Advancing the prevention and treatment of HIV in children: priorities for research and development

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Safe and effective paediatric formulations of the most promising antiretroviral drugs are crucial to advance the treatment and prevention of HIV in neonates, infants, children, and adolescents. The WHO Paediatric Drug Optimization for HIV (PADO-HIV) group brings together stakeholders and experts every 2–3 years to identify priority products and define research gaps in the development of new HIV drugs and formulations for children in low-income and middle-income countries. PADO-HIV 5 met from Sept 27 to Oct 15, 2021. The group evaluated HIV agents from known and novel drug classes, oral and parenteral long-acting formulations, and developments in broadly neutralising antibodies, and included focused sessions on neonates and new delivery technologies. A list of medium-term and long-term priorities was generated, and research questions were defined. This forward-looking analysis is intended to provide guidance to funders, drug developers, and researchers, and to accelerate access for children to the best HIV drugs and formulations.

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Introduction

The availability of suitable antiretroviral drugs and formulations for preventing and treating HIV in children and adolescents has traditionally lagged 7–12 years behind that of adults.[1] In 2020, only 54% of the estimated 1·7 million children living with HIV who were younger than 15 years were on antiretroviral therapy (ART), compared with 74% of adults, and 40% of children versus 67% of adults had suppressed HIV viral loads.[2,3] Part of the challenge contributing to lower ART coverage includes a small and fragmented paediatric antiretroviral drug market and suboptimal availability of appropriate age-adapted formulations for children. This market is further reduced by successful programmes to prevent vertical transmission that have seen a declining number of infants born with HIV, resulting in reduced investment in research and development, especially as new therapeutic options such as long-acting technologies are being considered. The aim of the Paediatric Drug Optimization for HIV (PADO-HIV) group is to identify priority antiretroviral formulations and products that are most needed for neonates, infants, children, and adolescents, particularly in low-income and middle-income countries, to guide industry and focus development efforts where they can have greatest impact.[4] The PADO-HIV group also aims to highlight research gaps and strengthen the evidence base to inform future WHO treatment guidelines.

Clarity on priorities to rapidly investigate and develop better antiretrovirals for children has already led to tangible results. The development and approval of a generic 10 mg scored dispersible tablet formulation of the integrase inhibitor dolutegravir in 2020, represents an important achievement in optimising HIV treatment for infants and young children as it can be used in infants weighing at least 3 kg and from 4 weeks of age. This product was first highlighted by the PADO-HIV group as a priority in 2014, with the specification in 2016 that a 10 mg scored dispersible formulation would be the most suitable dosage. A dolutegravir-based regimen is now recommended by WHO as the preferred first-line and second-line treatment for all children and adolescents.[5] Access to paediatric dolutegravir has substantially simplified dosing and provided opportunities for better viral suppression in infants and children.[6–9]

New drug delivery technologies and novel treatment approaches, such as combining antiretrovirals and broadly neutralising antibodies (bNAbs), offer potential future HIV paediatric treatment options. New treatment approaches must address the needs of infants, children, and adolescents across all age and weight bands. In addition, with approximately 1·3 million infants being born to women living with HIV annually,[3] new agents could also play a transformative role in improving postnatal prophylaxis for infants from birth and throughout breastfeeding. With this in mind, the fifth edition of PADO-HIV aimed to review medium-term and long-term priorities for the development of new drugs and formulations for paediatric HIV treatment and prevention, including a special focus on neonates and new technologies.

PADO-HIV 5

PADO-HIV 5 was held virtually from Sept 27 to Oct 15, 2021. Participants represented 21 countries and were identified from WHO expert advisory groups, partnerships, and HIV programmes.[10] In contrast with previous meetings, PADO-HIV 5 was held in conjunction with the adult Conference on Antiretroviral Drug Optimization 4 (CADO 4) and in parallel with the drug resistance network HIVResNet meeting, to foster harmonisation and alignment.[11] In addition, greater emphasis was placed on considering new technologies for drug delivery and their potential matching with HIV agents.

Before the meeting, two surveys were conducted using a decision science software tool Comparion Expert Choice to help guide discussions and inform the

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See Online for appendix

prioritisation exercise. The first survey focused on identifying the most important attributes to consider for the prioritisation exercise and was sent to PADO-HIV 5 participants and additional stakeholders (response rate 44% [53 of 121]). The first survey resulted in a weighted list of optimal attributes that were then used to score and rank products in the drug prioritisation process via the second survey, which was limited to PADO-HIV 5 participants (response rate 66% [39 of 59]).

With the support of dedicated evidence reviews, meeting sessions were focused on analysing the progress since the previous meeting (PADO-HIV 4 in 2018),[12] current antiretroviral pipelines for treatment and prevention, specific challenges and opportunities for neonatal treatment and prevention, and new drug delivery technologies across the age spectrum. Consensus on the PADO-HIV 5 priority list (for the future 3–5 years) and the PADO-HIV 5 watch list (5–10 years), and on missing products to treat and prevent co-infections, was reached through discussion and with the aid of virtual polls. Throughout the meeting, participants also reviewed and updated a list of research priorities.

Following the announcement of a temporary pause in the islatravir development programme in December, 2021,[13] the PADO-HIV 5 and CADO 4 groups reconvened virtually on March 3, 2022, to review information available and revise the outcomes of the previous consultation accordingly.

Identifying new opportunities for HIV drug optimisation in children

The HIV treatment landscape is evolving towards treatment regimens with fewer side-effects, greater tolerability, and potential for less frequent administration, and towards an increasing desire to promote alignment between drugs used for treatment and prevention of HIV. Across new antiretroviral drug classes, monoclonal antibodies, and new drug delivery technologies development needs to focus on what is needed for paediatric populations. Unfortunately, there is insufficient evidence on many new agents to fully determine the advantages and potential limitations specifically for the paediatric population. In addition, management of HIV in infants cannot be considered in isolation, and careful consideration needs to be given to future maternal antiretroviral regimens that infants will be exposed to in utero or through breastfeeding, potentially contributing to additional risk for toxicity or drug resistance. There might also be negative ramifications in terms of selection of drug resistance, which could result in reduced treatment efficacy if breakthrough infections occur.

As the HIV community strives for less frequent drug administration and considers pipeline agents with substantial long-acting potential, drug optimisation also needs to reflect how new approaches will fit into evolving HIV service delivery models and ensure that novel medicines can minimise the need for both short-term and long-term safety monitoring. Better linkage between research, development, and implementation in paediatric HIV treatment and prevention is not only necessary to develop products that are fit for purpose, but also to lay the groundwork for a conceptual and practical shift from research and development models that rely on traditional clinical trials, to those that make greater use of real-world evidence to inform policy and support product development and approval.

Antiretroviral agents

Several new promising antiretroviral agents are currently in the pipeline, and some are already under investigation in children and adolescents. Lenacapavir is a long-acting and potent inhibitor of the HIV capsid protein. Phase 2 and 3 trials are underway to study the efficacy of subcutaneous injections given once every 6 months in treatment-naive adults (CALIBRATE, NCT04143594 [>18 years old]) and treatment-experienced adolescents and adults (CAPELLA, NCT04150068 [>12 years old]). Studies in children are anticipated but not yet defined.

Islatravir is a long-acting nucleoside reverse transcriptase translocation inhibitor with potential for daily, weekly, and monthly oral dosing for both treatment and prevention. Efficacy and tolerability over 96 weeks have been shown in phase 2 clinical trials in treatment-naive adults (MK-8591A-017, NCT04223778). Studies of islatravir and doravirine in people between 12 and 18 years were started in 2021 (MK-8591A-028, NCT04295772). Unfortunately, the islatravir clinical development programme was put on hold in December, 2021, due to a potentially dose-related decrease in total lymphocyte and CD4 T-cell counts in participants receiving islatravir across treatment and prevention studies.[13]

MK-8507 is a novel long-acting, non-nucleoside reverse transcriptase inhibitor. A phase 2 trial of MK-8507 in combination with islatravir in adults was underway, but was interrupted following similar observations to other studies including islatravir that showed reduced total lymphocyte and CD4 T-cell counts.[14] Other agents of potential future interest include fostemsavir, a GP-120 attachment inhibitor; GSK3640254, an HIV-1 maturation inhibitor; ABX464, a novel drug that binds to cap-binding complex, and albuviritude, which is a fusion inhibitor. Questions remain about the use of these novel agents in different populations including children and adolescents, as well as about safety, pharmacokinetics, dosing, and potential drug–drug interactions.

bNAbs

Intravenously or subcutaneously administered bNAbs are a novel and safe approach with potential for HIV treatment and prevention, including prevention of vertical transmission. The Antibody Mediated Prevention (AMP) trial provides proof of concept that passive immunoprevention can prevent HIV sexual transmission when the virus is

	Microarray patches (home or clinic administration)	Long-acting injectables, subcutaneous (clinic administration likely)	Long-acting injectables, intramuscular (clinic administration)	Implants (clinic administration)
Neonates (0–4 weeks)	+ Avoids oral administration challenges + Can be administered by caregivers – Possible skin sensitivities	+ Can also be used for prophylaxis in neonates + Avoids oral administration challenges + Can align with already existing clinic visits for administration + Dose can be adjusted + Regulatory pathways already exist	– Depending on volume, pain and injection site irritation might be prohibitive – Possible challenges with low birthweight neonates and infants	– Inability to frequently dose adjust as needed is probably prohibitive
Infants (1–12 months)				
Children (1–10 years)	+ Avoids oral administration challenges – Depending on size of patch and duration of exposure needed, placement might be burdensome	+ Avoids oral administration challenges and daily dosing + Pain of administration is more tolerable than intramuscular injections + Regulatory pathways already exist + Could align with immunisations	+ Avoids oral administration challenges + Dosing might align with already existing clinic visits + Regulatory pathways already exist – Monthly injections might not be acceptable	? Depending on dosing, and length of action, administration might be possible in some children
Adolescents (10–18 years)	– Probable need for large patch with frequent redosing ? Possibility of using multiple patches	+ Pain of administration is more tolerable than intramuscular injections + Regulatory pathways already exist + High acceptability in previous surveys	+ Can allow for less frequent dosing + Overcomes adherence challenges in adolescents	+ No dose adjustments needed + Aligns with less frequent clinic visits and multi-month dosing + Overcomes adherence challenges in adolescents

Figure: **Advantages and disadvantages of new drug delivery technologies for different paediatric populations**

sensitive to the antibody administered, but also showed the need to combine multiple potent bNAbs.[15] Furthermore, bNAbs have been shown to be safe and well tolerated in adults, with no serious adverse drug reactions, bNAb–antiretroviral interactions or cross-resistance with antiretrovirals.[16–18] In newborn babies, bNAbs are quickly absorbed following subcutaneous administration and provide rapid protection against HIV acquisition. There is a potential role for bNAbs in neonates as postnatal prophylaxis as injections of bNAbs with long half-lives could surmount adherence challenges of daily oral approaches. In infants acquiring HIV, bNAbs could offer therapeutic advantages by potentially reducing the viral reservoir, enhancing acquired immunity, and, in the future, provide a pathway to functional cure.[19,20] Pre-existing and rapid development of high-level resistance with single bNAbs remains a limitation of current agents. However, 17 bNAbs or related products are currently in development with a range of binding epitopes and diverse sensitivity patterns, and the potential benefits of bNAb combinations are being explored for broad overall coverage. Three bNAbs, all of which are administered subcutaneously, have been studied in HIV-exposed neonates and young infants (birth to 5 days old) in the IMPAACT-P1112 study, including VRC01 and the Fc-modified long-acting bNAbs VRC01LS and VRC07-523LS, both which can be administered once every 12 weeks for prophylaxis. These products are rapidly absorbed, have a long half-life, and appear to be safe and well tolerated.[21,22] VRC01 is also being studied in high-risk HIV exposed and infected infants in the IMPAACT studies P1115 (from birth to 10 days old, NCT02140255) and P2008 (from birth to 12 weeks old, NCT03208231). In the Tatelo study (NCT03707977), intravenously administered VRC01LS and 10-1074 in combination are being evaluated in HIV-infected young children from 96 weeks to 7 years old who are virologically suppressed on antiretrovirals.

New technologies for drug delivery

A number of new technologies for delivering pharmaceutical products are currently under development.[23] Microarray patches containing tiny projections that deliver products subdermally might provide particular benefits for neonates and infants, in whom oral administration can be challenging (figure). Research is needed to evaluate the risk of skin reactions, the suitability and feasibility of these patches for preterm infants with delicate skin, and the need for varied patch sizes to deliver different doses as weight increases. For adolescents, the need for larger drug volumes could pose challenges in terms of patch sizes.

There is also strong interest in long-acting injectable formulations, which could provide benefits across the age spectrum, particularly if administered subcutaneously (figure). Advantages include avoidance of oral administration and the ability to adjust doses as children grow. Long-acting injectable formulations of cabotegravir and rilpivirine have already been shown to provide good virological suppression in adults with intramuscular administration.[24] A phase 1 and 2 study in adolescents 12–18 years old is also underway (IMPAACT-2017, NCT03497676), whereas the study in children (aged 1–12 years) is under development (IMPAACT-2036).[25] Although cabotegravir with rilpivirine is not a regimen prioritised for use in low-income and middle-income

countries, this study has the potential to show that long-acting injectable formulations can be used across different populations and serve as a proof of concept for other long-acting formulations in preclinical or clinical development.[26]

Long-acting products can also be delivered using implants, which might play a role in adolescents, with benefits including less frequent clinic visits, improved adherence, and the potential for combined contraceptive products for female adolescents (figure). However, such products were felt to have reduced potential in younger populations due to the need for frequent dose changes.

Although these new technologies have several appealing characteristics, qualitative data on preferences and acceptability of the different options across age groups will be needed. Frequency of administration and clinic contact also need to be contextualised within current service delivery models, which have shifted toward less frequent patient contact. Matching the appropriate technology with the right pharmaceutical agent is crucial to ensure that suitable products are accelerated for development and assessment in infants and children.

Strategic use of antiretrovirals

A number of strategies for optimising adult HIV treatment are under discussion, some of which are relevant to paediatric treatment. The transition to dolutegravir-based regimens has consolidated demand for future fixed-dose combinations containing dolutegravir and nucleoside reverse transcriptase inhibitors abacavir and lamivudine, but raises questions about optimal sequencing of regimens in children who do not respond to treatment on this new combination. Results from the NADIA trial indicated that in adults who did not respond to initial regimens, the choice of nucleoside reverse transcriptase inhibitor (tenofovir disproxil fumarate or zidovudine) in the subsequent regimen (with either dolutegravir or the protease inhibitor ritonavir-boosted darunavir) did not affect viral suppression at 48 weeks, even in people with resistance mutations.[27] Although extrapolating adult findings is typically appropriate, it is not certain whether children with unsuppressed viral loads on non-nucleoside reverse transcriptase inhibitor-based or protease inhibitor-based regimens can similarly undergo single drug substitution and remain on an abacavir/lamivudine backbone when switching to dolutegravir or ritonavir-boosted darunavir-based regimens. Additional evidence to provide reassurance in the paediatric population and in the context of abacavir-containing regimens remains of great interest for country programmes transitioning to dolutegravir-based regimens in children.

Alignment of prevention and treatment is particularly relevant for neonates, with increased access to maternal ART leading to both reduced transmission rates and reduced viral loads in neonates acquiring HIV infection in utero. Innovative research into new technologies and new drug classes could simplify the management of HIV-exposed neonates and provide novel options that bridge treatment and prevention, and allow for extended postnatal prophylaxis throughout breastfeeding. It is crucial that research and development of all new products include term and preterm neonates to ensure that appropriate data are available.

Panel 1: **PADO-HIV 5 priority list**

PADO-HIV 5 priority list: medium term, 3–5 years

- Dolutegravir/lamivudine/abacavir (5/30/60 mg dispersible)
- Ritonavir–boosted darunavir (20/120 mg)
- Lamivudine/emtricitabine combined with tenofovir alafenamide, with or without dolutegravir
- Cabotegravir for postnatal prophylaxis

PADO-HIV 5 watch list (products of potential interest for paediatric treatment in the longer term)

- Islatravir
- Broadly neutralising antibodies
- Microarray patches (with potent antiretroviral identified after appropriate matching)
- Lenacapavir

PADO-HIV=Paediatric Drug Optimization for HIV.

Neonatal treatment and prevention

Although vertical transmission rates continue to decline, there remains a need for suitable formulations and dosing recommendations for prophylaxis and treatment in neonates, particularly for those born prematurely or of low birthweight, and for potential use throughout breastfeeding. Nevirapine, zidovudine, and lamivudine are the only antiretroviral drugs for which pharmacokinetic and safety data are available for preterm neonates.[5,28] In the absence of other antiretroviral options for premature infants, nevirapine is likely to remain a key drug for this population group. However, there are still no dosing recommendations for nevirapine treatment in premature infants with less than 34 weeks' gestation. Pharmacokinetic data are also lacking on lamivudine dosing in very premature infants (<32 weeks' gestation). The group ranked both research areas as high priority, but the consensus was that adequate guidance could be generated through population pharmacokinetic modelling studies using data from several completed studies including MONOD-ANRS, IMPAACT-P1115, and IMPAACT-P1106 for nevirapine, and IMPAACT-P1106 for lamivudine.[10,29,30] For term infants, abacavir pharmacokinetic data have been generated from administering a single dose of abacavir liquid formulation to HIV-exposed neonates receiving routine postnatal prophylaxis.[31] These data were used in a population pharmacokinetic model with abacavir pharmacokinetic data from older infants (<12 months) to determine exact mg/kg dosing in term neonates.[29] However, pharmacokinetic and safety data

for abacavir solid formulations when administered daily or twice daily from birth until 3 months of age are still needed. At PADO-HIV 4, the study of a fixed-dose four-in-one combination formulation containing abacavir, lamivudine, lopinavir, and ritonavir was flagged as a priority. Initial investigation in the PETITE study in term neonates aged 0–4 weeks showed that the four-in-one formulation provided very low lopinavir concentrations with normal to high abacavir and lamivudine concentrations.[32] Given that the dose of lopinavir and ritonavir cannot be increased in the fixed-dose combination without also increasing the dose of abacavir and lamivudine, the PETITE study is evaluating using separate solid paediatric formulations of a fixed-dose combination of abacavir/lamivudine (120 mg and 60 mg, respectively) as a double-scored dispersible tablet, with ritonavir-boosted lopinavir (10 mg and 40 mg respectively) granules.

Establishing appropriate dosing for dolutegravir in neonates was confirmed as an urgent priority to enable use of the first once-daily regimen for this population. A phase 1 trial to investigate the safety, tolerability, and dosing of a liquid suspension of dolutegravir is currently in development (IMPAACT-2023). This study will also allow for assessment of the 5 mg dispersible dolutegravir tablet if initial data with the liquid formulation are

Panel 2: **PADO-HIV research priorities to inform development and optimal use of antiretroviral drugs in children and adolescents**

Existing antiretroviral drugs for treatment and prophylaxis

Neonates (0–4 weeks)

- Pharmacokinetics, efficacy, and safety of lamivudine, nevirapine, abacavir, tenofovir alafenamide, and dolutegravir in premature and low-birthweight infants (focus on nevirapine dosing in neonates born at <34 weeks' gestation and lamivudine dosing in neonates born at <32 weeks' gestation)
- Pharmacokinetics, efficacy, and safety of long-acting cabotegravir for infant prophylaxis throughout breastfeeding
- Use of the combination of tenofovir alafenamide/emtricitabine/dolutegravir, and tenofovir alafenamide/emtricitabine from birth
- Pharmacokinetics, efficacy, and safety of long-acting cabotegravir in neonates

Infants and children (4 weeks to 10 years)

- Pharmacovigilance and long-term safety and efficacy of dolutegravir and tenofovir alafenamide (when introduced)
- Pharmacokinetics, efficacy, and safety of a fixed-dose formulation of abacavir/lamivudine/dolutegravir in infants who weigh less than 6 kg and are older than 1 month
- Pharmacokinetics, efficacy, and safety of long-acting cabotegravir for infant prophylaxis throughout breastfeeding
- Duration and composition of infant prophylaxis throughout breastfeeding and maternal use of long-acting antiretroviral drugs

New drugs and delivery technology for paediatric populations

Novel prophylaxis and therapeutic agents

- Long-acting broadly neutralising antibodies for prophylaxis or treatment: identifying the right combination, dosing volumes and schedules, and pharmacokinetics and pharmacodynamics, including for premature and low birthweight neonates
- Long-acting oral and injectables lenacapavir (prophylaxis) and islatravir/lenacapavir (treatment): pharmacokinetics, optimal dosing ratios for single and dual combinations, safety, efficacy, and addressing study design challenges in neonates based on pharmacokinetic characteristics
- Potential for other long-acting combinations, more potent non-nucleoside reverse transcriptase inhibitors (compared with rilpivirine and doravirine) paired with cabotegravir or other integrase inhibitors, and stronger antiretroviral drugs paired with islatravir

New drug delivery tools

- Age, size, body surface, and skin qualities for use of microarray patches in paediatrics with age limits
- Acceptability and preferences of new drug delivery tools by caregivers, children, and adolescents
- Acceptability, feasibility, and preferences of new drug delivery tools for paediatric and adolescent use in real-life situations (schedules, capacity, and synchronisation with immunisations and maternal long-acting antiretroviral drugs)
- Feasibility and acceptability of antiretroviral drugs combined with contraceptives for adolescents

Treatment of co-morbidities

- Nested tuberculosis pharmacokinetics studies within ongoing clinical trials for new antiretroviral drugs and formulations in all age cohorts: efficacy and safety of tenofovir alafenamide plus rifampicin
- New paediatric formulations for tuberculosis prevention (cotrimoxazole/isoniazid/pyridoxine), hepatitis B and C viruses, and COVID-19: pharmacokinetics, efficacy, safety, optimal dosing schedules, and drug–drug interactions
- COVID-19 vaccination in immunocompromised children and adolescents with HIV: efficacy and safety
- Long-acting drugs and co-infection with tuberculosis: drug–drug interactions, dosing, and logistical implications
- Safety and efficacy studies of other co-morbidity treatments with novel antiretroviral drugs including long-acting antiretroviral drugs in children and adolescents

(Continues on next page)

(Panel 2 continued from previous page)

Novel strategies for use of antiretrovirals

- Sequencing of nucleoside backbone (keeping abacavir or lamivudine backbone) when switching to dolutegravir or ritonavir-boosted darunavir-based regimens in young children without viral suppression
- Efficacy and resistance surveillance following the switch to dolutegravir-based regimens from unsuccessful protease inhibitor-based regimens in children
- Sequencing strategy for children who do not respond to a dolutegravir-based regimen with nucleoside backbone resistance
- Dual antiretroviral regimens in treatment-naive and treatment-experienced paediatric populations (dolutegravir/lamivudine or dolutegravir/emtricitabine, dolutegravir/tenofovir alafenamide, dolutegravir/ritonavir-boosted darunavir with or without nucleoside reverse transcriptase inhibitors)
- Sequencing of paediatric antiretroviral regimens following failure of long-acting antiretroviral drugs (prophylaxis or treatment)
- For all long-acting antiretroviral drugs (oral and injectables), sequencing of neonatal or infant long-acting antiretroviral drugs for treatment or prophylaxis with maternal long-acting antiretroviral drugs in breastfeeding infant–mother dyads

PADO-HIV=Paediatric Drug Optimization for HIV.

acceptable. However, it was agreed that a parallel study to investigate the pharmacokinetics of the generic 10 mg scored dispersible dolutegravir tablet in neonates would be complementary and would help fast-track the safe use of the most widely available formulation in this population.

As we mentioned previously, novel candidates that hold promise for neonatal prophylaxis and potentially treatment include oral islatravir and bNAbs. Although an optimal combination of bNAbs has not yet been identified, studies of several bNAbs in neonates have shown them to be safe and tolerable, and other studies are underway. Formulations containing islatravir might also have potential for neonatal treatment in the long-term, if and when the drug development programme is resumed.

Priority agents for future treatment of HIV in children and adolescents (medium-term, 3–5 years)

Priority products retained from PADO-HIV 4

With the successful introduction of a scored dispersible 10 mg dolutegravir tablet, this formulation was removed from the PADO-HIV priority list.[10]

A dispersible tablet formulation containing 5 mg of dolutegravir, 30 mg of lamivudine, and 60 mg of abacavir that was investigated in the IMPAACT-2019 trial (NCT03760458)[33] is now at an advanced stage of development and remains a crucial formulation for delivering the preferred first-line ART for children (panel 1).[5] Substantial progress has also been made in the development of a ritonavir-boosted darunavir fixed-dose combination (120 mg darunavir plus 20 mg ritonavir), for second-line treatment in children following dolutegravir-based first-line treatment. The ongoing UNIVERSAL trial and the CHAPAS-4 trial (ISRCTN22964075), which are investigating several simplified second-line regimens in children weighing more than 14 kg, are expected to provide further evidence to inform the strategic use of this formulation in the paediatric population. Both formulations remained on the PADO-HIV priority list and will be essential for future refinement of the WHO treatment guidelines to allow access to optimised regimens.[5]

For more on the **UNIVERSAL project** see https://universalproject.org/

A fixed-dose combination formulation containing tenofovir alafenamide remained on the PADO-HIV 5 priority list either combined with lamivudine or emtricitabine as a dual formulation, or additionally with dolutegravir as a triple formulation (panel 1). Development of tenofovir alafenamide-containing regimens for adults will no longer be considered a priority due to concerns about weight gain and alterations in lipid concentrations when used in combination with integrase inhibitors, and the reduced benefit compared with tenofovir disoproxil fumarate when used in unboosted regimens.[34] However, a formulation containing tenofovir alafenamide is still needed for children, who cannot use tenofovir disoproxil fumarate due to renal and bone toxicities.[35] An approved paediatric formulation containing tenofovir alafenamide would provide an important alternative to abacavir-containing regimens and would give access to a tenofovir-containing backbone for all ages. A three-drug formulation would be of use in first-line and second-line dolutegravir-based regimens, and a two-drug formulation could also be paired with a boosted protease inhibitor for second-line treatment. Pharmacokinetic modelling and bioavailability studies of tenofovir alafenamide to guide the development of paediatric fixed-dose formulations are currently ongoing in the UNIVERSAL study.

New PADO-HIV 5 formulations

Injectable (long-acting) cabotegravir was also newly added to the priority list due to its potential to be administered monthly or every 2 months for postnatal prophylaxis. Extrapolating from the efficacy shown by the HPTN-083 and HPTN-084 trials,[36,37] and anticipating adoption and roll-out of injectable cabotegravir for adult HIV prevention, this drug was considered to be an important priority for

research in neonates and infants for whom it could transform provision of postnatal prophylaxis and provide protection against HIV during the breastfeeding period. Injectable cabotegravir is being investigated in adolescents (12–18 years old) in IMPAACT-2017 (NCT03497676) and in a sub-study of HPTN-084 (NCT04824131) with both awaiting further testing in younger children (aged >2 years) in the IMPAACT-2036 study.[25]

Looking ahead: potential future treatment of paediatric HIV

The aim of the PADO-HIV watch list is to highlight candidate products or technologies of interest for research and development in children over the next 5–10 years (panel 1). Doravirine was previously on the PADO-HIV 4 watch list but has been deprioritised due to its lower barrier to resistance compared with other available products and interaction with tuberculosis medications.

Islatravir was retained from the PADO-HIV 4 watch list to account for its potential role in neonatal prophylaxis and probable flexibility on dosing schedule, which could be adapted for treatment and prevention (panel 1). However, the pause in the islatravir development programme creates substantial uncertainty regarding the role that this drug could play in the future.

Lenacapavir (single entity) as either a once-daily or once-weekly oral formulation or as a multi-month subcutaneous formulation, is of particular interest for postnatal prophylaxis or for salvage therapy for treatment-experienced children as part of a combination ART regimen. Data would be required on pharmacokinetics in neonates and on drug–drug interactions with rifampicin.

A coformulation of islatravir and lenacapavir was considered to be of interest for treatment in ART-naive and ART-experienced populations. However, following the decision of the two originator companies to stop this joint programme following interruption of the islatravir development programme, inclusion of this formulation in the PADO-HIV 5 list was considered to be premature.

Various bNAbs remained on the PADO-HIV 5 watch list and were felt to be of particular interest for prevention in neonates and infants. A subcutaneous injection of a combination of two or more bNAbs was considered the most likely approach, with administration every few months. One potential approach might involve combining bNAbs with antiretroviral drugs for HIV treatment or prevention. Barriers to implementation in low-income and middle-income countries include the requirements for cold chain and high costs, with uncertain potential for cost reduction with generic manufacturing.

The new technology holding the most promise for paediatric HIV treatment and prevention is microarray patches (figure, panel 1). In young children these patches would avoid the need for oral dosing and might be more feasible in this age group due to the smaller patch size and doses required than in adolescents or adults. Another advantage is that patches could easily be administered outside of the health-care setting by caregivers or lay workers, reducing the burden on the health-care system. Microarray patches for HIV treatment and prevention could potentially be developed for children, but further work is required to pair this promising technology with pipeline agents that have suitable characteristics for the technology (eg, small dose, long half-life, and optimal safety).

In addition to prioritising products and formulations, the PADO-HIV 5 group also outlined a list of priority research areas relating to paediatric HIV treatment and prevention (panel 2).

Panel 3: Paediatric formulations for treatment and prevention of key HIV-associated co-infections and comorbidities*

Pneumocystis pneumonia (and tuberculosis)†
Alternatives to oral cotrimoxazole for children with allergy are needed for prevention or treatment. A cotrimoxazole/isoniazid/pyridoxine combination could be a priority for development, but there are issues around duration of isoniazid treatment for tuberculosis prophylaxis (vis-a-vis cotrimoxazole for pneumocystis), and the likelihood that rifapentine could replace isoniazid.

Cytomegalovirus
Oral valganciclovir was prioritised for treatment, during the PADO-HIV 5 meeting. Issues of accurate measurement of disease burden, diagnosis, availability, cost, and impact across age bands prevail. Other drug options might be required, such as letermovir or marabavir.

Cryptococcal meningitis
Ongoing studies and developments in adults might be relevant for children and adolescents (eg, extrapolating dosing for liposomal amphotericin B for adolescents from adult doses used in the AMBITION trial).[38]

Malnutrition
No paediatric antiretroviral development-related issues were prioritised.

Severe bacterial infections
Evidence for an optimal drug prophylaxis package for co-infections or co-morbidities is needed, especially for severe bacterial infections in children starting antiretroviral therapies. The potential need for a REALITY trial[27] focused on children younger than 5 years was discussed.

Cross-cutting issues
More data on antibiotic resistance are needed to guide severe bacterial infection treatments among children living with HIV, but there is currently no need for specific antibiotic recommendations for this group.

*Hepatitis B and C are not discussed here; list to be revised in December 2022.
†Tuberculosis list is to be revised in the third quarter of 2022. Tuberculosis is mentioned here in the context of fixed-dose combinations for co-infection prophylaxis.

Finally, as for previous PADO-HIV meetings, paediatric formulations for treatment and prevention of HIV-associated co-infections and co-morbidities were also reviewed (panel 3).

Conclusions

The PADO-HIV 5 meeting brought together stakeholders from around the world with the objective of developing a medium-term to long-term priority list of optimal and safe formulations for treating and preventing HIV in neonates, infants, children, and adolescents. The new PADO-HIV 5 priority list includes formulations previously identified as important and now at an advanced stage of development, as well as novel formulations reflective of a new era of HIV treatment, including drugs that are longer acting and require less frequent administration. Looking ahead, approaches to treatment and prevention are expected to evolve, with novel drug classes, combinations of long-acting antiretrovirals and bNAbs, and new delivery systems such as microarray patches, injectable formulations, and implants.

PADO-HIV 5 also addressed specific considerations and ongoing challenges surrounding treatment and prevention in neonates, and emphasised the need for formulations and dosing suitable for preterm and low birthweight infants. As adult HIV treatment evolves, approaches for optimising maternal treatment and neonatal prophylaxis and treatment will need to be considered in unison. Although this edition of PADO-HIV did not specifically focus on adolescents, the inclusion of adolescents in adult phase 2 and 3 clinical trials remains firmly on the agenda.

Regular expert reviews of key priorities for research and development of HIV drugs and formulations for neonates, infants, children, and adolescents remains an essential exercise to ensure that targeted efforts are in place and that these populations have access to optimal treatment and prevention throughout their lives.

Contributors

CLT and MP developed the outline. CLT developed the first draft of the manuscript and MP edited and finalised the manuscript for submission. All authors contributed to reviewing and editing the paper and approved the final draft.

Declaration of interests

AC received research grants from Merck, Gilead, and ViiV Healthcare, and a consultancy fee from Merck, all paid to AC's institution. PR received research grants from ViiV and has been on an advisory board for Merck. MV received educational grants from ViiV, Janssen, and MSD. All other authors declare no competing interests.

References

1 Penazzato M, Gnanashanmugam D, Rojo P, et al. Optimizing research to speed up availability of pediatric antiretroviral drugs and formulations. *Clin Infect Dis* 2017; **64:** 1597–603.

2 UNAIDS. 2021 UNAIDS global AIDS update—confronting inequalities—lessons for pandemic responses from 40 years of AIDS. 2021. https://www.unaids.org/sites/default/files/media_asset/2021-global-aids-update_en.pdf (accessed Feb 11, 2022).

3 UNAIDS. Start free, stay free, AIDS free, final report on 2020 targets. July, 2021. https://www.unaids.org/en/resources/documents/2021/start-free-stay-free-aids-free-final-report-on-2020-targets (accessed Feb 11, 2022).

4 WHO. Global accelerator for paediatric formulations (GAP-f). 2021. https://www.who.int/initiatives/gap-f (accessed Feb 11, 2022).

5 WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; July, 2021. https://www.who.int/publications/i/item/9789240031593 (accessed Oct 21, 2021).

6 Bacha J, Mayalla B, Jiwa N, Mwita L, Campbell LR. The 'DTGs' of DTG for children and adolescents living with HIV (CALHIV): descriptions, trends, and gaps of rolling out dolutegravir in CALHIV in Mbeya, Tanzania. 23rd International AIDS conference; July 20, 2020 (abstr PEB0297).

7 Iyer S, Pry J, Nyirenda G, et al. Dolutegravir and viral load suppression among pediatric patients in care in Zambia. Conference on Retroviruses and Opportunistic Infections (CROI); March 6–10, 2021 (abstr 600).

8 Clinton Health Access Initiative. HIV market report: the state of HIV treatment, testing, and prevention in low- and middle-income countries. Sept, 2020. https://www.clintonhealthaccess.org/the-state-of-the-hiv-market-in-low-and-middle-income-countries-3/ (accessed Nov 8, 2021).

9 Turkova A, White E, Mujuru HA, et al. Dolutegravir as first- or second-line treatment for HIV-1 infection in children. *N Engl J Med* 2021; **385:** 2531–43.

10 Penazzato M, Townsend CL, Rakhmanina N, et al. Prioritising the most needed paediatric antiretroviral formulations: the PADO4 list. *Lancet HIV* 2019; **6:** e623–e31.

11 WHO. WHO HIVResNet meeting report 2021. 2022. https://www.who.int/groups/who-hivresnet (accessed March 21, 2022).

12 WHO. Paediatric antiretroviral drug optimization (PADO) meeting 4. Geneva: World Health Organization, 2018. https://cdn.who.int/media/docs/default-source/hq-hiv-hepatitis-and-stis-library/pado4.pdf?sfvrsn=26d4169c_5 (accessed March 21, 2022).

13 Merck. Merck announces clinical holds on studies evaluating islatravir for the treatment and prevention of HIV-1 infection 2021. Dec 13, 2021. https://www.merck.com/news/merck-announces-clinical-holds-on-studies-evaluating-islatravir-for-the-treatment-and-prevention-of-hiv-1-infection/ (accessed March 21, 2022).

14 Merck. Merck provides update on phase 2 clinical trial of once-weekly investigational combination of MK-8507 and islatravir for the treatment of people living with HIV-1 2021. Nov 18, 2021. https://www.merck.com/news/merck-provides-update-on-phase-2-clinical-trial-of-once-weekly-investigational-combination-of-mk-8507-and-islatravir-for-the-treatment-of-people-living-with-hiv-1/ (accessed March 21, 2022).

15 Corey L, Gilbert PB, Juraska M, et al. Two randomized trials of neutralizing antibodies to prevent HIV-1 acquisition. *N Engl J Med* 2021; **384:** 1003–14.

16 Ledgerwood JE, Coates EE, Yamshchikov G, et al. Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults. *Clin Exp Immunol* 2015; **182:** 289–301.

17 Lynch RM, Boritz E, Coates EE, et al. Virologic effects of broadly neutralizing antibody VRC01 administration during chronic HIV-1 infection. *Sci Transl Med* 2015; **7:** 319ra206.

18 Mayer KH, Seaton KE, Huang Y, et al. Safety, pharmacokinetics, and immunological activities of multiple intravenous or subcutaneous doses of an anti-HIV monoclonal antibody, VRC01, administered to HIV-uninfected adults: results of a phase 1 randomized trial. *PLoS Med* 2017; **14:** e1002435.

19 Spencer DA, Shapiro MB, Haigwood NL, Hessell AJ. Advancing HIV broadly neutralizing antibodies: from discovery to the clinic. *Front Public Health* 2021; **9:** 690017.

20 Hessell AJ, Jaworski JP, Epson E, et al. Early short-term treatment with neutralizing human monoclonal antibodies halts SHIV infection in infant macaques. *Nat Med* 2016; **22:** 362–68.

21 Cunningham CK, McFarland EJ, Morrison RL, et al. Safety, tolerability, and pharmacokinetics of the broadly neutralizing human immunodeficiency virus (HIV)-1 monoclonal antibody VRC01 in HIV-exposed newborn infants. *J Infect Dis* 2020; **222:** 628–36.

22 McFarland EJ, Cunningham CK, Muresan P, et al. Safety, tolerability, and pharmacokinetics of a long-acting broadly neutralizing HIV-1 monoclonal antibody VRC01LS in HIV-1-exposed newborn infants. *J Infect Dis* 2021; **224:** 1916–24.

23 WHO. Innovative delivery systems for paediatric medicines: technology landscape. Geneva: World Health Organization, 2020. https://apps.who.int/iris/handle/10665/348336 (accessed March 21, 2022).

24 Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet* 2017; **390:** 1499–510.

25 IMPAACT 2036. Phase I/II study of the safety, tolerability, pharmacokinetics, and antiviral activity of oral and long-acting injectable cabotegravir and rilpivirine in virologically suppressed HIV-infected children >2 to <12 years of age and weighing >10 kgs and <50 kgs 2022. https://www.impaactnetwork.org/studies/impaact2036 (accessed March 21, 2022).

26 Flexner C, Owen A, Siccardi M, Swindells S. Long-acting drugs and formulations for the treatment and prevention of HIV infection. *Int J Antimicrob Agents* 2021; **57:** 106220.

27 Paton NI, Musaazi J, Kityo C, et al. Dolutegravir or darunavir in combination with zidovudine or tenofovir to treat HIV. *N Engl J Med* 2021; **385:** 330–41.

28 Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. 2021. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/PediatricGuidelines.pdf (accessed Dec 2, 2021).

29 Bekker A, Capparelli EV, Violari A, et al. Abacavir dosing in neonates from birth to 3 months of life: a population pharmacokinetic modelling and simulation study. *Lancet HIV* 2022; **9:** e24–31.

30 Pressiat C, Toni TD, Treluyer JM, et al. High nevirapine levels in breast milk and consequences in HIV-infected child when initiated on antiretroviral therapy. *AIDS* 2021; **35:** 2409–10.

31 Bekker A, Decloedt EH, Slade G, Cotton MF, Rabie H, Cressey TR. Single dose abacavir pharmacokinetics and safety in neonates exposed to human immunodeficiency virus (HIV). *Clin Infect Dis* 2021; **72:** 2032–34.

32 Bekker A, Rabie H, Salvadori N, et al. Pharmacokinetics, safety and acceptability of a single dose of abacavir/lamivudine/lopinavir/ritonavir (4-in-1) fixed-dose granule formulation in neonates: PETITE study. IAS Conference on HIV Science; July 18–21, 2021 (abstr PEBLB16).

33 Brooks K, Kiser J, Samson P, et al. Pharmacokinetics and safety of dispersible and immediate release FDC abacavir/ dolutegravir/ lamivudine in children with HIV weighing =14 kg: preliminary results from IMPAACT 2019. 11th IAS Conference on HIV Science; July 18–21, 2021 (abstr PEBLB15).

34 Hill A, Hughes SL, Gotham D, Pozniak AL. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? *J Virus Erad* 2018; **4:** 72–79.

35 WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach—2nd ed. 2016. https://apps.who.int/iris/handle/10665/208825 (accessed Feb 11, 2022).

36 Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. *N Engl J Med* 2021; **385:** 595–608.

37 Delany-Moretlwe S, Hughes J, Bock P, et al. Long acting injectable cabotegravir is safe and effective in preventing HIV infection in cisgender women: interim results from HPTN 084. HIV Research for Prevention (HIVR4P) Conference; Jan 27–Feb 4, 2021 (abstr HY01.02LB).

38 Jarvis JN, Leeme TB, Molefi M, et al. Short-course high-dose liposomal amphotericin B for human immunodeficiency virus-associated cryptococcal meningitis: a phase 2 randomized controlled trial. *Clin Infect Dis* 2019; **68:** 393–401.