Prioritising the most needed paediatric antiretroviral formulations: the PADO4 list

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Despite considerable progress in paediatric HIV treatment and timely revision of global policies recommending the use of more effective and tolerable antiretroviral regimens, optimal antiretroviral formulations for infants, children, and adolescents remain limited. The Paediatric Antiretroviral Drug Optimization group reviews medium-term and long-term priorities for antiretroviral drug development to guide industry and other stakeholders on formulations most needed for low-income and middle-income countries. The group convened in December, 2018, to assess progress since the previous meeting and update the list of priority formulations. Issues relating to drug optimisation for neonatal prophylaxis and paediatric treatment, and those relating to the investigation of novel antiretrovirals in adolescents and pregnant and lactating women were also discussed. Continued focus on identifying, prioritising, and providing access to optimal antiretroviral formulations suitable for infants, children, and adolescents is key to ensuring that global HIV treatment targets can be met.

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Introduction

Despite considerable progress in scaling up HIV services for children, we are still far from reaching global treatment targets. In 2018, only 52% of children living with HIV received antiretroviral therapy (ART), and more than a third of those on treatment received suboptimal regimens and formulations.[1,2] HIV viral suppression in infants (<1 year), children (1–10 years), and adolescents (10–19 years) on ART is consistently lower than in treated adults.[3] The 2019 WHO guidelines[4] recommend more potent and tolerable ART regimens for treatment of infants and children, but, as of 2019, optimal formulations to deliver those regimens across the entire age spectrum, from birth through to adolescence, are still lacking. In addition, substantial gaps in the investigation and use of existing and novel antiretroviral drugs for treating adolescents and pregnant and lactating women exist.[5]

Over the past few years, global stakeholders have come together to enable more focused and coordinated actions to accelerate the availability of optimal age-appropriate formulations for infants, children, and adolescents living with HIV.[6] Several initiatives and diverse work streams have been gathered under the collaborative platform of the Global Accelerator for Paediatric formulations (GAP-f).[7] The work of GAP-f takes identified priority formulations through the entire life cycle of the product by facilitating key steps to investigate, develop, and introduce the most needed paediatric medicines. The WHO-led Paediatric Antiretroviral Drug Optimization (PADO) group establishes and reviews medium-term and long-term priorities for drug development, and sets the foundation for GAP-f in the areas of paediatric HIV treatment and prevention.[7] Since its inception in 2013, PADO has provided an evidence-based list of priority products and a clear and consistent message to guide industry and interested stakeholders on the formulations most needed in low-income and middle-income countries (LMICs).[8] This list has eliminated several unnecessary formulations and continues to be an essential tool to focus efforts and resources.[9,10]

In December, 2018, WHO convened a fourth meeting on paediatric drug optimisation, PADO4, to assess the progress made, evaluate current and future needs, and further advance the paediatric and adolescent antiretroviral optimisation agenda.[11] This meeting sought to review the list of medium-term and long-term priorities for paediatric antiretroviral drug and formulation development and to identify gaps in research for HIV, as well as for prevention and treatment of HIV-associated infections. The group also discussed how to develop a better mechanism to accelerate access to suitable novel treatment strategies and address delays and gaps remaining in the investigation of new antiretroviral medicines in adolescents.[12]

PADO4 also provided an opportunity to review gaps and challenges in investigating antiretrovirals in pregnant and lactating women, with the goal of identifying key principles to guide more targeted and accelerated generation of critical data. These data could be used to increase access to safe and effective antiretrovirals for this population and in alignment with the treatment optimisation vision established for adults.[13]

These discussions had direct input from the community of people living with HIV and offered the opportunity to use their experiences and knowledge experiences to enhance community input throughout the process of drug development, including during design and conduct of clinical trials. Such input is key to ensuring that the needs of people living with HIV at all stages of life are understood and factored into decisions relating to the development and optimisation of antiretroviral regimens and formulations.

PADO4 meeting

PADO4[8–10] was convened by WHO on Dec 10–12, 2018, in Geneva, Switzerland. PADO4 participants were identified from existing WHO expert advisory groups (ie, Paediatric

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Antiretroviral Working Group, Adult Antiretroviral Working Group, and HIV Drug Resistance Network-ResNet) and from established partnerships in the area of antiretroviral drug optimisation (ie, GAP-f, Paediatric HIV Treatment Initiative, and Antiretroviral Procurement Working Group), and from HIV programmes in countries with high burden of paediatric HIV, such as Kenya, Malawi, Mozambique, South Africa, and Zimbabwe. PADO4 participants represented more than 15 countries and included paediatric HIV researchers, clinicians, programme managers, regulators, and other stakeholders involved in developing and introducing paediatric antiretrovirals in LMICs.

During plenary sessions, the group reviewed emerging evidence on paediatric antiretrovirals with a detailed summary of the literature, which was updated before the meeting. Information was also obtained on studies in progress and submissions received from pharmaceutical companies with ongoing paediatric antiretroviral development plans. Four work group sessions were organised to allow review of the PADO list and in-depth discussions of specific domains to be considered for prioritisation. These domains included consideration of pharmacokinetics and safety, potential drug interactions, opportunity for harmonisation with adult regimens, ease of administration, palatability, pill burden, and dosage flexibility. Three separate sessions were dedicated to discussing pregnant and lactating women, adolescents, and HIV-associated infections. Recommendations were formulated after discussion in breakout sessions and with the support of a prioritisation tool developed by the Clinton Health Access Initiative,[14] which was piloted for the first time at the meeting. Consensus was reached in plenary discussion.

Investigation of paediatric antiretrovirals

The newly developed four-in-one, taste-masked, granule formulation of abacavir, lamivudine, lopinavir, and ritonavir, with approval expected for infants from the age of 4 weeks, holds promise, particularly for very young children, because of better palatability and easier administration than available formulations.[15] This formulation is expected to receive regulatory approval and be available in countries in mid-2020.

Since the last PADO meeting in 2016, dolutegravir, an integrase inhibitor, has been approved for children aged 6 years and older (weighing at least 30 kg [US Food and Drug administration] or 15 kg [European Medicines Agency]) with paediatric 10 mg and 25 mg oral film-coated tablets and adult 50 mg oral film-coated tablet. Dolutegravir dosing for infants and young children is currently being studied across the paediatric age and weight spectrum from the age of 4 weeks in the International Maternal Paediatric Adolescent AIDS Clinical Trials (IMPAACT), P1093 trial (NCT03016533, with novel paediatric dispersible 5 mg tablets. The ODYSSEY trial (NCT02259127) is investigating a simplified dosing approach, including the extended use of adult 50 mg tablets for older children, and has informed the dosing currently recommended by WHO for children weighing more than 20 kg.[16] Finally, with full approval in November, 2017, for use of raltegravir in newborn babies at term, an integrase inhibitor option is now available for use in the first 4 weeks for life.[17] Raltegravir is available as a dispersible granule formulation in 100 mg packets requiring multistep administration including reconstitution in water, measuring specified small volumes with different size syringes, and frequent dose escalation during the first weeks and months of life. Considering the complexity of raltegravir administration, countries opting to introduce this product are advised to monitor their programmes carefully, assessing feasibility and outcomes and sharing their experiences more widely.

Several other antiretrovirals, already introduced in adult HIV treatment practice, are under investigation in adolescents and children. Some tenofovir alafenamide-containing fixed-dose combinations are approved for adolescents weighing 25 kg or more, at adult doses, and are also being investigated in phase 2 and 3 studies in children. Approval of tenofovir alafenamide dosing in children weighing 15–25 kg and less than 15 kg is expected by 2020 and 2021, respectively. Finally, doravirine, a novel non-nucleoside reverse transcriptase inhibitor (NNRTI), was approved for use in adults in August, 2018, and a trial in adolescents is underway (IMPAACT 2014, NCT03332095).

Programmatic reality in paediatric antiretroviral treatment

By contrast with the progress made in optimising treatment regimens for adults, children remain underserved in most treatment programmes, in which far too many children continue to receive suboptimal treatment with a fixed-dose combination of nevirapine, zidovudine, and lamivudine because of its low cost and ease of administration. Documentation of high levels of pre-treatment NNRTI resistance in several sub-Saharan African countries,[18] with up to 60% of children resistant to nevirapine, continues to raise important concerns about the efficacy of NNRTI-based regimens in children. These data correlate with the poor viral suppression consistently documented in population-based surveys.[3] Moreover, despite WHO recommending ritonavir-boosted lopinavir-based ART regimens for infants and young children since 2013, implementation of this recommendation has faced multiple challenges, including unpalatability and cold-chain requirements for ritonavir-boosted lopinavir syrup and inadequate supplies of heat-stable pellets, or challenges with administration and palatability, in programmes in which pellets were introduced. In study settings, implementation of ritonavir-boosted lopinavir pellets has been associated with a reasonably high proportion of children achieving a

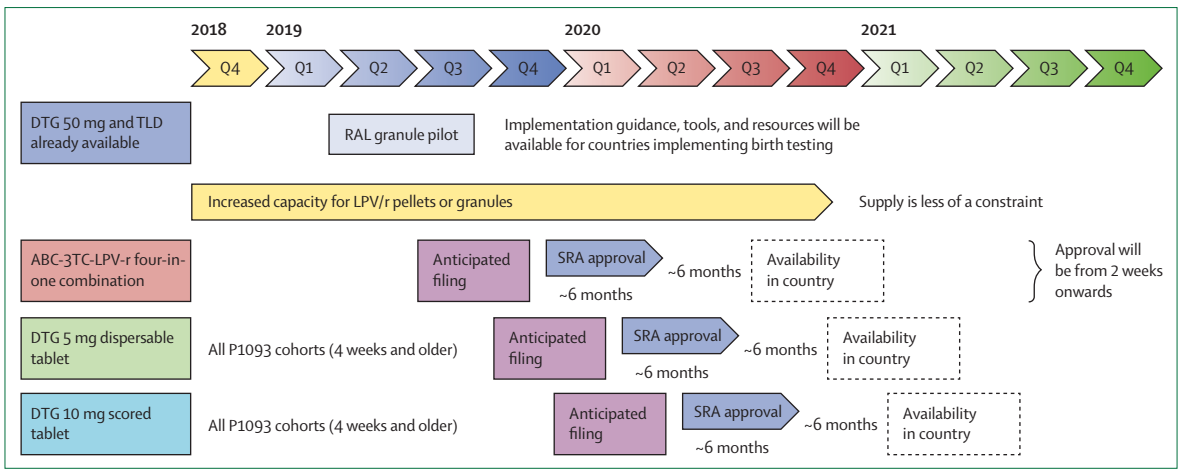

Figure: **Anticipated timelines for approval, introduction, and roll-out of new antiretrovirals (2019–2021)**
DTG=dolutegravir. TLD=tenofovir, lamivudine, and dolutegravir. RAL=raltegravir. ABC=abacavir. 3TC=lamivudine. LPV/r=lopinavir and ritonavir. SRA=stringent regulatory authorities.

viral suppression whereas lower rates of suppression have been reported among children on pellets in routine clinical service programs.[19] Administration of and adherence to ritonavir-boosted lopinavir pellets seems to be more challenging than expected and viral suppression has been somewhat lower in younger children than the rest of the children initiating this ART. Sites using the formulation as part of routine care programmes report similar viral suppression as with the use of ritonavir-boosted lopinavir syrup as a result of administration and palatability issues.[20]

Despite challenges with implementing the treatment regimens newly recommended by WHO, several countries are taking concrete steps to update their national formularies and increase access to optimal formulations. As of December, 2018, ten countries had agreed to introduce dolutegravir for children, according to the WHO recommended dosing, and to phase out nevirapine-based regimens by increasing use of ritonavir-boosted lopinavir solid formulations. Supply issues around existing ritonavir-boosted lopinavir pellets and the 2018 approved ritonavir-boosted lopinavir granules (10 mg ritonavir with 40 mg lopinavir sachet) are expected to be resolved from January 2020, following increased generic production. In addition, approval and full commercialisation of dolutegravir 10 mg scored dispersible tablets for younger children (weighting less than 20 kg) is expected by the end of 2020, with a dispersible fixed-dose combination containing dolutegravir, abacavir, and lamivudine becoming available thereafter (figure).

In this context, progressive consolidation of demand for a limited number of regimens containing either ritonavir-boosted lopinavir (for children weighing less than 20 kg) or dolutegravir (for children weighing more than 20 kg) in combination with an abacavir and lamivudine dispersible fixed-dose combination is likely to characterise paediatric treatment programmes over the next few months and years. This will enable infants, children, and adolescents to access more effective regimens and dramatically simplify programmatic scenarios resulting in more predictable demand and more reliable supply of paediatric formulations. However, we anticipate a future where failure of dolutegravir, abacavir, and lamivudine in children living with HIV will require a new line of treatment that might need to optimise available antiretrovirals without knowledge of treatment history. Whether a combination of dolutegravir and ritonavir-boosted darunavir with nucleoside reverse transcriptase inhibitor (NRTI) or without NRTI, or ritonavir-boosted darunavir in combination with an NRTI backbone (potentially recycled), would be appropriate in such scenarios needs to be evaluated.

Panel 1: Fourth meeting on Paediatric Antiretroviral Drug Optimization (PADO4) priority and watch lists

PADO4 priority list: medium-term, 3–5 years

- DTG/3TC/ABC (5/30/60 mg dispersible)*
- DTG (10 mg scored dispersible)
- DRV/r (120/20 mg)*
- DTG/XTC/TAF
- XTC/TAF

PADO4 watch list: products of potential interest for paediatric treatment in the longer term

- Broadly neutralising antibodies
- Long acting or extended release parenteral formulations
- Novel delivery technologies
- Doravirine
- MK-8591

3TC=lamivudine. ABC=abacavir. DRV=darunavir. DTG=dolutegravir. TAF=tenofovir alafenamide. XTC=lamivudine or emtricitabine. *Dosing and ratio are endorsed/recommended by the Pediatric Antiretroviral Working Group.

Panel 2: **Paediatric Antiretroviral Drug Optimization research priorities**

Research priorities to inform development and optimal use of antiretroviral drugs in children and adolescents

Drugs and formulations

- New delivery technologies (eg, patches, implants, injectables)
- Long-acting formulations (eg, oral, injectable)
- Adult doses in children (eg, dolutegravir 50 mg for children weighing less than 25 kg)
- Tuberculosis-HIV trials: include pharmacokinetic studies in all ongoing trials to gather data in children that acquire tuberculosis while in studies
- Malnutrition (pharmacokinetic and pharmacodynamic data)
- Long-term safety and efficacy (tenofovir alafenamide, dolutegravir)
- Coinfections (hepatitis C virus)

Sequencing strategies

- Future third line: dolutegravir and darunavir with or without nucleoside reverse transcriptase inhibitors
- HIV drug resistance surveillance

Innovative strategies

- Dual therapy (eg, dolutegravir and tenofovir alafenamide or ritonavir-boosted darunavir and dolutegravir) in ART-naive and ART-experienced children
- Short-cycle therapy or drug holiday strategies
- Contraception combined with ART

Implementation and quality of life research

High-quality service delivery for paediatric and adolescent treatment

Research priorities for prevention and treatment of HIV infection in neonates and infants

Prophylaxis or presumptive treatment for high-risk neonates and infants

- High priority: four-drug combination evaluated for safety and pharmacokinetics among infants aged 0–4 weeks (especially abacavir and lopinavir)
- Long-acting agents including broadly neutralising antibodies for neonatal and infant prophylaxis
- Products for low-birthweight infants
- Efficacy of extended infant prophylaxis in settings with extended breastfeeding
- Optimal ways to assist pharmacovigilance for fetal and neonatal exposure to antiretrovirals through maternal treatment or infant prophylaxis
- Optimal infant diagnosis algorithms, in context of increased and prolonged antiretroviral exposure through extended prophylaxis and breastfeeding

Neonatal treatment

- High priority: four-drug combination evaluated for safety and pharmacokinetics among infants aged 0–4 weeks (especially abacavir and lopinavir)
- Products for low-birthweight infants

Focus immediate efforts on priority products with highest impact

The PADO4 meeting reviewed and updated the list of priority antiretroviral formulations most needed in the short-term to medium-term for treatment of infants and children living with HIV in LMICs (panel 1). Although these priority formulations are broadly in line with those outlined in the PADO3 meeting,[10] several formulations were modified or removed after careful consideration.

Retained PADO3 formulations

With the introduction of dolutegravir in LMICs, high value continues to be placed on the 10 mg scored dispersible dolutegravir tablet, already in development, which will enable administration of the minimum dose strength (5 mg) while reducing pill burden. At the same time, a single tablet, once-daily regimen of a dolutegravir-based fixed-dose combination of dolutegravir, lamivudine, and tenofovir alafenamide or dolutegravir, emtricitabine, and tenofovir alafenamide, and dolutegravir, lamivudine, and abacavir dispersible tablets was confirmed as a priority to promote use of fixed-dose combinations. Specifically, a dolutegravir, lamivudine, and abacavir dispersible tablet, at a now confirmed dosing ratio, represents a crucial formulation to provide the currently preferred first-line ART; although the dolutegravir, lamivudine or emtricitabine, and tenofovir alafenamide combination represents an important future option for full harmonisation with adult ART, once dosing and ratios have been confirmed.

Following expected advancement in the development of paediatric tenofovir alafenamide dosing, and accounting for smaller tablet size and target product profile of tenofovir alafenamide-based products, PADO4 retained lamivudine or emtricitabine and tenofovir alafenamide dispersible tablets on the priority list to preserve flexibility of using tenofovir alafenamide with other anchor drugs, and to provide a dual NRTI fixed-dose combination to supplement and possibly to replace current NRTI therapeutic options.

A potent ritonavir-boosted protease inhibitor-fixed-dose combination of darunavir at a paediatric dose of 20 mg ritonavir plus 120 mg darunavir remained high on the priority list. This formulation, which unfortunately has made little progress in its development to date, represents the preferred choice in managing dolutegravir-based ART treatment failure in children. Being a robust protease inhibitor combination with a high threshold for resistance selection and with an option for once-daily dosing in children without prior protease inhibitor exposure, ritonavir-boosted darunavir also represents a potent alternative to other available paediatric protease inhibitor formulations for second-line use (ritonavir-boosted

lopinavir and atazanavir plus ritonavir) as we transition to an era of first-line integrase inhibitor-based ART.

Removed PADO3 formulations

With anticipated approval of dolutegravir dosing for young children by 2020 and with emerging concerns about the selection of integrase inhibitor resistance, with raltegravir use potentially compromising the subsequent use of once-daily dolutegravir, the need for a 50 mg or 5 mg dispersible tablet of raltegravir was considered to be of limited added value for future treatment strategies.

Coformulation of zidovudine with nevirapine for use in neonatal HIV prophylaxis, not yet developed despite its presence on the PADO list since 2014, was also removed because of the anticipated future transition toward presumptive antiretroviral treatment with a three-drug regimen for high-risk infants in lieu of enhanced prophylaxis with a dual regimen.

Furthermore, after consideration of the most recent evidence for dual regimens such as dolutegravir and ritonavir-boosted darunavir or dolutegravir and lamivudine, the PADO4 group decided to deprioritise the development of fixed-dose combinations to deliver such regimens because of concerns for hepatitis B virus coinfections and scarce data on safety benefit and long-term outcomes in children and adolescents. This area is a research gap (eg, dolutegravir and tenofovir alafenamide, dolutegravir and lamivudine, ritonavir-boosted darunavir and lamivudine, ritonavir-boosted darunavir and dolutegravir) for treatment-naive and treatment-experienced children and adolescents along with other simplification strategies currently investigated by ongoing trials such as SMILE (NCT02383108) and D3 (NCT03682848). We have summarised additional areas for further investigation (panel 2) and these add granularity to the paediatric and adolescent HIV research priorities identified by WHO and the Collaborative Initiative for Paediatric HIV Education and Research in 2017.[21]

Additional priority formulations for HIV-associated infections

Finally, the PADO4 group identified several unmet needs for paediatric formulations for treating HIV-associated infections, such as tuberculosis, severe bacterial infections, and cryptococcal meningitis in infants, children, and adolescents (panel 3).[22] Although these products are not formally included in the PADO list they will be considered in other prioritisation processes planned for 2019 under the GAP-f scope of work.[23]

Looking ahead: the future of paediatric HIV treatment

Several potentially promising products and technologies that are under investigation were deemed of interest for future paediatric treatment or prophylaxis by the PADO4 group (panel 1).

***Panel 3:* Management of HIV-associated infections in children**

WHO considers all children younger than 5 years presenting with HIV as having advanced disease. In children older than 5 years, adolescents, and adults, advanced disease is defined as having a CD4 count less than 200 cells per mm^3 or WHO stage 3 or stage 4 clinical event. Mortality of hospitalised children remains high and the most important causes of death are tuberculosis, pneumocystis, bacterial infections, malnutrition, and wasting. Cytomegalovirus is increasingly recognised as an important pathogen in young infants, and malaria remains important in Africa. Diseases such as leishmaniasis are of regional importance.

The recommended package of care for patients presenting with advanced disease focuses on diagnosis, prevention, and treatment of the most common infections, with presumptive treatment to be considered if diagnostic testing is not feasible. Information to inform treatment and prevention of advanced disease in children is currently limited, and questions remain about how to optimise the package of interventions for children, especially children younger than 5 years. Priority formulations are needed for treatment and prevention of advanced disease in infants and children. Consideration should be given to strategies that will allow for safe use of rifampicin, and other rifamycins, with antiretroviral therapy.

Medium-term priorities list

- Rifapentine (150 mg) and isoniazid (150 mg) fixed-dose combination for children
- Co-trimoxazole, isoniazid, and vitamin B6 fixed-dose combination for children
- Rifampicin, isoniazid, pyrazinamide and ethambutol fixed-dose combination for children with optimal rifampicin dosing
- Alternatives to oral co-trimoxazole (for children with allergy) for prevention and treatment; the suggested options include: dapsone, atovaquone, pentamidine and clindamycin plus primaquine, although data on outcomes are limited[22]
- Dapsone as prevention
- Primaquine with clindamycin as therapy

Long-term priorities list

- Valganciclovir liquid
- Letermovir
- Amphotericin B
- Flucytosine, should be available in an adult formulation that can be adapted to adolescents
- Nitazoxanide
- Fluconazole or terbinafine paediatric formulations
- Permethrin ivermectin for scabies

Long-acting or extended-release antiretroviral products have the potential for use in both treatment and prevention of HIV. Broadly speaking, long-acting or extended-release products include parenteral formulations (such as intramuscular or subcutaneous injectables, intravenous infusions, and biodegradable or non-degradable implants) and oral formulations.[24] Cabotegravir combined with long-acting injectable rilpivirine is in phase 1 and 2 studies as monthly maintenance therapy for adolescents (IMPAACT 2017 trial [NCT03497676]) after achieving viral suppression on oral ART. Regulatory applications have been submitted to the US Food and Drug Administration and to the European Medicines Agency for this monthly injectable combination for treating virologically suppressed adults, with ongoing phase 3b investigation of bimonthly administration.[25]

Long-acting or extended-release formulations have multiple advantages over daily oral therapy, including the potential for improving adherence, before avoiding pill fatigue and stigma.[26] These characteristics suggest a promising role for long-acting or extended-release formulations in neonatal prophylaxis and in the prevention and treatment of adolescents with HIV.[27] However, long-acting or extended-release formulations in advanced clinical development might find limited application in children, partly due to the requirement for frequent intramuscular injections with relatively large injection volumes. In the case of long-acting injectable rilpivirine, current reliance on cold-chain storage could make it unsuitable for use on a public health scale in LMICs. Furthermore, dose determination in long-acting or extended-release formulations across the age spectrum is likely to be challenging in children, given changes in weight, muscle mass and metabolic systems from infancy to adolescence.

Broadly neutralising antibodies, potent and long acting in nature, could play a key role in both paediatric HIV treatment and prevention. Apart from the potential for preventing HIV infection in neonates, animal studies suggest the exciting potential of these antibodies to eradicate very early newborn infection.[28] The IMPAACT P1112 trial (NCT02256631) is investigating the safety and pharmacokinetics of VRC01, VRC01-LS (a modified VRC01 with longer half-life), and VRC07-523LS when given subcutaneously to HIV-1-exposed infants alongside antiretroviral prophylaxis. VRCO1 has favourable pharmacokinetics, and preliminary results indicate that serial subcutaneous doses of VRC01 administered over the first 6 months of life are safe and well tolerated.[29] A few questions about broadly neutralising antibodies remain unanswered. For instance, the need for cold-chain and higher cost of production relative to small molecules; the protective titres and optimal route of injection and optimal combinations; and further safety data and risk of resistance transmission. Nevertheless, the research community sees great potential in broadly neutralising antibodies for postnatal prophylaxis. Future generations of these antibodies combining multiple epitopes (eg, a single trispecific antibody) might offer broad coverage of circulating strains while reducing volume of injection.[30]

Other long-acting or extended-release technologies involving alternative delivery systems are also under investigation for HIV, although at earlier stages of development. Examples of such technologies include microneedle patches (or microarray patches)[31–33] and ultralong-acting oral formulations (such as gastroretentive delivery forms[34]).

Among other antiretrovirals that could hold potential for paediatric treatment in LMICs, PADO4 highlighted antiretrovirals characterised by high genetic barrier to resistance or by high potency. One example is doravirine, a new NNRTI with a higher resistance threshold compared with existing NNRTIs,[35] which is being studied in adolescents aged 12–17 years (weighing more than 35 kg; IMPAACT 2014 study, NCT03332095). Given a lack of safety data in pregnancy and no efficacy data on second-line use, the exact role of this NNRTI in LMICs is yet unclear. Moreover, it is contraindicated for use in rifampicin-based tuberculosis cotreatment. However, the role of doravine in paediatric treatment should be reviewed as further data emerge, particularly if it is prioritised within the adult treatment agenda.

Another drug of importance, to both adult and paediatric research communities, is the novel reverse transcriptase translocation inhibitor, MK-8591 (4′-ethynyl-2-fluoro-2′-deoxyadenosine; islatravir), which is in development. MK-8591 has a long half-life and high potency, and such characteristics provide the potential for very low and less frequent oral doses,[36] which in turn could lower treatment costs. Furthermore, MK-8591 might be compatible with versatile long-acting formulation technologies, with the potential to further decrease dosing frequencies.[37] As no paediatric investigation plan has been identified for MK-8591, its further development should take into consideration the need for appropriate formulations and clinical data for infants, children, and adolescents. Clinical validation of high efficacy against notable resistance-associated reverse transcriptase mutations is also warranted.

Special considerations on enabling drug optimisation for neonates, infants, adolescents, and pregnant or lactating women

Neonates and infants

The PADO4 meeting once again focused attention on the special issues of neonates and infants. Meeting participants prioritised the study of pharmacokinetics and safety of this fixed-dose combination product from birth, especially as dosing data on abacavir in neonates are absent. The importance of studying the pharmacokinetics and safety of dolutegravir from birth was also highlighted, since current studies of dolutegravir begin at 4 weeks of age. The paucity of products that have been studied in low-birthweight infants and premature infants was also noted, and the study of key antiretrovirals in low-birthweight infants was identified as a research priority.

The group members endorsed a shift from the current infant prophylaxis approaches to a simplified framework harmonised with early treatment. They considered the multiple advantages of using the same regimen for prophylaxis of high-risk neonates that is recommended for neonatal treatment, including reducing the PADO product list by eliminating coformulation of zidovudine with nevirapine, using a potent combination regimen for those at highest risk of infection, and initiating early treatment in those determined to be infected. This approach would simplify the supply chain and increase demand for a single product. The potential for broadly neutralising antibodies for neonatal and infant prophylaxis generated much interest and the study of long-acting or

extended-release formulations in this population also received high priority. Other essential research questions are included in panel 2.

Adolescents

Research, treatment, and care of adolescents living with HIV pose several unique considerations including issues around disclosure, confidentiality, autonomy, and consent. Other considerations include potential pharmacokinetics challenges (eg, use of contraceptive drugs), and lower rates of care, treatment adherence and associated viral suppression than in adults. Transitioning from paediatric to adult management is challenging for the individual and for health systems, and drug harmonisation across the life course, from childhood through adolescence to adulthood, is crucial to ensure successful treatment. In the context of lifelong HIV treatment, careful sequencing of ART regimens between childhood, adolescence, and adulthood is needed to preserve and protect future treatment options.

Drug reduction strategies with regimens containing ritonavir-boosted darunavir plus dolutegravir dual ART have been considered in adults and are now being investigated in children and adolescents in the SMILE trial. Several other alternative strategies for simplifying ART are being investigated for adolescents. Such strategies might improve quality of life by reducing toxicity, preserving future treatment options, facilitating uptake, and decreasing costs. Simplification and other innovative approaches, including the use of dual oral antiretroviral regimens or long-acting injectables and reducing the number of days on treatment (short-cycle therapy), are attractive considerations for adolescent populations. However, several of these strategies might be difficult to implement in LMICs where frequent virological monitoring might not be feasible. Essential gaps in research into optimal treatment strategies in adolescent populations remain and studies including adolescents are needed before they can be considered on a public health level.

Early inclusion of adolescents in the product development cycle is needed to ensure that information on antiretroviral formulations and treatment approaches are optimised for adolescents. In particular, pharmacokinetic studies in adolescents should be done as soon as a dose is proposed and being studied in adults, and they should include adolescents as young as possible on the basis of weight rather than age limits. PADO4 supports the inclusion of adolescents in adult phase 2 or 3 studies, unless specific concerns exist. However, including adolescents in adult clinical trials can be challenging, and better collaboration with paediatric research networks during the trial design phase could help address barriers to recruitment and retention.

Finally, meaningful involvement of adolescents as advisors and peer representatives at all stages of trial design and planning, along with the establishment of youth trial boards, as has been done for the ODYSSEY trial, is likely to improve implementation, successful recruitment, and retention of adolescents in the trials.

Pregnant and lactating women

Despite the public health need for antiretrovirals that are safe and effective for use in women of childbearing potential, pregnant and breastfeeding women are generally excluded from clinical trials. This action has resulted in a paucity of data on the use of these drugs during pregnancy and breastfeeding, putting women and children at risk for potentially harmful or ineffective interventions.

PADO4 strongly emphasised that current approaches to studying drugs in pregnant and lactating women should be re-examined, with appropriate consideration of the risks of not including pregnant women in treatment and prevention research. These risks should be weighed against any preclinical data on risk in pregnancy, pharmacokinetics and dosing data, and whether the drug would offer direct benefit to the mother or fetus. The group supported the premise that pregnant and lactating women need to be included in clinical trials of antiretrovirals and agreed that there is a compelling need to accelerate the investigation of new antiretrovirals in this group to closely follow the timeline of development in non-pregnant adults.

Approaches to support an accelerated timescale for investigation of antiretrovirals in pregnant and lactating women were discussed. Key principles to assess pharmacokinetics and include this population in clinical trials with non-pregnant adults were deliberated. In collaboration with the Conference on Antiretroviral Drug Optimisation group, these principles will be fully delineated in 2019. Furthermore, the Paediatric Antiretroviral Working Group will continue to work to address relevant questions about antiretrovirals in pregnant and lactating women and advocate with regulatory, industry, and research partners to create an enabling environment to study antiretrovirals in this population. PADO4 also recognised the crucial importance of the other stakeholders working in this area (ie, the Pregnancy & HIV/AIDS: Seeking Equitable Study Project at US universities) and placed high value on early and consistent involvement of the community, particularly of informed and vocal participation of women, to inform this agenda.[38]

For the **Pregnancy & HIV/AIDS: Seeking Equitable Study Project** see http://www.hivpregnancyethics.org/

Conclusion

The outcomes of the PADO4 meeting renew the commitment of key stakeholders to better target global efforts and accelerate research and development of the most critical formulations. The PADO4 group reviewed the antiretroviral landscape, the expected timelines for introducing and rolling out new antiretrovirals in LMICs countries and confirmed the essential role of ritonavir-boosted darunavir fixed-dose combination and of

formulations containing dolutegravir and tenofovir alafenamide. These priority products will be the core HIV component of the product portfolio that the GAP-f will focus on to ensure that every step is taken to investigate, develop, and introduce better formulations in the shortest possible time.

As innovative strategies to simplify and better sequence antiretroviral regimens over time are being tested, more efforts should be put into exploring the value of long-acting and extended-release formulations. It is paramount that the development plans include consideration of potential use in infants, children, and adolescents, and in pregnant and lactating women. Manufacturers are encouraged to consult with PADO for guidance on paediatric requirements for specific novel products.

PADO4 retained a strong focus on adolescents and promoted stronger collaboration of innovators and adult researchers with existing paediatric and adolescent HIV research networks to speed up approval of optimal ART options for youth globally. An urgent need to investigate new antiretrovirals in pregnant and lactating women more thoroughly and more rapidly was also clearly endorsed by the group. The group acknowledged that optimal child health outcomes cannot be ensured without supporting mothers to be virologically suppressed and clinically stable.

Without continued focus on identifying, prioritising, and ensuring access to optimal formulations suitable for infants, children, and adolescents, global HIV treatment targets will not be met.

Contributors

MP, CLT, NR, YC, and EJA developed the first draft following the PADO4 meeting. All authors contributed to drafts and revisions of this paper.

PADO4 participants

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Declaration of interests

EJA participated in ViiV Pediatric Advisory Boards. TRC reports personal fees from the IMPAACT Group, outside the submitted work. AT reports personal fees from the PENTA Foundation, outside the submitted work; and he is trial clinician in the ODYSSEY randomised controlled trial. TDR reports other from ViiV and GlaxoSmithKline, outside the submitted work. All other authors declare no competing interests.

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