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Using Observational Data to Inform HIV Policy Change for Children and Youth

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Abstract: Observational data characterizing the pediatric and adolescent HIV epidemics in real-world settings are critical to informing clinical guidelines, governmental HIV programs, and donor prioritization. Global expertise in curating and analyzing these data has been expanding, with increasingly robust collaborations and the identification of gaps in existing surveillance capacity. In this commentary, we describe existing sources of observational data for children and youth living with HIV, focusing on larger regional and global research cohorts, and targeted surveillance studies and programs. Observational data are valuable resources to cross-validate other research and to monitor the impact of changing HIV program policies. Observational studies were among the first to highlight the growing population of children surviving perinatal HIV and transitioning to adolescence and young adulthood, and have raised serious concerns about high rates of treatment failure, loss to follow-up, and death among older perinatally infected youth. The use of observational data to inform modeling of the current global epidemic, predict future patterns of the youth cascade, and facilitate antiretroviral forecasting are critical priorities and key end products of observational HIV research. Greater investments into data infrastructure are needed at the local level to improve data quality and at the global level to faciliate reliable interpretation of the evolving patterns of the pediatric and youth epidemics. Although this includes harmonized data forms, use of unique patient identifiers to allow for data linkages across routine data sets and electronic medical record systems, and competent data managers and analysts are essential to make optimal use of the data collected.

Key Words: children, adolescent, HIV, cohort, data, observational

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INTRODUCTION

The pediatric HIV epidemic is shifting with increasingly complex program and policy needs around implementing diagnosis, treatment, and retention interventions. Although fewer children are becoming infected as prevention of mother-to-child transmission programs are scaled up, those who are perinatally infected and receiving antiretroviral therapy (ART) are living longer.[1,2] The total annual number of children and adolescents living with HIV is therefore a function of the decreasing number of perinatal infections, longer survival into adolescence, and aging up out of adolescence into adult care of previously perinatally infected children. Such factors related to the timing of infection and transition from pediatric into adult-focused HIV care impact how pediatric HIV clinical and program data are interpreted, and require different analytical methods from those used to study adult observational cohorts (eg, disaggregation by age and mode of infection; tracking patients as they transition).

Causal analyses of observational data have provided valuable evidence to support policy changes where trials may not be feasible, such as around "when to start" ART in African children outside of infancy.[3] Methodological studies suggest that there is little evidence for significant effect-estimate differences between observational studies and randomized controlled trials.[4–6] Observational studies and trials may have differing but complementary results, and understanding observational study designs and their potential for bias is central to applying their findings to the real world.[7–12]

WHAT ARE OBSERVATIONAL DATA?

Observational data are largely collected from routine health care settings, with prospective or retrospective data collection. Because the data are from programs rather than controlled trials, they reflect routine patient clinical management. In their simplest form, observational studies simply count the number of people in a given population with

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specific characteristics. This can involve counting of observed clinical and programmatic factors, such as the numbers of patients who have been tested, are in care, are taking a given ART regimen, and have been loss to follow-up, transferred, or died. Data collection can be passive, for example, a clinic registration system designed to track appointments and retention, or active, where data are intentionally gathered through bespoke data collection forms or in specific populations.

The earliest examples of case series in pediatric HIV were studies in high-income countries describing infant mortality.[13,14] In resource-limited settings, early reports from observational cohorts on the feasibility and outcomes of ART programs for HIV-infected children were important in advocating for expanded ART access.[15,16] Some of the first cohorts of HIV-infected infants are ongoing today,[17,18] whereas others have been developed for specific purposes, such as to systematically evaluate the effects of in utero exposure to HIV and antiretroviral drugs on outcomes in HIV-exposed but uninfected children.[19]

Observational data from clinical care cohorts can fill evidence gaps by providing detailed information on critical outcomes, including age and CD4 at ART start, retention and loss to follow-up, and mortality.[3,20–22] Such data are particularly valuable for addressing clinical questions that are unlikely to be evaluated in randomized controlled trials and for assessing the real-world impact of implementing new guidelines or interventions.

NATIONAL DATABASES AND COHORTS OF PEDIATRIC AND ADOLESCENT DATA

National ART program data, using passive reporting at individual health care settings, count patients taking ART and collect a limited number of variables, can often simulate a cohort design, and can be analyzed longitudinally.[23] Countries also can conduct focused or nationally representative surveys of risk behaviors and HIV testing to complement these data, allowing for data capture from community settings.[24,25] The Population-based HIV Impact Assessment Project (http://phia.icap.columbia.edu/) is creating additional data resources describing children and youth in the community and in HIV care from 13 focus countries of the US President's Emergency Plan for AIDS Relief (https://data.pepfar.net/).

However, as data are aggregated up to regional and national levels, granularity may be lost, as is the ability to analyze longitudinal patient trajectories, which is important for being able to identify risk factors for particular outcomes. Many countries do not have the capacity to disaggregate their pediatric and adolescent HIV program data by 5-year age groups and sex, and reporting of key population status for older adolescents is rare. Countries frequently rely on modeled data to characterize those receiving treatment and assess outcomes, which are then fused to inform modeling globally through the UNAIDS Spectrum platform and Global AIDS Monitoring program.[26] Modeled global estimates disaggregated by pediatric and adolescent ages and sex have been publicly accessible through UNAIDS (http://aidsinfo.unaids.org/), and data visualizations on their website are becoming increasingly detailed.

The Collaborative Initiative on Pediatric HIV Education and Research of the International AIDS Society has developed a database of HIV cohorts for those 0–19 years of age (http://www.ias-cipher.org/FrontEnd/iasapp/map.html), which offers a platform for cohorts of varying sizes to share their scope of work. Smaller subnational cohorts can be unique in their ability to characterize experiences of patients and providers who may be in rural areas or district-level health care settings.[27,28] There are multiple regional and global research-focused pediatric cohort collaborations, including the European Pregnancy and Pediatric HIV Cohort Collaboration,[29,30] which links national cohorts across Europe with sites in Thailand, and the International Epidemiology Databases to Evaluate AIDS,[31–33] which brings together 6 regional pediatric cohort collaborations on 3 continents. Both use a common data exchange standard (http://iedea.github.io/; http://www.hicdep.org/) to promote harmonization and facilitate comparison. Collaborative Initiative on Pediatric HIV Education and Research also has a global cohort collaboration that brings together research-focused and service-delivery cohorts from low- to high-income settings that have conducted analyses of key priority outcomes, including on adolescent epidemiology and first-line durability.[34,35]

Because of the relative paucity of data for children compared with adults, cross-regional and global research efforts combining observational data have been essential to characterizing pediatric and adolescent HIV outcomes, particularly when investigating subgroups and rare exposures and outcomes. These analyses have offered practical perspectives into how well global testing and treatment guidelines are being implemented,[31,36] and can identify gaps in care and guide the development of future interventional trials. Relevant data may also be extracted for the purpose of modeling that can project future treatment monitoring and medication forecasting needs.[37,38] However, more could be done to expand the utilization of existing databases, such as grant funding to promote research that links and compares surveillance and research databases, and online data visualizations that make results more easily accessible to policymakers.

HOW CAN OBSERVATIONAL DATA BE USED TO INFORM PROGRAMS AND POLICY FOR CHILDREN AND ADOLESCENTS?

National surveillance data allow for tracking responses to policy changes in HIV testing, ART uptake, retention or loss to follow-up, and mortality, and progress in achieving the UNAIDS 90-90-90 targets for ending AIDS.[39–41] However, pediatric data are frequently incomplete relative to adult data, as evidenced by lower rates of overall and detailed reporting to Global AIDS Monitoring, requiring a greater reliance on modeling estimates.[41] Observational cohort data consequently provide a key alternate source to cross-validate national data (Boxes 1 and 2).

BOX 1. Using observational data to guide birth polymerase chain reaction (PCR) implementation in South Africa

Achieving targets for early infant diagnostic testing has been a continual challenge in low- and middle-income country settings. In 2015, South Africa implemented a policy to obtain routine HIV PCR testing on all HIV-exposed infants at birth and at 10 weeks of age in an effort to improve testing coverage.[57] However, there were acknowledged risks regarding the level of additional technical resources that would be needed, and the potential for infants with negative birth PCRs to miss their follow-up testing.

Observational research has shown that, although high infant birth testing rates of >90% could be achievable, programs would need extensive counselor and other provider support to maintain consistent testing uptake.[58] In addition, there have been lower rates of repeat testing (eg, 73% vs. 85%) among those with negative birth PCRs, in this primarily breastfeeding population.[59] These studies highlight where targeted improvements would be needed at the national level to support successful policy implementation.

BOX 2. Using observational data to complement trial results on when to start ART in infants

Before recent global guidelines recommending universal ART, regardless of age or CD4 level, there was substantial variation in when countries from low- to high-income settings recommended to start therapy in infants. This was in part due to limited access to and inconsistent scheduling of infant PCR testing, and concerns around exposure to available antiretroviral drugs. The CHER trial in South Africa clearly demonstrated the benefits of early HIV diagnosis and early ART to substantially reduce HIV progression and infant mortality compared with delayed ART, definitely changing pediatric HIV treatment policy.[60]

Complementary evidence was provided the following year through similar findings from a meta-analysis of cohort studies in Europe, confirming the effectiveness of early ART initiation in those settings.[61] Further cohort analyses of longer-term outcomes beyond the median of 40 weeks of follow-up in the first CHER paper showed that evolution of immunological and virological responses of those successfully started on ART after 12 months was similar.[62]

Observational data are especially useful for monitoring outcomes of perinatally infected children. HIV treatment cascades frequently focus on 12- or 24-month outcomes, whereas cohorts may follow children infected perinatally to adolescence and adulthood. Observational studies were among the first to highlight the growing population of children surviving perinatal HIV and transitioning to adult care.[42,43] Long-term monitoring studies in the United States and United Kingdom and Ireland have raised serious concerns about high rates of treatment failure, loss to follow-up, and death among older perinatally infected youth.[44–46] These have complemented clinical trials to identify strategies to simplify ART and improve adherence among youth, such as the BREATHER study of weekend-structured treatment interruptions.[7]

Another key role of observational data has been in phase 4 studies, also known as safety studies, and pharmacovigilance studies.[47] These studies identify and evaluate the long-term use and safety of drugs beyond the common 48- or 96-week endpoints of clinical trials, and are important to monitor for toxicities that may only emerge with long-term use (eg, lipoatrophy from stavudine and nephrotoxicity from tenofovir disoproxil fumarate) or use in populations different from those included in trials.[48,49] EPPICC has conducted meta-analyses of safety data from participating cohorts, including studies of darunavir, atazanavir,[50] and tenofovir,[51] and results have been used by pharmaceutical companies as part of their postlicensing commitments with the European Medicines Agency, as well as HIV treatment guideline committees.

LIMITATIONS OF OBSERVATIONAL DATA

Routine program and other forms of observational data can frequently be incomplete, necessitating careful interpretation of outcomes. For example, it may be difficult to distinguish within routine program data between true losses to follow-up and documented or silent transfers because of transitions in care as adolescents age outside of the pediatric age range used for national surveillance reporting. In South Africa, a study of adolescents in the Western Cape with linked patient identifiers across health care (eg, clinic, laboratory, and pharmacy) to facilitate tracking, and showed that 81% were confirmed to have completed their transfer to another facility.[52] However, in the Eastern Cape, another cohort that lacked these linked patient identifiers reported only 67% were successfully transferred.[53] Moreover, as losses to follow-up increase with older age, the risk of unascertained mortality over time remains unclear, and may differ between perinatally and behaviorally infected youth. Although this issue has been extensively studied in adult cohorts in sub-Saharan Africa, with mortality of up to >30% in the first year after being lost,[54,55] there are fewer tracing data in children and adolescents.

There also are biases inherent to pediatric cohort data that prevent overgeneralization of study findings. These include selection bias, as cohorts may over-represent those receiving care in tertiary and urban centers, and under-represent rural populations. Because of generally low rates of early infant diagnosis, those children who are in care were more likely to have presented to care in early childhood as opposed to being diagnosed in infancy through prevention of mother-to-child transmission programs. This indication bias would favor survivors or those infected later during breastfeeding. Recall bias may be a factor when data are collected from caregivers of children and youth. Use of the STROBE criteria to improve the quality of observational research can help to address some of these limitations.[56]

THE NEED FOR MORE ROBUST ROUTINE HEALTH DATA INFRASTRUCTURE

Although observational data represent a valuable and practical resource on which to base HIV policy decisions, cohort studies rely on existing data collection infrastructure that needs improved maintenance to be used most effectively. This begins with investing in local data systems, including supporting data entry by clinic and program staff, and harmonized forms that consistently document priority demographic, clinical, and laboratory data. It also includes supporting and training local data managers to be able to competently analyze and interpret large data sets to guide clinicians and implementers. Such investments in HIV programs in low- and middle-income settings would strengthen health care systems overall and could build capacity toward implementation of electronic medical record systems, which could both improve clinical care as well as facilitate data retrieval and promote quality controls.

Funding for implementation research to understand and then improve how interventions and programs are delivered are critical to improving efficiency in the increasingly restricted global HIV donor environment. Studies tracing those lost to follow-up, would help to bridge current data gaps and inform modeling to more accurately characterize the size, outcomes, and future treatment needs of children and adolescents. However, the inability of most countries to establish population-level unique identifiers remains the single greatest challenge to cohort data management. In their absence, researchers have developed sophisticated methods to deal with missing data.

CONCLUSIONS

Although lacking the benefits of randomized selection, cohort studies offer the opportunity to analyze data collected in real-world settings of busy clinics coping with limited resources, providing valuable and reliable evidence of the "on the ground" reality of HIV care in children and youth. Greater investments into data infrastructure are needed at the local level to improve data quality, and at local and global levels to facilitate reliable interpretation of the evolving patterns of the pediatric and youth epidemics. Until demographic data infrastructure improves in the settings with the greatest burden of HIV, we will need observational data to provide essential evidence to guide HIV policy decisions.

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