Optimising research to speed up availability of paediatric antiretroviral drugs and formulations

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Abstract

Globally 1.8 million children are estimated to be living with HIV, yet only 51% of those eligible actually start treatment. The completion of research and development (R&D) for paediatric antiretrovirals (ARVs) is a lengthy process and licensing of new paediatric ARVs continues to lag considerably behind adults. Providing safe, effective, and well-tolerated drugs for children remains critical to ensuring scale-up of paediatric treatment globally. In this manuscript we review current approaches to R&D for paediatric ARVs and suggest innovations to enable simplified, faster, and more comprehensive strategies to develop optimal formulations. Several approaches could be adopted, including enrolment of multiple age-cohorts concurrently and the early introduction of dosing approaches for both single and fixed-dose combination (FDC) drug formulations (preferably scored and dispersible) that match WHO weight-bands. Efforts to speed up development of optimal drugs and formulations for children should focus on a limited number of prioritised formulations. This work should build upon existing partnerships and collaborations to ensure that paediatric investigation plans are developed early in the drug development process but can be modified in a streamlined manner as more information becomes available. In addition, simplified and more efficient mechanisms to undertake R&D need to be put in place, and financing mechanisms must be made more efficient and sustainable. Registration, implementation, and strategic use of drugs should not be seen as a sequential process, with research designed to address multiple questions simultaneously to respond to the needs of HIV-infected children where they live. It is imperative that lessons learned from HIV should be shared to support progress in developing paediatric formulations for other diseases with similar treatment challenges, including tuberculosis and viral hepatitis.

Background

Globally, 1.8 million children are currently estimated to be living with HIV [1], 95% living in sub-Saharan Africa[2]. New World Health Organization (WHO) treatment recommendations state that all children should start antiretroviral therapy (ART) irrespective of their clinical and immunological status, which is set to increase the number of children now eligible for ART[3]. Benefits of early treatment include decreased mortality and morbidity, improved survival, growth and neurodevelopment, and prevention of pubertal and cognitive delays[4]. Yet only half of children eligible for ART globally actually receive it[2] and much more needs to be done to ensure sustainable supplies of effective and well-tolerated drugs for children if we are to successfully scale-up of paediatric treatment to achieve global targets[5] and to ensure sustained virological suppression in HIV-positive children. [2]

HIV treatment research and development (R&D) has been a highly innovative and fast moving area of infectious disease medicine. Innovations have continually been introduced by originator and generic manufacturers that have marketed compounds to maximise efficacy, minimise toxicity and pill burden, and optimise drug sequencing. This has been coupled with important initiatives dealing with intellectual property (IP) that have allowed generic manufacturers to collaborate with originators and engage with reliable production and swift development of fixed-dose combinations (FDCs)[6]. These new formulations have shown to improve rates of adherence compared to separate-pill regimens and have provided programmatic advantages by simplifying procurement and supply management as well as prescribing practices and administration[7,8].

Unfortunately, infants and children have benefited less than adolescents and adults from this progress. Around a quarter of antiretroviral (ARV) medicines and combinations approved by the US Food and Drug Administration (FDA) (12 of 46) or the European Medicine Agency (EMA) (8 of 30) for

adults are approved for use in children below 2 years[9,10]. The decreasing number of new paediatric infections – as a result of major advances in reduction of mother-to-child transmission – has further de-incentivised manufacturers to engage with paediatric drug development, despite ongoing additional need for better drugs for first- and second-line treatment with children needing life-long treatment. Although existing regulatory frameworks have made paediatric drug development a requirement for approval of adult formulations, to date the completion of paediatric R&D plans has been lengthy, slow, and insufficiently streamlined to focus on priority formulations.

While treatment guidelines have strived to recommend the best available treatment for those in need, implementation of these guidelines for children has been challenging for several reasons, including lack of age-appropriate formulations and mis-alignment with preferred regimens for adolescents and adults. The global paediatric community has now established a set of priority formulations to maximise drug efficacy and safety and optimise drug sequencing, and has established platforms to support the different stages of drug development and product introduction.[11] Increasing therapeutic options for children is critical, but it is also important that these efforts remain focused to avoid market fragmentation and promote programme simplification. The establishment of a limited set of optimal formulations is considered important to ensure sustainability of production and effective procurement[12]. The work undertaken as part of the drug optimisation agenda has largely clarified what the urgently needed paediatric ARV formulations are, yet the process from R&D to regulatory approval and availability of medicines in country needs to be accelerated.

In this manuscript we review current approaches to R&D for paediatric ARVs and suggest innovations to enable simplified, faster and more comprehensive strategies to develop optimal formulations that will ultimately support scale-up of treatment for all infants and children living with HIV.

The long road from drug discovery, formulation development, to patients

To date, paediatric drug development has received less attention and funding than drug development targeting adults, resulting in fewer appropriately labelled paediatric drugs and fewer age-appropriate dosage forms. To try to improve the situation, the FDA and the EMA have developed specific regulations to incentivise paediatric drug development. Paediatric assessments have been required and incentivized by the FDA in initiatives beginning in 1994 and codified into law as the Best Pharmaceuticals for Children Act (2002) and the Pediatric Research Equity Act (2003); and both continue to this day[13,14]. In Europe, the Paediatric Regulation entered into force in 2007 requiring all companies seeking drug registration for adults to establish a paediatric drug development programme[15]. The WHO Prequalification Programme does not have specific paediatric regulation requirements but has nevertheless been a critical enabler to introduce paediatric FDCs in countries with the highest burden of disease (Table 1).

Table 1. Key features of Stringent Regulatory Authority (SRAs) requirements to develop paediatric medicines.

Theoretically the PIP in the EU is required to be submitted to the EMA upon availability of adult pharmacokinetic studies, which means at an early phase of a new drug development plan (after phase I). The PSP in the US must be submitted shortly after Phase 2 development when there is preliminary evidence of efficacy in adults. In both regions, at an early stage of the development strategy, direct support and advice from competent authorities can be obtained. In addition, regular monthly teleconferences are taking place between the major stringent regulatory authorities (EU, US with Japan, Canada, Australia) to discuss possible differences of approaches. The EMA and FDA are in fact working to develop 'compatible' paediatric programmes to avoid exposing children to unnecessary trials.

SRAs	Requirements
European Medicines Agency	• All new medicines and fixed-dose combinations (FDCs) developed must have a Paediatric Investigation Plan (PIP) agreed, before the marketing authorisation application is submitted (both for the adult and paediatric population). • A PIP should be agreed even when a marketing-authorisation holder wants to add a new indication, pharmaceutical form, or route of administration for a medicine that is already authorised and covered by intellectual property rights. • As a reward for completing the paediatric development an extension of the drug patent is granted at national level, thus incentivising research and development (R&D) companies to plan early the paediatric developments. • The PIP for a medicine can be modified at a later stage as knowledge increases. Modifications can also be made if the applicant encounters such difficulties with the implementation of a PIP, which render it unworkable or no longer appropriate. • PIP deferrals can be granted. These allow an applicant to delay development of the medicine in children until, for instance, there is enough information to demonstrate its effectiveness and safety in adults. • Waivers can be granted when development of a medicine in children is not needed or is not appropriate, such as for diseases that only affect the adult population.
US Food and Drug Administration	• All new medicines or FDCs must have a Pediatric Study Plan (PSP) agreed upon prior to filing the New Drug Application

	(NDA). Except under specific circumstances, this is required at the end of Phase II development. The PSP outlines the sponsor's paediatric development programme and their plans to request a deferral, waiver, or partial waiver when they file the NDA. • At the time of filing the NDA, the pharmaceutical sponsor can request a deferral of paediatric studies if the drug is otherwise ready for approval and paediatric studies have not been completed. A waiver of paediatric studies can be requested if: 1) clinical trials in one or more paediatric age-groups are determined to be impossible or highly impractical to conduct; 2) there is evidence the drug would be unsafe or ineffective in paediatric patients; 3) the product does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of paediatric patients; or 4) the sponsor can demonstrate that reasonable attempts to produce a formulation necessary for that age-group have failed.
WHO Prequalification Programme	• In close cooperation with national regulatory agencies and partner organisations, the WHO Prequalification Programme undertake evaluation and inspection activities, and build national capacity for sustainable manufacturing and monitoring of quality medicines. • Comprehensively evaluate the quality, safety, and efficacy of medicinal products, based on information submitted by the

	manufacturers, and inspection of the corresponding manufacturing and clinical sites. • Prequalify quality control laboratories of pharmaceuticals and build the capacity of staff from national regulatory authorities, quality control laboratories, and from manufacturers or other private companies, to ensure medicines quality. • The list of prequalified medicinal products has become a vital tool for any agency or organisation involved in bulk purchasing of medicines, be this at country level, or at international level, as demonstrated by the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Drug and formulation development is a sequential process, starting with identifying therapeutic targets, developing screening tools, screening molecules, identifying and optimizing lead compounds before preclinical toxicity evaluations and absorption, distribution, metabolism, and excretion studies. It is only after all these studies have been completed that a drug candidate can be tested in human beings. Phase 1 studies in healthy volunteers examine pharmacokinetics (PK)/short-term safety and Phase 2 studies in HIV infected individuals and continue to evaluate dose-finding, longer term safety, and preliminary evidence of efficacy. It is generally only at this stage that paediatric drug development is envisaged, with the design of a Paediatric Investigation Plan (PIP) and/or a Paediatric Study Plan (PSP) and its submission to stringent regulatory authorities (SRAs), the FDA, and the EMA. EMA PIPs are usually submitted at the end of the Phase I study, FDA PSPs are submitted at the end of Phase II.

The way paediatric FDCs of ARVs have historically been developed – with the aim of improving adherence in children and simplify procurement and supply – requires multiple stages with barriers translating into serious delays. The process, as illustrated in Fig 1, typically included starting with investigating a new single-agent drug in an age-staggered (ie. testing a drug in an older age cohort, then sequentially moving to the next lower age cohort) dose-finding and safety study supported by extrapolation of efficacy from adult trial data that would allow SRA approval typically obtained in an age-staggered fashion. For inclusion in global treatment guidelines, the drug would ideally be used in studies to explore efficacy compared to a standard of care where possible, and then introduced in treatment guidelines using a weight-band dosing algorithm. PK and clinical data for all component drugs in a proposed FDC would need to be modelled and validated to identify optimal drug ratios, after which the FDC could then be formulated. The candidate FDC formulation would then require bioequivalence testing and complete stability data in order to obtain regulatory approval and in country registration for final market introduction.

Fig 1: Development and introduction of fixed-dose combinations (FDCs) for children living with HIV.

A number of issues merit consideration. While an age-staggered approach to paediatric drug development was intended to protect the youngest children from potential additional toxicity or lack of efficacy that may result from known or unknown differences in drugs absorption and metabolism, there is no rationale for having a fully age-staggered approach based on the existing age bands (12-18 years, 6-12 years, 2-6 years, 4 weeks to 2 years, birth to 4 weeks). Most differences (from adults and older children in weight-adjusted dose or surface-area-adjusted dose) are confined to neonates (birth to 4 weeks) and in infants and young children (4 weeks-2 years). This is due to developmental differences in the physiologic processes underlying drug absorption, distribution, metabolism, and excretion,[16] and developmental changes in diet and feeding pattern. As a result, drug dosing

regimens for neonates and young infants often cannot be extrapolated from those used in older children and adults but must be developed based on further age-specific PK data.[17] When appropriate formulations are not developed early enough in the drug development plan, this can have a particular impact on the timeline for drug approval across the age spectrum, and ultimately affect introduction of critical therapeutic options in treatment guidelines.

For simplification and ease of implementation, the WHO has established paediatric ARV doses expressed per weight-band rather than per kilogram or per square metre of body surface area[18]. The approval of drug dosing, which optimises drug exposure for the individual but does not consider weight-band dosing recommendations, can generate a critical mis-match between the SRA-approved drug label and the ultimate use of the drug. As a result, pragmatic recommendations based on WHO weight-bands require an additional step to validate those dosing recommendations. The validation of weight-band dosing should preferably be supported by data; however, conducting such studies in the population of interest can be challenging and they are often undertaken as sub-studies of larger treatment strategy studies that may have long timelines for completion.

Another key challenge is our ability to conduct studies in the target population. As maternal ART is scaled up and the number of new HIV infections progressively decrease, enrolment of infants and children in drug trials will become more difficult, particularly when particular indications are sought (ie, drug naive, class-naïve, or treatment-experienced patients). In addition, studying a drug when there is no intention by policy-makers to prioritise it and support its market introduction may also present an ethical concern that ethics review boards may need to consider, further limiting the ability to recruit patients into studies in a timely manner.

Combining multiple drugs in a single formulation can be challenging because of compound compatibility, solubility, stability, absorption characteristics, pharmacokinetics, or palatability. As in

the case of a lopinavir and ritonavir (LPV/r) paediatric solid co-formulation, additional biopharmaceutical development to verify the compatibility of the separate drugs, their joint stability, taste evaluation, dissolution, as well as phase 1 bioequivalence studies, were required.

Finally, individual drug dosing recommendations may not be suitable for simple ratio and dosing across all weight or age-groups and merging existing datasets to undertake PK modelling may be required. In addition, generic manufacturers engaging with the development of formulations need to undertake bioequivalence studies and demonstrate that the same quantity of active ingredients leads to the same drug exposure as that of the originator product (or products) of reference (i.e. show bio-equivalence). The lack of a reference product against which to compare bioequivalence requires comparison with originator products such as paediatric liquid formulations, which may not have comparable bioequivalence to solid formulations (eg. 3TC liquid and dispersible tablets; or LPV/r liquid and solid formulations). This has led to additional complexity and further delays in gathering the data required to develop and approve a new formulation of one or multiple ARVs.

Opportunities for change

Certain diseases such as diabetes or asthma have specific characteristics in adults or children and treatment efficacy may differ in the two populations. By contrast, treatment of HIV and other infectious diseases is based on anti-infectives directed against the specific pathogen and often the same treatment outcomes are expected irrespective of the subpopulation considered, provided that drug exposure lies within the therapeutic range established in adults. For this reason, extrapolation of efficacy from adult drug trials has informed ART treatment guidelines to manage children living with HIV.

In this context, fully powered phase III efficacy trials for ARVs in children are unlikely to be needed. However, dosing and safety remain of paramount importance and innovative approaches can be adopted to speed up generation of the necessary data. For instance, phase I and II safety and dose-finding trials included in PIPs and PSPs – that have been historically conducted in an age-staggered approach, as requested in the past by regulators such as EMA[19] – could be expedited and happen simultaneously for all children older than 2 years. In addition, if there are no specific clinical concerns this could even occur from 4 weeks of age. Importantly, this depends upon developing age-appropriate formulations and assessing drug exposure early in the drug development life cycle, rather than at a later stage in the drug development plan after the adult development is complete.

As age is de-emphasised in the design of such trials, opportunities arise to directly explore dosing schedules based on weight bands. Enrolling subjects based on weight-band strata in initial paediatric PK trials, provided that adult data support this approach, would enable generation of PK data that directly inform the use of the drug according to WHO weight-bands and would remove the need to conduct PK and clinical studies to validate dosing schedules developed post-hoc.

Obtaining good quality pharmacokinetic data is crucial to determining appropriate dosing and to inform the optimal ratio to enable development of FDCs of existing drugs[20]. Regulators recognise that PK data, which demonstrates similar drug exposure to that observed in adults, can be used to extrapolate clinical efficacy under certain conditions and – to a certain extent – safety in paediatric patients[21]. Differences in patient physiology can influence the concentration of drug within the plasma or tissue, but the most noticeable differences have been reported in neonates and children younger than 2 years. For these reasons, a number of innovative approaches should be encouraged to speed up enrolment and generation of critical information to inform drug development (Fig 2). These approaches could include:

1. PK modelling to develop FDC of approved drugs: WHO gives preference to recommending age-appropriate FDCs for any regimen for children if such a formulation is available. To develop FDCs of approved drugs PK modelling should be used. The Paediatric Antiretroviral Working Group (PAWG) has put forward weight-band dosing of EFV/ABC/3TC FDC for children 3-10 years of age based on PK modelling which has received preliminary FDA support[22].

2. Investigate the washout period from maternal ARVs to inform PK studies for the first days of life: The neonatal period is the most challenging from the PK perspective and only five ARVs are currently FDA approved for use in neonates less than 14 days of age. Because very early diagnosis and treatment is recommended there is a need for more research on ARVs for neonates. Research should be done in newborns to study the washout PK and safety of ARVs given to the mother during pregnancy and labour. Such data would then inform dosing that would be studied in a formal PK study of this age-group. The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1097 was designed to describe the washout PK and safety of *in utero*/intrapartum exposure to raltegravir in full-term neonates born to HIV-infected pregnant women who received raltegravir-based ART during pregnancy[23]. A similar study is planned for dolutegravir.

Fig 2: Strategies to innovate research and speed up collection of critical data to develop and introduce paediatric drug and formulations more rapidly

Nevertheless, there may be instances where there is a strong rationale for conducting efficacy trials, for example in a subset of the population with specific characteristics such as neonates and older infants who have typically high viral load counts, who rapidly progress to AIDS, and whose resistance profile may be affected by exposure to maternal ARVs. Given that recruitment of such a trial population would be extremely difficult, there is a need to use innovative trial designs[24]. Some

efficiency could be gained by adopting alternative study designs (Table 2). Multi-arm multi-stage (MAMS) designs for examples offer the opportunity to adapt trial and/or enrolment procedures after its initiation without undermining the validity and integrity of the trial[25]. Adaptations could include adaptive randomisation, sample size re-estimation, dose-finding design, or comparator drug regimen. Bayesian trials offer the opportunity to substantially decrease the number of children required by using existing evidence to make a priori assumptions about likely outcomes.[26] Factorial trials allow for the investigation of a number of questions within a single trial, and could be a useful approach.

Table 2: Innovating trial designs to increase efficiency of clinical efficacy trials for paediatric treatment

Multi-arm multi-stage (MAMS) designs: these offer the opportunity to adapt to trial and/or enrolment procedures of the trial after its initiation without undermining the validity and integrity of the trial. The purpose is to shorten the development process (speed) without compromising the safety and efficacy of the drug product under investigation (validity) by maximising the power for identify best clinical benefit of the drug product under investigation with limited number of subjects (efficacy)5. This approach was used to develop a child-friendly fixed-dose artemisinin combination therapy (ACT) of pyronaridine and artesunate (Pyramax)[27].
Bayesian trials: these offer the opportunity to substantially decrease the number of children required by formally leveraging the evidence available. This approach is particularly efficient when assessing the effect of therapeutic agents on a rare event. The PHPT-5[28] trial investigated the effected of enhanced postnatal prophylaxis in children at high risk of mother-to-child transmission. A meta-analysis of all perinatal prevention trials done in the same populations was performed (n= 3965) and intrapartum transmission modelled to generate initial transmission probabilities in high-risk children with and without an enhanced postnatal prophylaxis. During the following prospective

trial where children at low risk of transmission received no postnatal ARV intensification and children at high risk (per partum detectable via maternal viral load) received postnatal intensification, initial transmission were updated and the study stopped after inclusion of 88 high risk infants with no intrapartum transmission. The modelled posterior Bayesian transmission probability in high-risk infants receiving single-drug prophylaxis was 2% (95%CI: 0.3%-5.2%) whereas it was 0.4% (95% CI: 0.1%-1.4%) in children receiving 3-drugs prophylaxis. The probability of superiority of intensification over single drug prophylaxis was 94% and that of at least a 2-fold reduction of risk was 83%.[29 30 31]
Factorial design: these trials allow investigation of a number of questions at the same time and maximise the amount of data collected as a result of a randomised trial. The ARROW trial was a 5-year trial conducted in Uganda and Zimbabwe and had a number of randomisations. The key initial randomisations were to three different first-line regimens and, in a factorial design, to two monitoring strategies. An opportunity was taken in this long-term trial to add two further randomisations: to once versus twice daily dosing of abacavir and lamivudine and to stop or continue cotrimoxazole. Finally, a number of PK sub-studies were undertaken within the trial thus maximising efficiency.

Fig 3. Translating Novel Approaches: Potential Immediate applications to the development of DTG/TAF/FTC

Experts agree that DTG/TAF/XTC represent the most promising combination for an optimised paediatric first-line regimen across all age-groups and weight bands. This regimen could also align with that for adults, but there are a number of steps and barriers before it will be available as a child-friendly fixed-dose combination (FDCs). DTG is currently under evaluation

in IMPAACT P1093, an ongoing phase I and II, multicentre, open-label, pharmacokinetic (PK), dose finding and safety study of DTG plus optimised background regimen in infants, children, and adolescents. This evaluation takes a staggered approach with de-escalated, age-defined cohorts. ODYSSEY (PENTA 20) is a phase II and III randomised non-inferiority trial that will compare once daily DTG plus two NRTIs to standard therapy. This is a multi-country study in 700 children aged 18 years or younger either starting first-line (n=310) or switching to second line ART (n=390). The primary endpoint is time to virological failure (>400 copies/mL) over 96 weeks and it will include a substudy to confirm the DTG dose with concomitant rifampicin-containing TB treatment. These two trials should be able to capture enough PK and clinical data to inform weight-band dosing using the existing dosage strengths.

Tenofovir alafenamide fumarate (TAF) is approved by FDA and the EMA as part of an FDC containing elvitegravir/cobicistat/emtricitabine/TAF (E/C/F/TAF) for adolescents aged 12 years and older weighing at least 35 kg. This study is ongoing in treatment-naive children and adolescents aged six to18 years.[8] TAF is also being studied in paediatric patients as a co-formulation with FTC in a phase 2/3 switch study. Children and adolescents aged 6 to 18 years will switch their current NRTI-containing regimen to F/TAF (while continuing on their third antiretroviral agent) for 96 weeks. A TAF study in infants and children aged 4 weeks to 6 years is planned but at present there is no clear timeline. Reduced dose tablets and a non-solid formulation are in development.

Furthermore, in the context of serving different populations and ensuring that the formulations are targeted to the population with the highest burden of the disease, acceptability and feasibility of the formulations are critical elements to assess from the early steps of formulations development and to potentially require in dose finding and safety trials. Ensuring that acceptability data are robust without adding another layer of complexity is an important goal that needs to be more fully explored.

Continuing to promote innovations

Long-acting formulations and alternative drug-delivery systems such as implants or pouches, should be considered when developing a long-term vision for treating infants, children, and adolescents living with HIV. In addition new treatment strategies ought to be explored with the goal of

optimising the drug sequencing of drugs in the context of limited options for this life-long treatment required by patients.

Existing regulatory frameworks promote development of paediatric formulations, but implementation of those frameworks has resulted in delays and inefficient allocation of resources, with R&D investments channelled towards formulations that are not expected to meet the needs of the population of interest. As of November 2014, of the 22 PIPs submitted to the EMA, only five were considered priority formulations according the PADO priority list[32]. In addition, the success in preventing mother-to-child transmission has reduced the number of new HIV infections, making it increasingly challenging to conduct robust clinical studies to assess all new paediatric drugs and FDCs across the age spectrum, particularly in infants and young children.

For these reasons, in order to ensure the sustainability of new approaches to develop new paediatric drugs and formulations, there is an urgent needs to develop alternative financing mechanisms that build upon existing regulatory processes, optimise the investment in paediatric ARVs, maximise the paediatric expertise available in the HIV community, and enable a more sustainable development of prioritised products. Approaches that focus regulatory requirements on unmet paediatric needs can free resources to support the development of priority formulations. This requires promoting an open dialogue between manufacturers, policy makers, research networks, regulatory agencies, and other relevant stakeholders. Assessing feasibility and developing concrete next steps to innovate financing of paediatric R&D must be explored, leveraging the political commitment generated by the adoption of a specific resolution on paediatric medicines during the most recent 69th World Health Assembly[33].

It is worth noting too that the challenges of paediatric drug development for HIV are similar challenges to other infectious diseases that are common in low- and middle-income countries –

including, tuberculosis[34 35], malaria[36], and viral hepatitis[37]. For these other priority diseases, drug optimisation principles should also be used to target R&D efforts. The lessons learned from the rapidly evolving field of HIV treatment should be used to ensure that neonates, infants, and children are not left behind.

Conclusions

As the global community strives to reach ambitious treatment goals for HIV[5], with the aim of ensuring 90% of all HIV positive people globally are receiving sustained ART by 2020, providing the right medicine to children remains a critical imperative for policy makers as well as for the research community. Meeting global treatment targets will require new ways to develop the most potent and tolerable drugs in formulations that are appropriate for infants and children living with HIV.

While the knowledge and the framework to develop paediatric drugs and formulations are available, with important progress made over the last decade, new efforts are clearly needed to accelerate development of optimal drugs and formulations for children. In an era when a new drug such as dolutegravir is approved by SRAs in 2014, included in WHO guidelines in 2015, and is expected to become available for adults in low- and middle-income countries via generic production at the end of 2016, the substantial delays in paediatric formulations development and introduction are now unacceptable. Furthermore, life-long daily triple ART cannot be our goal for children living with HIV: innovative delivery mechanisms as well as new therapeutic strategies need to be investigated.

The research community can play an essential role by driving innovations with rigorous but simplified approaches. The simultaneous enrolment of different age cohorts, the investigation of WHO-weight band dosing in any paediatric development plan, the concomitant assessment of

acceptability and feasibility while products are developed, and the use of PK modelling to inform dosing as well as a more efficient study designs, are all innovations that have the potential to speed up the generation of the evidence required to inform development and introduction of the most optimal formulations. Registration, implementation, and strategic use of drugs should not be seen as a sequential process, and research should be designed to address multiple questions simultaneously to respond to the needs of HIV-infected children where they live. This will mean anticipating the future challenges posed by selection of HIV drug resistance and the programmatic reality as well as the shifting landscape of the HIV epidemic.

These innovations will have to occur as part of a strategic and pragmatic approach to product prioritisation that takes into account the programmatic reality. They must acknowledge the constraints of the exiting regulatory framework as well as the lack of incentives for manufacturers to develop paediatric formulations. Efforts should focus on a limited number of optimal formulations and build upon existing partnerships and collaborations to ensure that PIPs are developed from the early stage in consultation with the scientific community, that simplified and more efficient mechanisms to undertake R&D are put in place, and that the knowledge and the enrolment capacity of existing research networks is maximised. It will be vital that we ensure collaboration and coordination between research community, pharmaceutical companies, regulators, and policy makers. This will require the funding and the political will to keep paediatric development outside of current market dynamics and to develop innovative financing mechanisms that can be sustained over time.

Declaration of interest:

MP and NF are staff member of the WHO; ASR is employed EMA, which reviews all new HIV medicines in the European Union; EJA has participated in advisory boards for Merck and ViiV, PR is running trials sponsored by ViiV and Gilead.

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Figure

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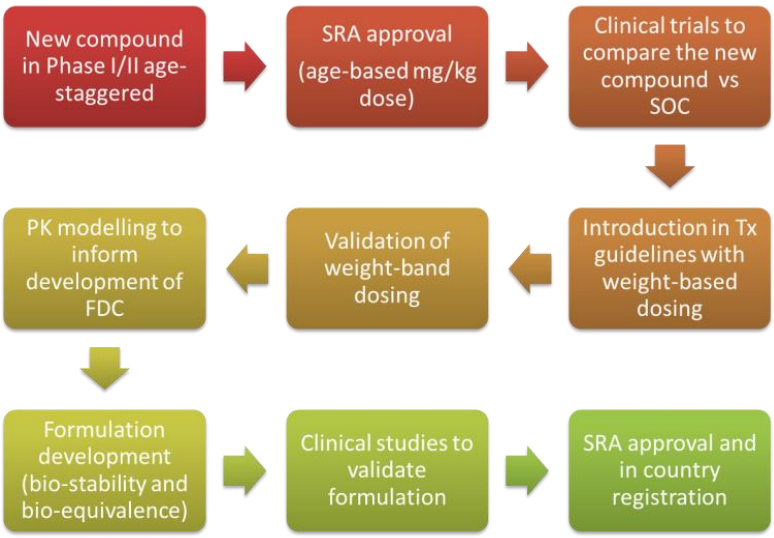

Figure

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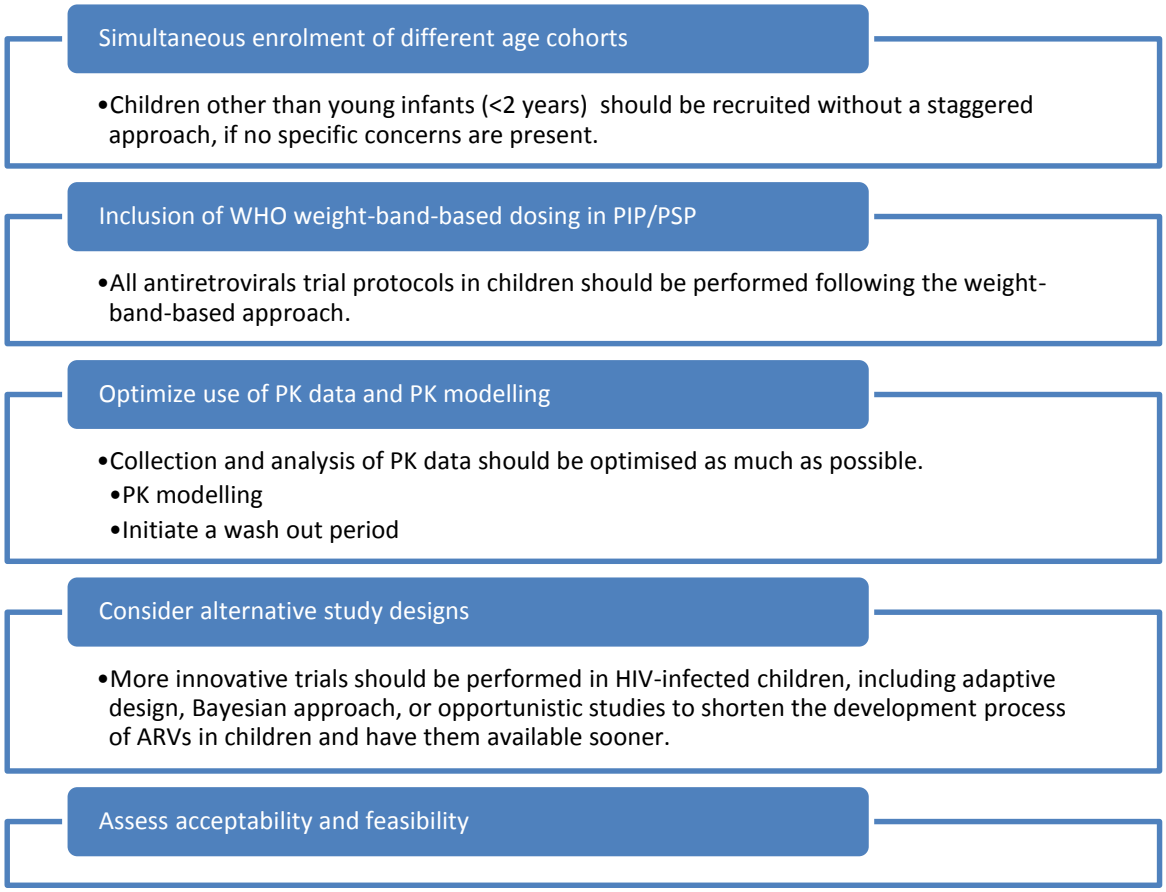

Figure

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