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Propelling the Pediatric HIV Therapeutic Agenda With Science, Innovation, and Collaboration

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Background: A number of well-described obstacles to the pediatric therapeutic agenda have resulted in substantial delays in the introduction of new medications, formulations, strategies, and approaches to treat infants, children, and adolescents living with HIV.

Setting: Global landscape.

Methods: The authors will provide a summary of current and emerging initiatives to accelerate the pediatric therapeutic agenda including illustrative case studies of innovations and scientific discovery in diagnosis and treatment of very young children with HIV infection.

Results: The challenges posed by rapid physiologic and developmental changes that characterize the trajectory of childhood as well as the complex regulatory and fiscal milieu of HIV therapeutics have hampered pediatric HIV therapeutic research. Recent efforts to accelerate this agenda include prioritizing agents and formulations, defining dosing by weight bands, applying innovative study designs, synergizing work across research networks to achieve common goals, and the establishment of a global prioritized research agenda. A case study of initiatives to diagnose and effectively treat newborns and infants will illustrate the critical role of basic science research and novel approaches to study design and implementation that are informing global efforts to end AIDS.

Conclusions: A pediatric therapeutic agenda informed by basic science and achieved through innovation and global cooperation is essential to achieve an AIDS-free generation.

Key Words: very early antiretroviral treatment, pediatric antiretroviral drugs

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INTRODUCTION

Since the early 1990s, the public health response to the HIV epidemic has been driven by scientific discovery, innovation, and collaboration. Many landmark discoveries including the identification of the human immunodeficiency virus (HIV),[1,2] the ability of the potent antiretrovirals (ARVs) to arrest viral replication,[3] the effectiveness of ARVs to prevent vertical and horizontal transmission,[4,5] and the health benefits of universal ARV treatment[6–8] have transformed public policy and clinical practice. Furthermore, the timeline from development to regulatory approval for ARVs has been markedly accelerated, resulting in a new generation of highly potent, well-tolerated ARV agents that can be taken once daily, and revolutionizing the treatment landscape for adults living with HIV.[9] The door has also been opened for long-acting ARV formulations, therapeutic vaccines, and immunotherapies to improve treatment and prevention and in the long term, to achieve epidemic control and HIV remission.[10,11]

The pediatric therapeutic agenda has generally lagged behind advances in the adult population, resulting in substantial delays in new medications, formulations, and approaches to treat HIV infection in infants, children, and adolescents.[12–14] Historically, a number of well-described obstacles have thwarted drug development as well as intervention and pathogenesis research.[12,13] The rapid growth and physical development that characterize the trajectory of childhood generally necessitates dose changes as well as unique formulations that can easily be administered to infants and young children. Traditionally, new drugs have been studied by age group, advancing from older to younger children, resulting in complex study designs with long

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timelines. Other impediments have included regulatory hurdles, cautious engagement and investment of pharmaceutical companies, limitations on blood volumes that can be obtained from small children, and ethical conundrums around participation of children and adolescents in research.[12]

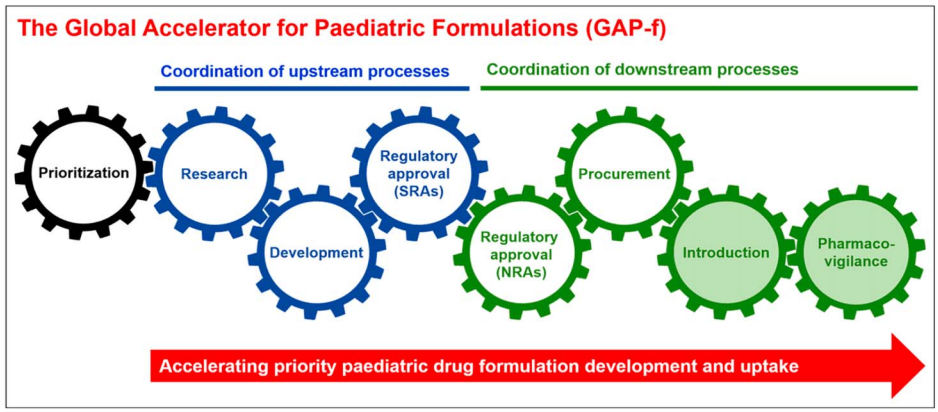
Adding further complexity, unlike in adults where HIV infection can be diagnosed using a rapid antibody test, diagnosis in infants requires virologic testing (nucleic acid amplification test).[15–17] Despite broad efforts to build laboratory and program capacity and infrastructure for early infant diagnosis (EID), less than half of all HIV-exposed infants globally received a virologic test by 2 months of age in 2016.[18] Identification of older children and adolescents with HIV infection, where HIV antibody testing can be used, has also been suboptimal.[19] Low rates of HIV diagnosis among children and adolescents are a major contributor to the poor rates of treatment coverage and virologic suppression. In 2016, only an estimated 43% of children less than 15 years of age living with HIV infection were receiving ARV treatment and ARV options remain limited.[18] Despite an increased incidence of pretreatment nonnucleoside reverse transcriptase inhibitor resistance in infants, nevirapine with 2 nucleoside reverse transcriptase inhibitors remains the only available treatment regimen in many Sub-Saharan African countries.[20–22] In 41 countries reporting on adolescent treatment, median antiretroviral therapy (ART) coverage was only 36% in 2016.[23] Not surprisingly, viral suppression rates are lower among children and adolescents compared with adults. In the 2017 Swaziland HIV Incidence Measurement Survey, 91% of adults 25 years and older receiving ART were virally suppressed to $<$1000 copies per milliliter compared with 76% of 15–24-year-olds.[24] In the Malawi Population HIV Incidence Measurement survey conducted in 2016, low rates of viral suppression on ART were found among children, 51.8% and 19.3%, respectively, among 5–9-year-olds and those younger than 4 years.[25]

Emerging evidence, however, suggests that there is renewed attention to the pediatric and adolescent HIV agenda as well as new opportunities to address many of the bottlenecks and challenges delaying progress.[26,27] The development of a shared prioritized global research agenda for children and adolescents living with HIV was a critical step, underscoring the importance of research to achieve optimal outcomes for children and adolescents and to focus efforts of scientists, clinicians, policy makers, and the greater global community on the most pressing and relevant scientific questions.[26–28] Momentum and change have been particularly evident in the area of therapeutics where science, innovation, and collaboration are propelling efforts to accelerate the availability of optimized ARV treatments for children.[29] Of note, the prioritization exercise identified the study of the safety, efficacy, acceptability, pharmacokinetics, and optimal dosing of existing and new ARV drugs, formulations, and novel delivery systems as among the most important issues in the field.[26]

Spearheaded by the World Health Organization (WHO), diverse actors working in drug development, research, regulatory, and service delivery sectors are converging to address the urgent need to accelerate the availability of better ARVS for children from birth to 18 years of age. Several activities already in place include the Pediatric Antiretroviral Working Group (PAWG), a group of experts in pediatric and obstetric HIV prevention and treatment that provides key clinical, pharmacokinetic, and programmatic advice for new drug development. The PAWG develops dosing recommendations for existing and new ARV formulations, reviews pediatric investigational plans, provides technical input to pharmaceutical companies, and defines standards and new approaches to optimize clinical research on ARVs for children (Table 1).[12] Researchers and research networks have already embraced the PAWG guidance, transforming approaches to studying ARV dosing and safety. The PAWG is currently developing a research toolkit to support and accelerate drug and formulation development for children. Pediatric antiretroviral drug optimization (PADO) is an annual review and prioritization of medium- and long-term priorities for the development of new ARV drugs and formulations for pediatric HIV treatment and prevention in the context of a public health approach.[14] PADO produces a Pediatric ARV Drug Optimization List that guides pharmaceutical companies producing pediatric products (http://www.who.int/hiv/pub/paediatric/en/.) Another important innovation for pediatrics has been the preparation of the Optimal Pediatric Formulary.[30] Updated regularly, it establishes a minimum set of formulations to provide optimal ARV regimens for children. By informing country-level planning and procurement, the demand for products is consolidated across countries, reducing market fragmentation and allowing industry to produce a limited number of pediatric ARV formulations. Plans are also in development for a global accelerator for pediatric formulations (GAP-f), a collaborating platform supported by an innovative financing mechanism to promote a faster, more efficient, and more focused approach to pediatric formulation development and introduction.[31] The GAP-f would coordinate upstream and downstream processes to accelerate priority drug development, availability, and uptake and would serve as a novel approach for drug development for other pediatric conditions (Fig. 1). Through collaboration across the private and public sectors, with researchers, clinicians, and community, processes are being established to ensure greater, more rapid availability of and access to more potent, robust, better-tolerated ARVs for children. The multistakeholder engagement is critical to promoting child-centered ethical research conduct.[32] Social research to understand decision-making and perception of

TABLE 1. Innovations in Study Design to Accelerate Availability of Pediatric ARV Drugs

- Weight-band rather than age-band dosing
- Simultaneous rather than sequential enrollment of weight-band cohorts
- Inclusion of adolescents in adult registrational trials
- Increased emphasis on pharmacokinetics modeling to inform study design
- Consideration of novel study designs including adaptive designs, Bayesian approaches, and opportunistic studies
- Early development of formulations for infants and young children and fixed-dose combination formulations for children



- Prioritize products included in the PADO list to ensure products developed improve the treatment portfolio
- Formulation development (or reformulation of existing drugs)
- Generate clinical evidence that meet regulatory requirements
- Support regulatory approval at global and national level
- Invest to secure prioritized commitment from manufacturers
- Accelerate product introduction by early engagement with MOHs, primary care physicians, HCWs, and community activists
- Incentivize suppliers and coordinate procurement to catalyze uptake
- Establish pharmacovigilance/enhanced monitoring of paediatric patients

FIGURE 1. GAP-f. Adapted from Shortening the decade-long gap between adult and paediatric drug formulations: a new framework based on the HIV experience in low- and middle-income countries by Penazzato M, Lewis L, Watkins M, et al. (in press), 2017. HCW, health care worker; MOH, ministry of health.

children and families in research could further inform best practices. Another high priority area of inquiry that arose from the research prioritization process is to increase our understanding of the short- and long-term outcomes of starting very early treatment in infants living with HIV: the impact on reservoir, remission, and cure.[26] Historically, multitudes of challenges have complicated efforts to diagnosis and initiate ART close to the time of birth. New technologies, and innovative scientific approaches and collaborations have catalyzed new research efforts. Neurobehavioral abnormalities associated with HIV are common in children and require further research to inform preventive and rehabilitative interventions. The following case studies focus on infants and young children and initiatives to diagnose and effectively treatment newborns and infants. they will illustrate the critical role of basic science research and novel approaches to study design and implementation that are informing global efforts to end AIDS.

INNOVATIONS, SCIENTIFIC DISCOVERY, AND COLLABORATION: DIAGNOSIS AND VERY EARLY TREATMENT OF INFANTS WITH HIV INFECTION

Innovation Along the Diagnosis to Treatment Cascade

ART saves lives, and EID is the gateway into the pediatric treatment cascade. Despite recommendations from WHO to implement EID using nucleic acid amplification test at 4–6 weeks of life,[15] only 9%–60% of infants exposed to HIV are tested before 2 months of age.[33,34] This is primarily due to loss to follow-up between birth and first EID test.[35] Moreover, it often takes over 4–10 weeks from obtaining samples to receiving results.[36,37] Tragically, late treatment, illness, and deaths from HIV in infants remain common.

Routine HIV virologic testing at birth was added to existing diagnostic algorithms as a conditional recommendation in the 2016 WHO Guidelines.[15] Its main goal is to lessen time to HIV diagnosis and ART initiation in infants infected with HIV in utero. Birth testing is particularly attractive for countries with a high rate of in-facility deliveries. Its cost-effectiveness and favorable outcomes were supported by mathematical modeling data from South Africa.[38] To date, there are limited published data on the effects of birth EID on the infant testing and treatment cascade countries such as South Africa, Thailand, and Kenya that have adopted this strategy.

Linkage between testing and ART initiation, and retention in care are vital to achieving survival benefits of EID.[35,39] Mobile health technology could improve linkage and retention in care. The HITSystem that was evaluated in Kenya provides a link between the laboratory, clinician, and caregiver. The system generates text messages to caregivers when EID results are available and prompts action, which has resulted in faster ART initiation and higher retention in care.[40] MomConnect, a short-message service in South Africa, offers pregnancy advice and appointment reminders to pregnant women that could be extended to include EID reminders.[41]

Electronic health systems could be key in facilitating result notifications to health care workers and improving flow

of information to key stakeholders including the ministries of health and implementation partners. Successfully piloted in South Africa, the national health laboratory service provides key stakeholders and clinical teams a weekly electronic list of HIV polymerase chain reaction test results performed per facility, district, or province. Infants diagnosed with HIV are actively traced by community health care workers and tracing teams based at a facility or district using a polymerase chain reaction registry that contains contact details of the caregiver.[16] A similar web-based tracking system in Kenya has led to a shorter turnaround time from sample collection to patient notification.[42] Next steps include continued evaluations of new technologies, and devising strategies for implementation in communities with high HIV burden, and limited access to telecommunication, electricity, and health services.

Very Early ART and HIV Cure

Children face a lifetime of ART and HIV stigma that makes finding a cure to HIV immensely important. In 2013, the case of the Mississippi baby propelled the interest of the public and the research community in early ART and HIV cure in children.[43,44] Very early ART during the first 1–2 days of life in this infant subsequently led to undetectable viral load for 27 months after ART interruption at 18 months of age. The ability to maintain suppressed viremia in the absence of ART or HIV remission is also observed in adult cohorts,[45] whose low HIV reservoir size after early treatment is a predominant feature.[46]

The Mississippi baby and the pediatric cure agenda in general provided an enormous impetus globally to identify and start treating infants as early as possible. Although only a few settings can engage in "cure" approaches, the approach shifted the timeline earlier along the cascade, drawing attention to the realities of delayed diagnosis, limited ARV options, and high rates of early morbidity and mortality in settings with high numbers of new infections.[47] In the race to limit HIV reservoir seeding with early ART, the research and public health priorities merge. For example, in Thailand, researchers studying the HIV reservoirs and public health officers collaborated as part of the Active Case Management Network to increase the numbers of infants on ART and lower the age at ART initiation.[48] Measures are being taken to strengthen EID programs and point of care virologic testing is gaining momentum,[10,49–51] and applications now extend to monitoring of pediatric and adult HIV treatment.[52,53] Over the past several years, new efforts have been made to find safe and potent ARVs with appropriate formulations and dosing for neonates and young infants[54,55] (clinicaltrials.gov NCT01828073; NCT 02778204).

Studies of HIV persistence under therapy have generated unique opportunities to incorporate science into pediatric therapeutic agenda that is important for the long-term goal of improving child health. When viral replication is inhibited early with ART, children display low levels of cell-associated HIV DNA and HIV RNA,[56–59] shorter half-life of replication-competent virus from latently infected cells,[57,60] and their noninduced proviral genomes are mostly defective.[61] Young children have high frequencies of naive $CD4^+$ T cells that are likely more resistant to HIV.[62] Adolescents on ART since infancy with more than a decade of viral suppression are a unique population: their viral reservoirs continue to decay and only traces of HIV can be detected in their blood $CD4^+$ T cells.[63]

Exciting data from an infant nonhuman primate model showed that simian/HIV immunodeficiency virus can be eradicated when combined broadly neutralizing antibodies were instituted within the first day or second day of infection.[64] This is highly relevant to the pediatric HIV cure agenda with known timing of infection affording immediate HIV diagnosis and treatment. The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) is investigating broadly neutralizing antibody given in addition to ART to HIV-exposed (P1112, clinicaltrials.gov NCT02256631) and newly HIV-infected infants (P2008, clinicaltrials.gov NCT03208231). The global Early-treated Perinatally HIV-infected individuals: Improving Children's Actual Life with Novel Immunotherapeutic Strategies (EPIICAL) network is dedicated to advancing therapies for HIV cure in the early treated pediatric population.[65] Unlike adults, children have an active thymus and immune regeneration ability that is key to mounting responses to vaccines. Vaccine responses in children can be as good or better compared with adults for both non-HIV[66] and HIV vaccines.[67–70] HIV-exposed uninfected infants who received ALVAC (canarypox vector containing env, gag, pol)/AIDSVAX (engineered gp120 protein) had 22-fold higher levels and longer durability of the correlate for HIV protection, anti V1V2 IgG, than adults in the RV144 Thai trial.[69] Perinatally, HIV-infected children mounted higher HIV-specific immune responses to new epitopes after HIVIS DNA vaccine (7 plasmids of env, gag, Rev, and RT) compared with adults given the same vaccine.[67] Together, these data support the notion that early treated children may be more likely to respond to immunotherapeutics for cure.[71] Pediatric HIV cure research is poised to critically contribute to the global research efforts to curing HIV and to further drive the pediatric agenda to optimize treatments for the youngest children.

ARTs for Neonates and Young Infants

Emerging evidence of the potential benefits of very early treatment of HIV-infected neonates has propelled efforts to expand therapeutic options for infants. Currently, there are only 5 ARVs with appropriate formulations, dosing, and safety data to recommend their use in full-term neonates [zidovudine, lamivudine, nevirapine, lopinavir/ritonavir (at 2 weeks of age), and raltegravir].[72,73] The dosage and therapeutic use of nevirapine in newborns is investigational. However, important strides are being made to accelerate the development, study, and availability of the most potent ARVs to treat young babies.[12]

Historically, there has been little impetus to develop ARVs for newborn treatment. With routine infant diagnosis scheduled for 6 weeks of life, most infants who were successfully diagnosed and engaged in care did not begin ART until well beyond the second month of life. Furthermore, distinct aspects of early life make both the development

and study of drugs substantially more complex compared with adults and older children.[72–74] The first months of life are a dynamic developmental period characterized by rapid physiologic changes that influence drug metabolism, and in turn, dosing and toxicities. High rates of prematurity, low birth weight, and concomitant health conditions among infants born to women living with HIV infection add another set of considerations when determining dosing and safety of new agents.[75,76] The need for formulations other than liquids that are safe, acceptable, and feasible for use in low- and middle-income settings has further delayed access to new medications for infants.

The landscape of early infant treatment is slowly shifting, accelerated by collaboration among key stakeholders as well as the application of recommended innovations to drug development and study design.[12] For example, after a long period of development, lopinavir/ritonavir pellets, an alternative to the poorly palatable, heat-sensitive liquid formulation, were approved for children older than 3 months.[77,78] Dosing and acceptability of the new formulation were determined in the CHAPAS-3 study.[77,78] The LIVING study is now evaluating the effectiveness of the pellet formulation in combination with zidovudine and lamivudine fixed-dose combination tablets under routine conditions in Sub-Saharan Africa in infants and young children who cannot swallow tablets (clinicaltrials.gov NCT02346487).[79] In lieu of a separate study for children younger than 3 months, LIVING has been designed to include children starting treatment at birth to obtain safety and acceptability data for this age group. A lopinavir/ritonavir granule formulation and a four-in-one (lopinavir/ritonavir with abacavir and lamivudine) granule/powder product are anticipated to be available in the near future."

Scientific networks and investigators have embraced the weight-band dosing approach in lieu of the age-range dosing approach traditionally used in pediatric pharmacokinetic studies. Investigators are now using sophisticated modeling and simulation techniques using data from older children and adults to inform dosing strategies for neonates and infants.[72,73] Washout pharmacokinetic studies, measuring newborn blood levels during the first days to weeks of life of transplacentally transferred maternal ARVs, have also given insight into the behavior of specific agents during this period of rapid physiologic change. Raltegravir, available in a chewable tablet and a granule formulation, was recently approved for use in full-term neonates and is an excellent example of optimizing data sources to inform pediatric dosing.[80] Investigators used pharmacokinetic data from older children and adults, a small phase I trial in newborns, and maternal washout studies to select a daily dosing regimen that was then tested and ultimately approved for very early treatment.[81–83] Studies are underway to extend dosing to low birth weight babies. The development plan for dolutegravir is following a similar pathway, maximizing data sources, modeling pharmacokinetics and dosing, and testing doses in small mini-cohorts of children (clinicaltrials.gov NCT01302847).[84,85] In parallel, efficacy and additional dosing and safety data are being studied in the ODYSSEY trial (clinicaltrials.gov NCT02259127). These combined efforts should lead to more rapid approval and availability of dolutegravir for all children including neonates.

HIV, ART, and Early Brain Development

Brain development begins during the first trimester and continues into early adulthood. The immaturity of the central nervous system (CNS) through adolescence makes it vulnerable to insults from HIV and its treatments, and places infants and children with HIV at particular risk of damage to developing structures and functions. Thus, timing of infant HIV infection (in utero, intrapartum, postnatal),[86] maternal health status,[87] and effective ART initiation are major determinants of frequency and severity of abnormalities. Although severe CNS effects from HIV (ie, encephalopathy) are uncommon since the introduction of earlier ART, more subtle neurobehavioral abnormalities remain in some children and may be related to host,[88] viral,[89] and treatment factors.[90] There may be a critical window of opportunity when abnormalities can be prevented by early ART,[91,92] but the precise timing is under investigation. The effects of early therapy on the CNS are being studied and include CNS penetration of ART drugs on neurologic outcome and use of comprehensive neurobehavioral assessments.[93]

Studies are underway to better characterize subtle abnormalities[94] that are also observed in virologically suppressed children, as well as to understand their potential impact on daily life.[95] These abnormalities may be static because of delayed or suboptimal treatment or progressive because of ongoing immunologic or virologic processes.[96] Some static neurologic deficits may only manifest at an older age as a possible consequence of "growing into a deficit."[97,98] An example of the latter is mathematics ability, compromised at an early age, but evident only with maturity and reliance on such ability. Neurobehavioral HIV studies benefit from recent developments in behavioral and brain-imaging assessments. Brain-imaging studies with higher specificity and resolution have identified abnormalities in specific cerebral structures[99,100] that are related to specific neuropsychological deficits. Similarly, computerized neurocognitive testing may provide more standardized and reliable administration and results, and improve implementation in a less resourced environment.[101] Longitudinal neurobehavior and neuroimaging control data from children in the general population are being generated.[102,103] In addition, pediatric HIV research networks, both treatment-oriented such as the IMPAACT[104] and PENTA-ID[105] as well as cohort studies such as the Pediatric HIV/AIDS Cohort Study (PHACS)[106] and CIPHER,[107] are addressing HIV-associated neurobehavioral and psychiatric issues.

HIV-exposed uninfected children born to mothers on ART during and after pregnancy form a growing population impacted by HIV. Exposures to HIV and perinatal ART have been related to potential acute as well as late neurobehavioral sequelae.[98,108] Timing of exposure to a specific ARV agent and maternal immunologic and virologic status during pregnancy may be contributing factors.[109] However, longer follow-up is needed particularly for newer ARVs. Moreover,

available evidence has not unambiguously linked currently available ARVs to adverse clinical outcomes.

Although much of the earlier work characterized the neurobehavioral abnormalities, current research has focused on the prevention and rehabilitation of the deficits.[110] Besides very early ART,[91] ability-based and parent-based interventions may ameliorate some of the neurobehavioral deficits.[111–113] Even as effective ART is available to prevent and treat infant HIV infection, long-term outcomes with respect to brain structure and function remain a concern and require continued monitoring and tailored preventive and rehabilitative interventions.

CONCLUSIONS

Scientific discovery, innovation, and collaboration are key drivers propelling efforts to improve diagnostics, optimize treatments, and enhance the health outcomes of children living with HIV infection. Scientists, policy makers, implementers, and industry have aligned to advance the pediatric therapeutic agenda and results are paying off. Key examples are the prioritized global research agenda, PAWG guidance, PADO prioritization list, and GAP-f. New medications and formulations for children are under development and a number of new ARVs are becoming available at a more rapid pace than ever before. Interest in very early treatment to achieve a cure and to prevent CNS disease have focused attention on treatment of neonates and given new urgency to efforts to improve the EID cascade and have potent, safe, and well-tolerated ARV regimens for youngest children.

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