (provides rates and associations)</p> <p>Case-control study of children with nervous system and mental effects (cases) and without (controls) (efficient design; provides a measure of association)</p> <p>Self-control case series (efficient design; adjust for confounders within each person)</p>	<p>Cross-sectional (no temporal association)</p>

have investigated this relationship between exposure and outcome, such as cohort (47) and case-control designs (48), randomized trials (49) and, more recently, a systematic review (50). Together, these and other reports have highlighted clinically relevant adverse renal and bone effects of regimens containing tenofovir disoproxil fumarate among children.

## 4.2 Abacavir and hypersensitivity

Abacavir is a nucleoside reverse-transcriptase inhibitor recommended by international guidelines and available in Africa. However, there have been concerns about its toxicity, including hypersensitivity reactions, which are more likely for people with the HLA B5701 genotype. Studies of adults with HIV receiving abacavir-based ART have reported an increased risk of hypersensitivity reactions and myocardial infarction (51).

One key study investigating hypersensitivity among children taking abacavir was the Antiretroviral Research for Watoto (ARROW) trial, which investigated new ART strategies for children living with HIV in Africa and had an active surveillance component. In the main trial,

grade 3 and 4 adverse events by treatment arm were compared, suggesting good tolerability of abacavir and also lamivudine (52). Follow-up continued beyond the primary endpoint, to evaluate longer-term outcomes, including safety. In ARROW, hypersensitivity related to abacavir was found to be rare, being experienced by 0.3% of trial patients (53). This finding was later confirmed in a systematic review of the evidence from trials and observational studies (54).

## 4.3 Safety of ARV drugs among HIV-exposed and uninfected children

Although surveillance studies in low- and middle-income countries are evaluating the safety of ART in pregnancy and effects on infants at delivery (55), including in Botswana (56) and South Africa (57), these studies are not following up ART-exposed infants subsequently.

In high-income countries, the Surveillance Monitoring for ART Toxicities Study in HIV-uninfected Children Born to HIV-infected Women is a cohort study measuring the safety of exposing HIV-uninfected children born to mothers living with HIV to ART in utero, using

an active surveillance approach (58). Areas of interest include effects on metabolism and growth, the heart, the nervous system and its development, behaviour, language and hearing. A novel trigger-based design provides efficient use of study and patient resources, in which trigger thresholds dictate additional prespecified evaluations rather than randomly selecting subgroups of patients to study with detailed assessments.

Other cohorts and studies use novel data linkage designs to ascertain very long-term outcome measurements from national cancer and death registries in cohort studies of children born to mothers living with HIV. For example, in France, children born to women living with HIV are linked to the National Cancer Registry (59). Findings from France's registry cohort suggested a strong association between didanosine exposure in the first trimester and transplacental oncogenicity, which led to the avoidance of didanosine during pregnancy.



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## 5. SUMMARY

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A huge number of children globally have been exposed to ARV drugs during early life, and this trend will continue for the foreseeable future. In addition, many children living with HIV are expected to continue to need ART for lifelong HIV treatment (5,51,60). In recent years, appreciation has increased of the importance of generating safety data specific to children since they are exposed to ARV drugs throughout critical growth and development phases in addition to differing from adults in absorption, distribution, metabolism and excretion of ARV drugs and concomitantly administered drugs (61).

The poor level of evidence for adverse drug reactions among children reflects some of the challenges of conducting pharmacoepidemiological studies involving children exposed to HIV and ARV drugs. In low- and middle-income countries in particular, regulatory systems are commonly weak, with the main focus being on passive surveillance.

Issues that need to be addressed include the cost of pharmacovigilance, difficulty in attributing causality, dosing errors, the generalizability of findings, data quality, the heterogeneity of exposure and populations, loss to follow-up and multiple outcomes of interest. However, many recent developments have strengthened and improved reporting, and there is a need to further capitalize on progress by improving the regulatory framework, building capacity, focusing on active surveillance, pooling existing data and harnessing WHO technical support.

All of these aspects are important for the future, when focus is likely to be increased on the role of DTG as a priority for children, as well as two-drug regimens and long-acting formulations. These new trends demonstrate a clear need for more robust pharmacovigilance monitoring to better understand the risks and safety profile of ART for children, especially in low- and middle-income countries.

## 6. KEY CONSIDERATIONS

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- Pharmacovigilance of adverse drug reactions is key to ensuring that medicines are safe.
- Pharmacovigilance studies can range from passive surveillance, which can be relatively simple and cheap to implement, to active surveillance, which may be more costly but generates more informative results.
- Major challenges of pharmacovigilance in low- and middle-income countries include a lack of robust regulatory systems that enforce manufacturer commitments to support longer-term approaches to pharmacovigilance and competing resources and capacity challenges.
- Training opportunities are available, and WHO provides technical support to implement both passive and active surveillance approaches.
- Issues of drug safety in HIV will continue for the foreseeable future, and approaches therefore urgently need to be implemented, strengthened and scaled up.

## 7. USEFUL RESOURCES

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### WHO links

- Technical guidance for Global Fund HIV proposals: treatment – pharmacovigilance for antiretroviral drugs ([http://www.who.int/hiv/pub/toolkits/3-2-8\\_Pharmacovigilance\\_3Nov.pdf](http://www.who.int/hiv/pub/toolkits/3-2-8_Pharmacovigilance_3Nov.pdf))
- Pharmacovigilance: ensuring the safe use of medicines (<http://apps.who.int/medicinedocs/pdf/s6164e/s6164e.pdf>)
- A practical handbook on the pharmacovigilance of antiretroviral medicines ([http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/HIVhandbook.pdf](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/HIVhandbook.pdf))
- Venter WDF, Ford N, Vitoria M, Stevens W. Diagnosis and monitoring of HIV programmes to support treatment initiation and follow up and improve programme quality. *Curr Opin HIV AIDS*. 2017;12:117–22 ([http://www.who.int/hiv/pub/journal\\_articles/diagnosis-monitoring-hiv-programmes/en](http://www.who.int/hiv/pub/journal_articles/diagnosis-monitoring-hiv-programmes/en))

### Training courses

- WHO adverse events following immunization (<https://www.who-umc.org/global-pharmacovigilance/communication-in-pharmacovigilance>)
- Uppsala Monitoring Centre education and training opportunities (<https://www.who-umc.org/education-training/education-training>)
- Uppsala Monitoring Centre internships (<https://www.who-umc.org/about-us/contact-us/career-page>)

### WHO collaborating centres

- Uppsala, Sweden: <https://www.who-umc.org>
- Accra, Ghana: [http://apps.who.int/whocc/Detail.aspx?cc\\_ref=GHA-1&cc\\_region=afro&](http://apps.who.int/whocc/Detail.aspx?cc_ref=GHA-1&cc_region=afro&)
- Utrecht, Netherlands: <http://www.pharmaceuticalpolicy.nl>
- Rabat, Morocco: <http://www.capm.ma/pv-pharmacovigilance>

### Data exchange formats

- International Epidemiology Databases to Evaluate AIDS Data Exchange Standard; <http://iedea.github.io>
- HIV Cohorts Data Exchange Protocol: <http://www.hicdep.org>

### Other links

- Eu2P programme: <https://www.eu2p.org>
- International Society for Pharmacoepidemiology Pediatric Special Interest Group: <https://www.pharmacoepi.org/communities/sigs/pediatrics>
- INDEPTH network: <http://www.indepth-network.org>

## 8. ACKNOWLEDGEMENTS

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# CONCLUSION



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# 1. CONTEXT

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This toolkit is part of a wider global initiative to raise awareness of the historical and ongoing delays in developing and commercializing HIV drugs in formulations suitable for children and adolescents and to find innovative ways to accelerate this process (1,2). Efforts in recent years have focused on promoting intersectoral collaboration, giving priority to the most needed formulations for children, establishing a formulary of existing drug formulations

required for optimal treatment of children and coordinating the procurement of antiretroviral (ARV) drugs in low- and middle-income countries (2).

Building on these ongoing initiatives, this toolkit brings together the knowledge and experience of key experts on HIV to suggest pragmatic ways to further accelerate the drug development time scale.

## 2. SUMMARY OF KEY CONSIDERATIONS

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The key considerations arising from this toolkit centre around:

- earlier planning and coordination to facilitate the design and conduct of key research studies;
- including key population groups (young children, adolescents and pregnant and breastfeeding women) in the research process;
- more efficiently using the available data to fill knowledge gaps and minimize the need for additional studies; and
- increasing collaboration and coordination among key stakeholders throughout the key stages of drug development.

### 2.1 Earlier planning and acceleration of research studies

This toolkit provides many examples of ways to accelerate the development of drugs for children by establishing communication channels between key stakeholders early in the drug development process and accelerating appropriately designed

research studies, which should include key population groups from the start.

- Early communication between all stakeholders is needed to facilitate timely planning of studies of novel drugs involving children and pregnant women.
- The development of age-appropriate formulations suitable for low- and middle-income countries should be initiated as soon as reassuring safety and efficacy data are available from Phase II trials involving adults.
- For this to happen, clinical trials, pharmacokinetic studies and acceptability studies involving children should be designed alongside research studies involving adults and in close collaboration with regulatory authorities to establish what data are needed early on.
- Community engagement should occur as early as possible in designing clinical trials and acceptability studies. Community groups should be engaged throughout the process of drug development, including during the planning and design of clinical trials involving children.

- Target product profiles should be developed early in the drug development process, to enable formulations to be adapted if needed.
- Specific country regulatory requirements need to be considered early on to avoid additional hurdles and obstacles to importation and in-country approvals.
- Generic drug manufacturers also need to be involved early in the drug development process.

## 2.2 Including pregnant women, children and adolescents in clinical trials

A more inclusive approach to clinical trial eligibility should be embraced, with more widespread inclusion of pregnant and breastfeeding women, adolescents and children of all ages, including those with coinfections.

- Novel drugs with well established safety and metabolic profiles should be evaluated concurrently across weight and age ranges, taking advantage of pharmacodynamic and pharmacokinetic modelling to estimate starting doses. The age groups or weight bands should be staggered only if there is a specific safety concern.
- Adolescents should be included in clinical trials involving adults, since they usually use the formulations and doses for adults, and no major differences in safety and efficacy are expected compared with adults.
- Adolescents coinfecting with hepatitis B or C virus should be considered for inclusion in coinfection studies of adults.
- Children and adolescents coinfecting with tuberculosis or hepatitis B or C virus should be included in clinical trials and pharmacokinetic studies. Innovative strategies to retain coinfecting children in ARV drug studies should be incorporated into study designs.
- Regulatory authorities and ethics committees should require and support the inclusion of pregnant women in pre-marketing clinical trials. Women enrolled in Phase II or Phase

III clinical trials should not be excluded from the study or taken off the study drug if they become pregnant during the trial unless there are specific reasons to do so.

## 2.3 Efficient data collection and data sharing

More carefully planning studies of novel ARV drugs for children and more efficiently using existing data can accelerate and streamline the drug development process.

- Pharmacokinetic data for adults can be used in modelling and simulation studies, along with knowledge of physiological changes among infants and other children, to establish starting doses for trials involving children.
- Clinical trials should be carefully designed to maximize efficiency and make best use of resources, by employing innovative designs and statistical methods.
- Early planning and intersectoral communication should ensure that the data generated in clinical trials involving children are fit for purpose; for example:
  - that the weight bands used for dosing within the trial are in accordance with WHO ARV drug dosing recommendations for children; and
  - that the results generated are sufficient for regulatory approval to be granted.
- Washout data obtained from neonates exposed to ARV drugs in utero should be used to support the design of neonatal trials.
- Acceptability data should be collected systematically as part of clinical trials involving children. If data on acceptability of formulations are already available, regulatory authorities should routinely make them available.
- Pooling of data, potentially through large paediatric HIV networks, can maximize the use of existing data on subpopulations such as coinfecting children.

- Pharmacovigilance data on pregnant women receiving novel drugs and their exposed infants should be routinely collected, and pharmacovigilance systems in low- and middle-income countries should be expanded.

## 2.4 Intersectoral communication and coordination

In the past few years, the need for intersectoral collaboration to facilitate the process of developing ARV drugs for children, including supply and logistics, has become increasingly apparent. Several initiatives have emerged, linking drug manufacturers, research networks, regulatory agencies, funding bodies and policy-makers (1). This toolkit highlights approaches for further improving intersectoral communication at various stages of the drug development process, including the following.

- In designing clinical trials, all potential stakeholders should be involved at an early stage, to ensure that trials are aligned as closely as possible with the objectives of funders, regulators and clinicians.
- Drug manufacturers should work closely with clinicians, expert groups and stringent regulatory authorities to ensure that collection of key data is feasible and that the data generated are clinically relevant and meet regulatory requirements.
- Close collaboration and improved coordination between disease areas is also critical to ensure that issues relating to the treatment of coinfecting children are considered and that data on these subpopulations are collected in a timely way.
- Collaboration is also needed between formulation scientists, the paediatric HIV research community and social scientists to establish consensus around the assessment of acceptability of ARV formulations for children, including standard criteria for measuring acceptability.
- Target product profiles should be used to communicate product characteristics and anticipate potential problems and should be developed with input from manufacturers, suppliers and regulatory agencies.
- Improved harmonization of regulatory requirements and pathways and regulatory interpretation of stability studies across different regulators would positively influence drug development and supply and logistics.
- Both the United States Food and Drug Administration and the European Medicines Agency are already committed to improving communication across stakeholders, and such efforts should be expanded.
- Donors, funders, country programmes and implementing partners should continue to work together, for example through the Antiretroviral Procurement Working Group, to anticipate and coordinate the procurement of ARV drugs for children.
- Overall, the approach to drug development needs to be harmonized, with efficient communication between policy-makers, the paediatric HIV research community, the pharmaceutical industry, regulatory agencies and funders.

# CONCLUSION

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This toolkit contributes to a global programme of work encompassed by the Global Accelerator for Paediatric Formulations to ensure faster, more efficient development of optimized treatment options for infectious diseases such as tuberculosis, viral hepatitis and HIV (2). Although it focuses on HIV, many of principles discussed within this toolkit can be extended to other disease areas with similar delays in obtaining treatment options for children. We therefore call on drug manufacturers, researchers, regulatory agencies, funders and other stakeholders to strengthen intersectoral partnerships and work together to incorporate these recommendations into standard practice.

The recommendations outlined in this toolkit aim to simplify, unify and accelerate research and development of drug formulations for children and, ultimately, to expand access to safe, effective and well tolerated ARV drugs for children living with HIV in low- and middle-income countries. This is an essential step towards ensuring that WHO universal treatment guidelines can be adopted and that the Start Free, Stay Free, AIDS Free targets of ending AIDS among children, adolescents and young women by 2020 can be achieved (3).

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ISBN 978-92-4-151436-1



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