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

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 treatment6–8 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
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
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. Historically, multitudes of challenges have complicated efforts to diagnose 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, only 9%–60% of infants exposed to HIV are tested before 2 months of age. This is primarily due to loss to follow-up between birth and first EID test. Moreover, it often takes over 4–10 weeks from obtaining samples to receiving results. 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. 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. 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. 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. 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.

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. A similar web-based tracking system in Kenya has led to a shorter turnaround time from sample collection to patient notification. 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. 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, whose low HIV reservoir size after early treatment is a predominant feature.

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. 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. Measures are being taken to strengthen EID programs and point of care virologic testing is gaining momentum and applications now extend to monitoring of pediatric and adult HIV treatment. 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 (clinicaltrials.gov NCT01828073; NCT 02778204).

Studies of HIV persistence under therapy have generated much interest in exploring the potential for treating infants who are already on ART. For example, the RV144 Thai trial 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. 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 (EPICAL) network is dedicated to advancing therapies for HIV cure in the early treated pediatric population. 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 and HIV vaccines. 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. 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. Together, these data support the notion that early treated children may be more likely to respond to immunotherapeutics for cure.

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]. 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.

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.80

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 abnormalities96 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 structures99,100 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 IMPAACT104 and PENTA-ID105 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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