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.
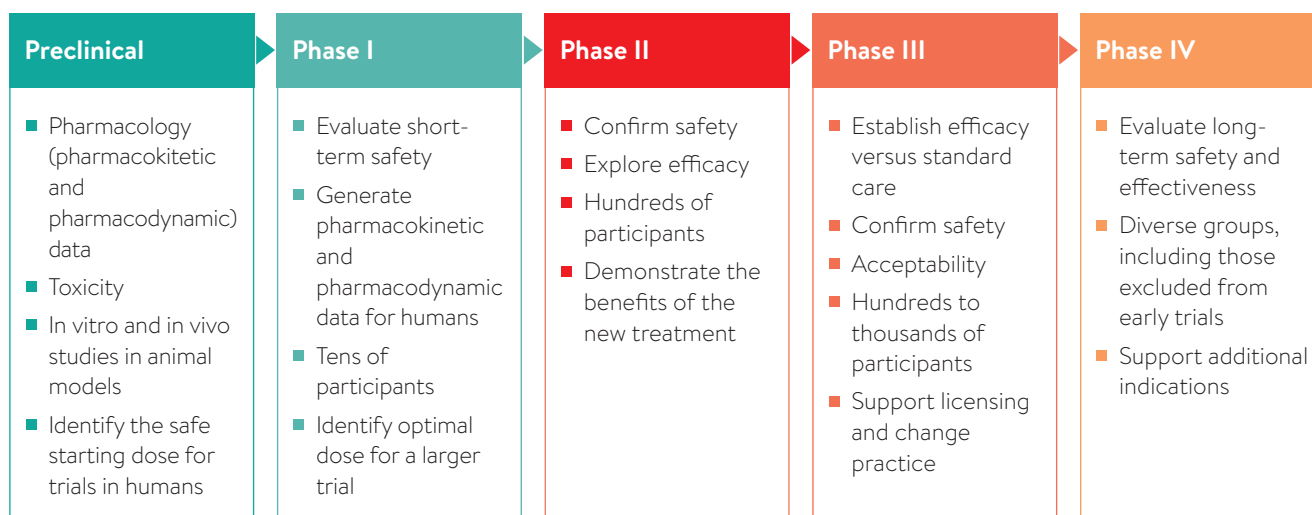
The development and evaluation of ARV drugs for children has historically been slow, with some agents being approved for children as long as a decade after they were approved for adults (1,2). The limited number of agents with age-appropriate ARV drug dosing and formulations for children has remained 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

Preclinical	Phase I	Phase II	Phase III	Phase IV
■ Pharmacology (pharmacokitetic and pharmacodynamic) data ■ Toxicity ■ In vitro and in vivo studies in animal models ■ Identify the safe starting dose for trials in humans	■ Evaluate short-term safety ■ Generate pharmacokinetic and pharmacodynamic data for humans ■ Tens of participants ■ Identify optimal dose for a larger trial	■ Confirm safety ■ Explore efficacy ■ Hundreds of participants ■ Demonstrate the benefits of the new treatment	■ Establish efficacy versus standard care ■ Confirm safety ■ Acceptability ■ Hundreds to thousands of participants ■ Support licensing and change practice	■ Evaluate long-term safety and effectiveness ■ Diverse groups, including those excluded from early trials ■ Support additional indications

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
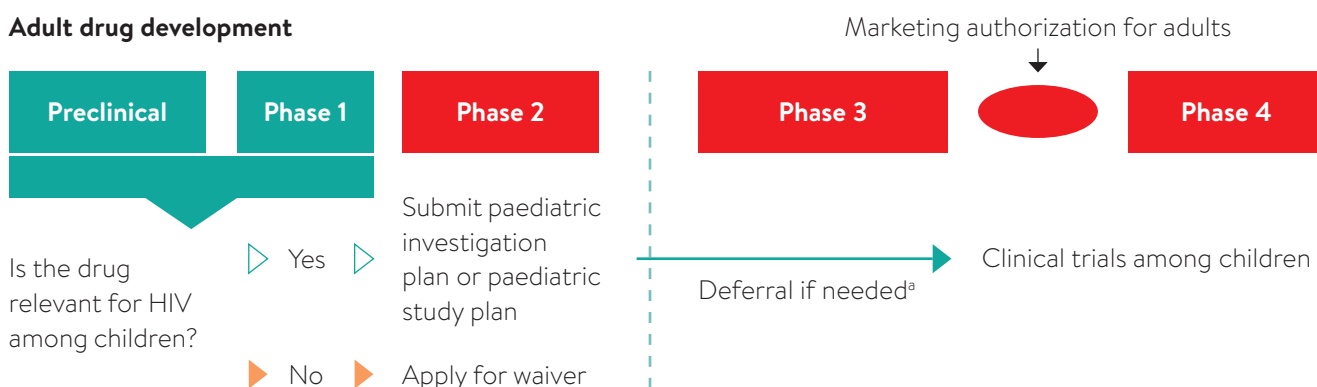
ªAdditional efficacy and safety data for adults are needed before initiating studies among children.
*Source:* reprinted from The Lancet Oncology, 14, Vassal G, Zwaan CM, Ashley D, Le Deley MC, Hargrave D, Blanc P et al., New drugs for children and adolescents with cancer: the need for novel development 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
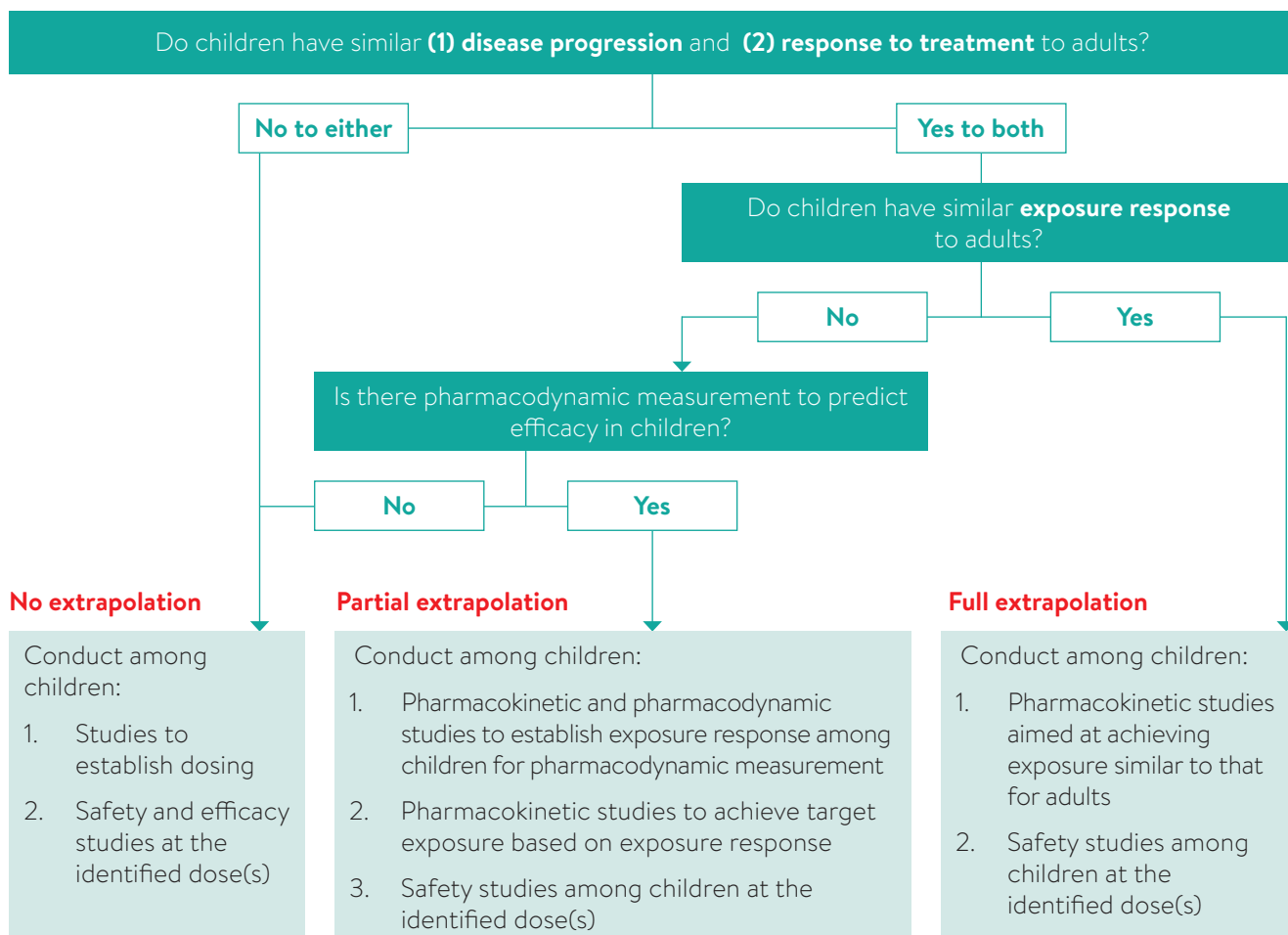
Sources: adapted from General clinical pharmacology considerations for pediatric studies for drugs and biological products: guidance for industry 2014 (4) and Dunne et al. (6).

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
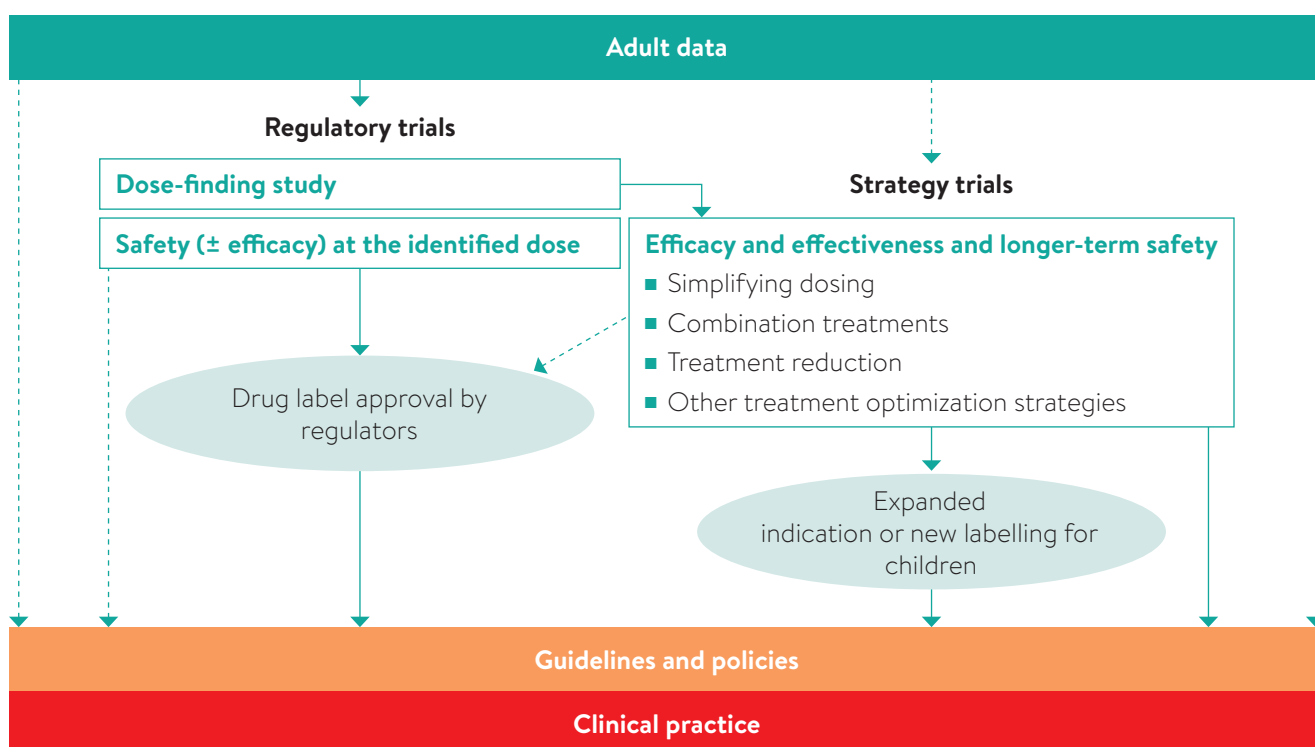
objectives. Primary outcomes answer the most important questions and are measured by the primary endpoints. In trials evaluating drugs, a primary endpoint can be targeted drug exposure parameters, safety outcome (such as the proportion or rate of clinical and laboratory adverse events) or efficacy outcome (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)*.
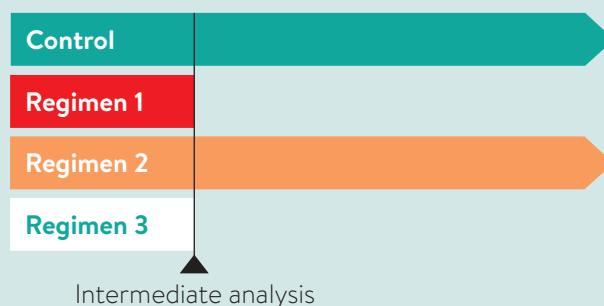
Multi-arm trials (Fig. 1.5)

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 randomczed 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

A. Multi-arm trial

| Control |
| Regimen 1 |
| Regimen 2 |
| Regimen 3 |

B. Multi-arm multistage trial

| Control |
| Regimen 1 |
| Regimen 2 |
| Regimen 3 |

Intermediate analysis

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**
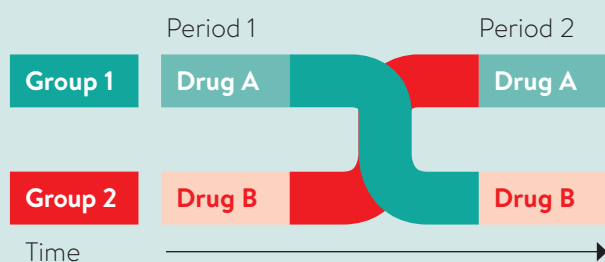
B. Crossover pharmacokinetic study
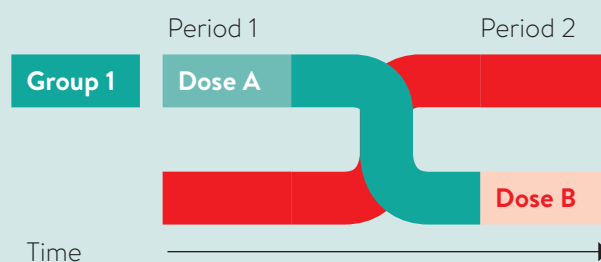
Factorial randomized controlled trials (Fig. 1.7)

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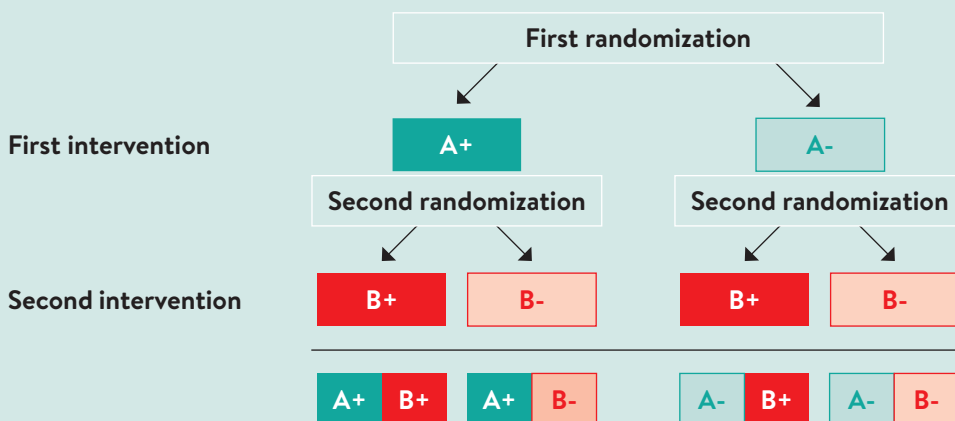
A, B: allocated interventions; +: randomized to receive intervention;
−: randomized to receive standard of care.

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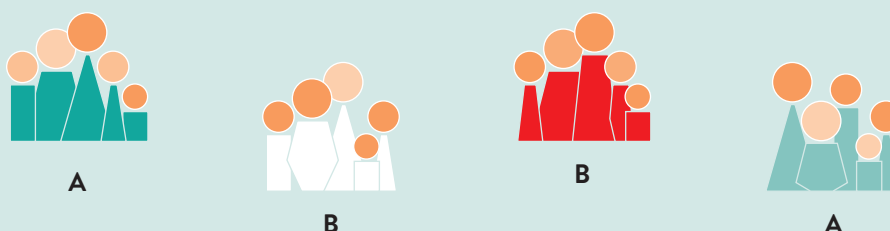
Randomization of groups of individuals (households and communities) rather than individuals.
A, B = allocated interventions

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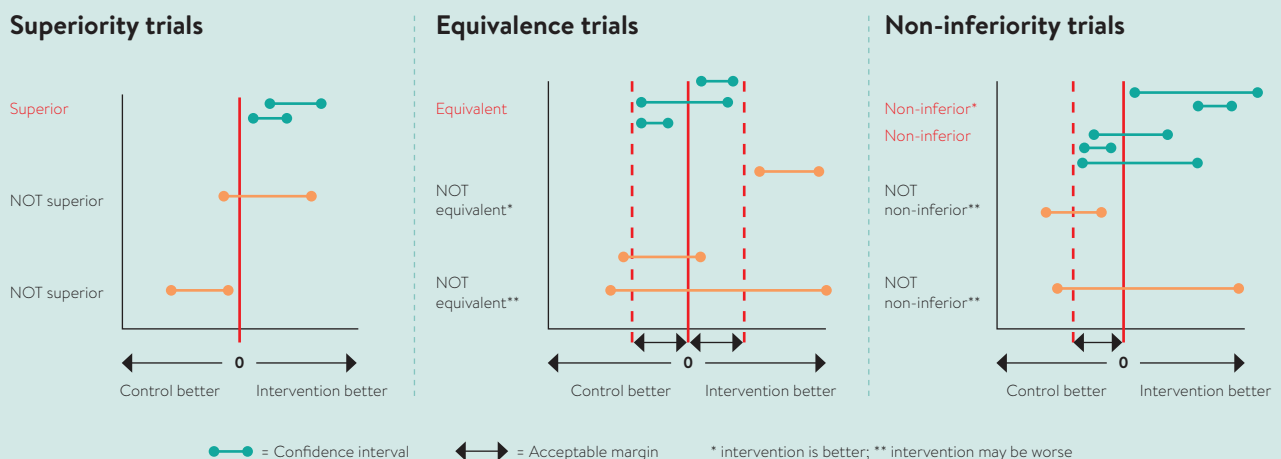
Source: adapted from a personal communication from Elizabeth Chappell, University College London, 2017.

2. CHALLENGES

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

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.

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. Maturational 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 ≥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 coinfected 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)

	IMPAACT P1093	**ODYSSEY**
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 (AUC24 h; primary pharmacokinetic endpoint) and 24-hour plasma concentration (C24 h; secondary pharmacokinetic endpoint)	Treatment failure (clinical or viral) by 96 weeks, estimated using time to the first occurrence of: ■ Insufficient viral response, defined as <1 log10 drop at 24 weeks ■ HIV-1 RNA ≥400 copies/ml at or after 36 weeks, confirmed by next visit ■ Death due to any cause ■ Any new or recurrent AIDS-defining event (WHO stage 4) or severe WHO stage 3 event
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 ■ Treatment failure (clinical or viral) by 48 weeks ■ New resistance mutations ■ Clinical events (new or recurrent severe WHO stage 3 or 4 events and death) ■ Immune recovery (change in CD4 or CD4:CD8 ratio) Safety outcomes ■ Severe adverse events, grade 3 or 4 clinical and laboratory events and events of any grade leading to ART modification 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

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

- 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.
  - 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.
- 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.

7. ACKNOWLEDGEMENTS

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