## The post-pediatric HIV generation in Asia

*Adolescent HIV care, treatment, and transitions into adult life*

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The post-pediatric HIV generation in Asia: Adolescent HIV care, treatment, and transitions into adult life

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# CONTENTS

CHAPTER 1

# General Introduction

There are books, music, musicals, theater plays, documentaries, movies, television, and other forms of art that reflect on the early years of the HIV epidemic. They often focus on the confusion, fear, despair, and resilience of the individuals and communities living through a time when we did not know what caused AIDS nor how to stop it. The stories they tell highlight the injustices of being abandoned by the medical and scientific establishments, and the kindness of tribes of friends who came together to support each other when stigma and discrimination drove others away. Our remembrances of the history of HIV in the world still resonate after almost 40 years, and continue to reach new generations – as evidenced by the popularity of the UK television show *It's a Sin* and the US Tony award for best play for *The Inheritance* in 2021. However, few of these biographical or fictional accounts include the experiences of children with HIV.

This is at least in part because children represent the smallest global sub-group of people living with HIV – in 2020, there were an estimated 1.7 million children under the age of 15 years compared to 36 million adults (1). Yet, infants who acquire HIV through perinatal transmission are the most immunologically vulnerable population to live with HIV (2, 3). As a result, they bear the highest morbidity and mortality of any age group, with few surviving after early childhood if untreated (4-6). There are now an estimated 1.7 million adolescents 10-19 years of age, with 140,000 in the Asia-Pacific and 1,540,000 in sub-Saharan Africa (1). Adolescents with perinatally acquired HIV represent an even smaller subset of those who were diagnosed and started on antiretroviral therapy (ART) early enough to reverse their disease progression. Previous UNAIDS analyses have estimated that 35% of females and 57% of males 15-19 years of age with HIV are those with perinatal infection (*Chapter 4*; Figure 1) (7). These proportions are likely to change as more children born earlier in the ART era survive into older adolescence, and are counterbalanced by reductions in vertical transmission.

As they continue to age, these adolescents face a combination of challenges to their health and quality of life that are directly related to their HIV infection – both because of the long-term impact of the virus on their immune systems and the persistent stigma they have experienced from childhood. Although adolescents with non-perinatally acquired HIV also struggle with stigma after their HIV diagnosis, those with perinatal HIV have had to cope with negative social impacts of HIV from birth. The fear of stigma starts with concerns around disclosing the HIV status of their mother or both parents (by the parents themselves or other caregivers when children are orphaned), which reflects complicated family dynamics around placing blame for their child's HIV infection. These fears can be combined with grief over the loss of their parents due to HIV, which has been reported in 23% of Asian adolescents with

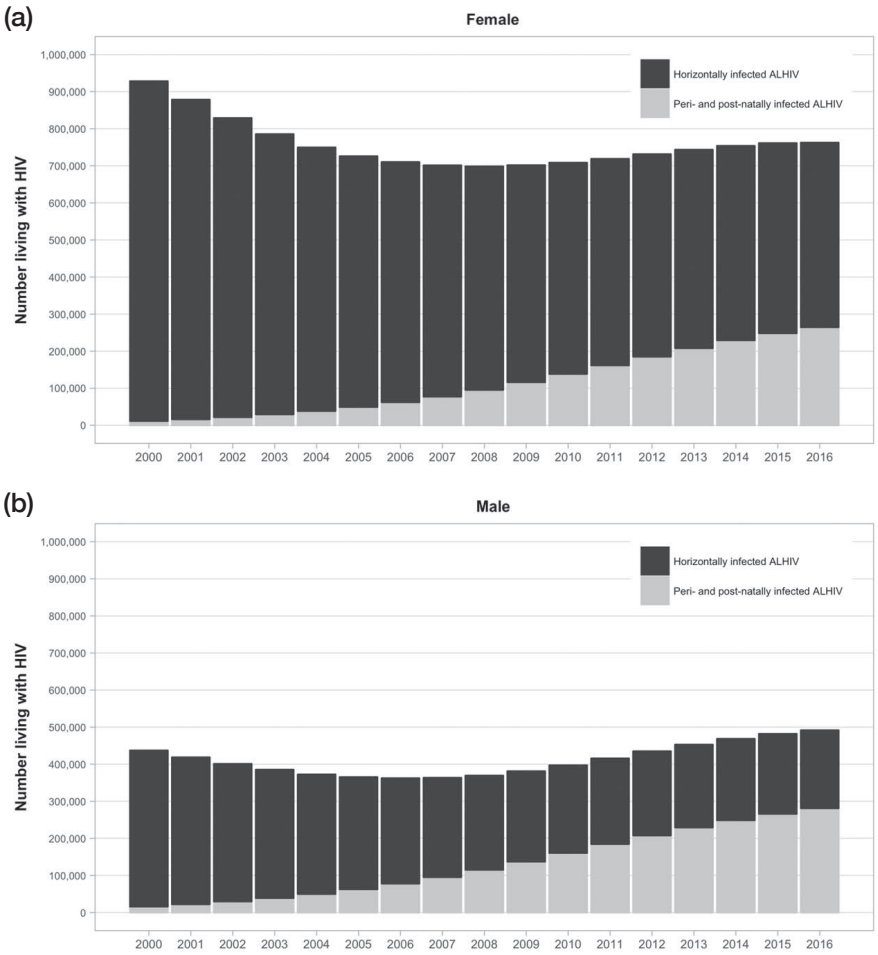


**FIGURE 1.** Numbers of older adolescents (age 15–19 years) living with HIV globally by sex and mode of transmission: 2000–2016 (data source: UNAIDS 2017 estimates). Female **(a)** and male **(b)** older adolescents (age 15–19 years) globally living with HIV by mode of transmission (peri/postnatally infected in grey and "horizontally infected" [non-perinatal acquisition] in black). (7)

perinatal HIV (8). These factors drive delays in initial HIV status disclosure to children, which often is out of concern that they will not be able to "keep a secret" and avoid telling others (9, 10). Instead, parents and non-parental caregivers hide or lie about the reasons why their children have to take daily ART, which is associated with poor adherence to ART, risking antiretroviral drug resistance that can compromise future

treatment options (11, 12). These are only some of the unique aspects of growing up with perinatally acquired HIV which merit multidisciplinary study and intervention, and will be the primary focus of this thesis.

In the Asia region, more adolescents with perinatal HIV are reaching the age where they are expected to transition into independent adults (13, 14). This includes taking responsibility for their health care management and leaving behind their pediatric HIV providers. They are becoming a "post-pediatric" generation of young adults who are meant to move forward with their lives into a complex adult world (15). Unfortunately, this transition process is fraught with difficulties at both the individual and societal levels. They are arriving at this crossroads after a lifetime of having HIV shape and define how they view themselves and how they are viewed by others. In order to understand these personal and environmental factors more deeply, it is useful to review the global and regional histories of the pediatric HIV epidemic.

## THE BEGINNINGS OF THE PEDIATRIC HIV EPIDEMIC

The first report of immunodeficiency due to HIV in the US was by the US Centers for Disease Control and Prevention (CDC) in 1981, before the term AIDS had been defined or the virus identified (16). In 1985, the CDC reported on cases of "pediatric acquired immunodeficiency syndrome," which noted the sole risk factor for infection was having a mother from a high-risk group (17). At that time, public health experts could only encourage women with HIV to "delay pregnancy," because they did not know how to prevent transmission. Almost all children in those early years acquired HIV from vertical transmission, with some becoming infected through transfusions of contaminated blood/blood products (18). Their immature immune systems were no match for HIV, and most died by early childhood of *Pneumocystis carinii* (now *jirovecii*) pneumonia and other opportunistic infections (19-21).

While enzyme-linked immunosorbent assays and Western blot testing allowed for hundreds of pediatric cases to be diagnosed in Western countries by the mid-1980s (22), limited provider awareness and laboratory capacity made it harder to identify those with HIV in low- and middle-income countries. However, it rapidly became clear that the global pediatric HIV epidemic was already expanding. The first children with HIV in Africa were reported on in the literature in 1986 by Dr. Jonathan Mann and colleagues working in Zaire, now the Democratic Republic of the Congo (23, 24). With the World Health Organization (WHO), their team developed a simple clinical case definition that expanded the ability to diagnose children, guide medical management and contribute to surveillance in contexts without access to laboratory testing (25).

Very small numbers of pediatric cases were initially reported in Asia in association with both perinatal and transfusion-associated transmission in the late 1980s (26-28). In the early 1990s, Thailand became the epicenter for perinatally acquired pediatric HIV in the region (29, 30). While this was initially associated with infections among female sex workers and female partners of clients of sex workers (31, 32), it also was because Thailand was among the first in the region to acknowledge the importance of HIV and embark on widespread testing and prevention campaigns, with the backing of both the government and an emerging civil society (33, 34). This created the need and opportunity for research into prevention interventions that could be implemented in low-resource settings, and the country became a global hub for HIV research. Not surprisingly, one of the first major pediatric HIV clinical trials to be conducted in Asia was in Thailand, where researchers evaluated the efficacy of short-course zidovudine regimens to prevent mother-to-child HIV transmission (35-37).

## CHILDREN ARE NOT SMALL ADULTS

Advocacy has been at the heart of the global HIV response. People living with and at risk for HIV were the first who demanded that governments and scientific institutions acknowledge an emerging epidemic and support the research needed to find treatments. Beginning with movements sparked by US-based organizations like ACT UP, advocates have long demanded respect for their self-leadership, which emerged from among the most affected gay communities and their supporters (38). They have fought for their right to equitable care, and for meaningful involvement in the development of research and health policies that impact them (39, 40). This advocacy has achieved substantial benefits for HIV civil society more broadly, and built up powerful national, regional, and global networks of people living with HIV.

However, children have seldom been in positions to publicly speak out for themselves. In addition, their parents and caregivers often are from socially and economically marginalized communities who are unlikely to themselves be part of organized advocacy. While there were examples of children with HIV whose struggles with their disease captured global attention, like Ryan White in the US and Nkosi Johnson in South Africa, they have been the exceptions. Most children are not even told they are living with HIV until they are adolescents (10), and few families are willing to risk discrimination at school and in their communities by disclosing that they are HIV-affected families (41). Instead, when it came to pediatric HIV, clinical providers and child health policy makers were those at the forefront of most advocacy efforts. However, building on the example of women like Elizabeth Glaser in the US, global movements to build leadership across the communities of women living with HIV have grown.

A perennial challenge in the field of pediatric HIV has been to secure the development and production of safe and effective antiretroviral drugs for children of all ages (42). The first ART regimens were created for adults, and the evidence supporting their safety and efficacy could not be directly extrapolated to infants and children – as they were not "small adults" (43, 44). It took many years to push for the development and production of formulations that could be administered to children – a battle that continues today (45, 46). Pediatricians and community advocates negotiated with pharmaceutical companies and research agencies to conduct the trials and pharmacokinetic studies needed. Federal policies have helped to solidify the rationale for pediatric drug development. The 2003 Pediatric Research Equity Act of the US Food and Drug Administration and the 2007 Paediatric Regulation of the European Medicines Agency mandated manufacturers to outline pediatric studies for new products (47). However, the process remains time-consuming, and regulators in LMIC contexts seldom have such requirements. Moreover, even after pediatric formulations had been developed by "originator" companies, they were usually not available outside of Western countries, due to their high cost or lack of regulatory approvals.

In low- and middle-income countries, providers split and crushed the available and usually generic adult antiretroviral tablets, hoping that the actual amounts of active drug ingested would be sufficient for their patients (Figure 2) (48, 49). Specific to pediatric HIV, doses had to regularly be adjusted as children gained weight. To simplify the process, policymakers came up with weight-band dosing tables that advised

**FIGURE 2.** Sachets with crushed antiretroviral medicines for use in an Indonesian child, 2012.

using half tablets at different ranges of weight and age. Unfortunately, those at the low and high ends of each weight band were at the greatest risk of being overdosed (associated with drug toxicity) or under-dosed (leading to inadequate drug levels). In addition, certain medicines were only available in capsules and could not be split at all or were available solely in badly tasting liquid formulations, which often required cold storage, making them even more difficult to use in LMICs. The pill burden for a small child could be up to 10 a day for those on more complex second-line regimens, which in LMICs often included drugs that were no longer recommended for use in high-income countries, as no other options were available (50).

These early difficulties in delivering weight- and age-appropriate pediatric ART put children at especially high risk of treatment failure and drug resistance, as well as drug toxicities like lipodystrophy, due to overdosing of drugs like stavudine. After this first generation of treated children reached adolescence, studies from low- to high-income countries showed that some bore the consequences of our initial failures to adequately and consistently suppress their virus (51-55). For example, a European study showed that youth with perinatally acquired HIV had almost twice the rate of triple-drug class resistance than youth with heterosexually acquired HIV (9.6% vs. 4.7%) (52). Studies in South and Southeast Asia found that most adolescents who survived through childhood were on effective first- and second-line ART regimens, but that between 15-20% of them were experiencing treatment failure and opportunistic infections (56, 57). Other studies in sub-Saharan Africa showed increasing rates of multi-class resistance to first-line regimens. Because switches to second-line often occurred only after prolonged viral failure, as much as 95-100% of children had resistance mutations to nucleoside and non-nucleoside reverse transcriptase inhibitors (58). This likely contributed to pre-treatment resistance that was already 24% by 2013 among African children who were not exposed to antiretrovirals for perinatal prevention (59). On top of the social, behavioral, and developmental challenges inherent to adolescence they had to cope with, these youth were beginning to run out of ART regimen options before they reached adulthood (13, 60).

## ADOLESCENTS ARE AT THE CROSSROADS OF LIFE

The trajectory of pediatric HIV infection, care, and treatment is unique on multiple levels. Although research has shown that adults who are diagnosed early and started on ART before severe immunosuppression can achieve standard lifespans in comparison to their peers without HIV (61), this is clearly not the case for those with perinatally acquired infection. For these reasons, it is critical that providers, researchers, and policymakers carefully monitor trends in adolescent HIV outcomes and mortality

in ways that can then guide individual and programmatic interventions to improve their health outcomes and quality of life.

The current generation of adolescents and young adults have stumbled through their own version of the AIDS documentary "*How to Survive a Plague*" (62), and now find themselves about to transition into becoming adults. Unlike most of *their* peers without HIV, they will have to do this while learning to self-manage an as-yet incurable disease, often living as orphans who have been denied opportunities for education and employment, and in fear of disclosing their HIV status to others. These young people are facing a crossroads beyond which few have survived to the third decade of life (Figure 3). While it is the privilege of pediatric providers and advocates to help facilitate these transitions out of our direct care, we cannot allow these young people to be lost in our societies or health systems.

**FIGURE 3.** "The point of change in one's life," by Kawi, age 18 (at the time of the painting), Children and Youth Program, Thailand, 2015.

*"This picture reflects my life at present. The river represents the challenge. It represents pain and suffering. If I can cross the river, I have to change my life, and there will be hope for the future."*

## AIM AND OUTLINE OF THIS THESIS

This thesis examines the period of adolescence and young adulthood of those who grew up as children with perinatally acquired HIV. The main aim of this body of work has been to explore how this population is transitioning into new phases of health and care across life stages, focusing on the Asia regional experience, recognizing that they are especially vulnerable to poor HIV treatment outcomes. Because adolescents with perinatally acquired HIV represent a very small proportion of the people living with HIV in Asia, there is a substantial risk of their priorities being "lost" within local and regional HIV programs. In order to develop and advocate for adolescent-specific clinic infrastructure and interventions that are tailored to their health needs, we need data. Epidemiology research is essential to building a robust evidence base that can be used to guide HIV-related policies and programs. That research also needs to extend beyond traditional pediatric HIV treatment outcomes to study sexual and reproductive health, mental health, and how young people who are transitioning to adulthood cope with the responsibilities of adult lives.

Part 1 looks at the global picture of adolescent HIV. *Chapter 2* is an editorial commentary that summarizes the challenge to pediatric HIV providers who were watching their patients age and preparing them to move on to adult HIV care, in a world where prevention of vertical transmission was leading to fewer new children in their clinics (15). It was written prior to and inspired the thesis research that followed, and provides context for the discussion in subsequent chapters. *Chapter 3* is a commentary that reviews how routinely collected data can and should be used to guide changes in program policies, especially in low- and middle-income country settings (63). Compared to adult research, pediatric HIV data are often harder to come by, and such observational data can be used to complement trial and other research data. *Chapter 4* is a review that presents an example of how these data resources can be re-examined in creative ways to provide even more granular data to help direct program resources to more effectively support youth who are lost to care, or encourage retention through differentiated service delivery (7). *Chapter 5* applies these principles to a global analysis of mortality and loss to follow-up in the global IeDEA pediatric cohort, including youth from Asia (64). By disaggregating data by likely perinatal HIV infection status, this research began to tease out adolescent treatment outcomes.

The focus shifts to Asia in Part 2, which begins with a regional survey of adolescent HIV care and treatment services in *Chapter 6* (65). Pediatric providers had often been trying to manage transition without guidelines or training resources. In addition, they were less prepared to cope with family planning needs of sexually active youth

or how to care for young key populations. *Chapter 7* was a study of standardized causes of death from childhood to adolescence (66). This was the result of a multi-year effort to rigorously detail the medical reasons for death, rather than to lump them all as being due to HIV, as is most often done. *Chapters 8* (67) and *9* (68) are from the same longitudinal cohort study to examine the sexual health and cervical cancer risk of adolescents and young women with perinatally acquired HIV, compared to their peers. *Chapter 10* ends the thesis with a study of youth who had already transitioned to adult HIV care, and provides a deeper look into how they are either thriving or just surviving (69).

*Chapter 11* is an overall summary that highlights the themes raised in these publications, and emphasizes opportunities for improving both the quality of adolescent HIV-related data and their health outcomes.

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PART 1

# GLOBAL CHALLENGES AND SOLUTIONS FOR THE ADOLESCENT HIV EPIDEMIC

CHAPTER 2

# Old Problems for New Providers: Managing the Postpediatric HIV Generation

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For the past few years, increasingly dire predictions have been made about the future of adolescents living with human immunodeficiency virus (HIV). HIV-associated mortality is increasing when it has decreased for other age groups, adherence to antiretroviral therapy (ART) is worse than in adults, and treatment failure and drug resistance are consequently increasing—all at a time when pediatricians are handing over a generation of these patients to their adult infectious diseases counterparts. In this issue of Clinical Infectious Diseases, Collins et al's analysis of the United Kingdom and Ireland's national HIV program's patients as they transition out of pediatric care (1) gives us reason to hope that things may not be as bad as we fear, as well as data to show why some of these patients are still unlikely to reach the population-comparable life expectancies promised to adherent patients who acquired their infections as adults.

The Collaborative HIV Paediatric Study (CHIPS) follows almost all perinatally HIV-infected children receiving care in the United Kingdom and Ireland. This report on the one-third (N=644) who have moved on to adult HIV care is the largest published to date on adolescents with HIV at transfer from pediatric care. Almost all of the infections in their cohort were perinatally acquired (91%), and the numbers of those who were locally born have been exceeded by those born abroad (62%), primarily in African countries (85%). The overall immunologic and virologic characteristics at transfer were worse in earlier years, but substantially improved over time. Those with CD4 counts ≤350 cells/mm3 went from 67% in 2000–2002 to 32% in 2012–2014, with half of transferring patients having CD4 counts >500 cells/mm3 in the latter period. Viral suppression at a threshold of <50 copies/mL went from <20% up to 68% in the latter period for those on any ART.

Despite these clear improvements in care outcomes, the ART regimen use and drug resistance observed in this cohort reflect the consequences of both earlier and current challenges to optimizing pediatric HIV care. While 26% were still on their first combination ART regimen, 44% were on a subsequent regimen, 6% were on a mono- or dual-ART regimen, and 13% had interrupted treatment—showing that almost three-fourths were already on second-line or on alternate regimens. While not surprising given the median 11 years of follow-up time in the cohort, it is important to recognize that by the time of transfer, perinatally infected young adults are generally highly treatment experienced.

About half of those on any ART had an HIV genotype that was matched through the UK HIV Drug Resistance Database. Overall, 82% had resistance mutations to at least 1 drug class: 26% to 1 class, 44% to 2 classes, and 12% to 3 classes. Although availability of drug resistance testing was likely subject to bias, the proportion tested

is similar to a US multicenter pediatric cohort study that reported 72% with high-level resistance to at least 1 drug class and 18% with triple-class resistance (2). Similar to the findings in that cohort, the availability of integrase inhibitors now means that despite extensive resistance, the goal for salvage therapy in this population should still be undetectable viral load.

Effective treatment of children is challenging, and major barriers include a small range of useable, potent antiretrovirals owing to lack of data, concerns for inadequate exposure, intolerance, and toxicities. Thus, treatment in the presence of ongoing viral replication is not uncommon in pediatric HIV care, leading to the risk of very early multiclass resistance. This is consistent with the finding in this report that those who were diagnosed and initiated on antiretrovirals earlier in life were more likely to have triple-class exposure.

As children age into adolescence, other challenges emerge that are associated with normal development—impulsivity, sensation seeking, increased peer influence—which can lead to poor adherence. A real tension exists for their practitioners between wanting to prescribe effective treatment and a fear of "running out of options" for those with adherence problems. Adolescents with poor adherence may be put on extended drug holidays as a last resort or a compromise to get them to come to clinic, even though US data have shown that the resultant immunologic decline may be substantial and difficult to reverse (3). Another situation is that providers may be unwilling to make changes to an outdated regimen that still seems to be working. It is as if adherence is so tenuous that the practitioner does not want to do anything to upset the current balance. While the potential for undertreating is real, so is the struggle to balance the psychosocial issues intrinsic to adolescence and limited available options for regimen sequencing (4).

Adult HIV providers may recall an earlier time when their patients had similar ART management problems due to suboptimal drug combinations and extensive multi-class resistance. Young adults with complex ART histories are now in need of the multidisciplinary team approach that helped address those issues in the past by constructing regimen sequencing strategies that took into account anticipated access to newer antiretrovirals combined with individualized adherence interventions. If we view the current situation of transitioning youth through the lens of the history of the HIV epidemic, these are old problems that we can overcome again.

Changes to optimize regimens can begin prior to transfer. There are feasible management interventions that can lead to the immunologic and virologic improvements observed in the UK/ Ireland cohort. A report on an antiretroviral stewardship program in an

urban US referral hospital described a 5-year effort to objectively assess ART regimens by pediatric HIV clinical and medicines experts (5). Half of the 106 patients they reviewed had an issue with their regimen, which included relying on older resistance data on which to base drug selection and the persistent use of stavudine. Some of the drug changes that were made led to increases in CD4 and reductions in viral load, side effects, and drug–drug interactions.

Notably, preliminary post transfer data from the CHIPS cohort showed that both CD4 and viral suppression levels increased after transfer to adult HIV care, which may have been related to developmental maturation of the patients leading to improved adherence or management interventions that the adult providers made (6). These outcomes differ by setting and patient mix, as a Canadian study reported that CD4 fell after adolescent transfer (7). The emerging message may be that better outcomes can be achieved for young adults when pediatric and adult providers work together, which has been observed in smaller cohorts (8, 9).

Collins et al show that the majority of their postpediatric patients who have grown up with HIV are now arriving in adult clinics with a high CD4 cell count and a suppressed viral load. However, there remains a socially complicated and difficult-to-manage subgroup of young adults who need more intensive efforts to construct optimal regimens and support adherence to help reverse the increasing trends in HIV-associated mortality (10, 11). The next steps for similar cohorts around the world will be to document and report on outcomes after transition to adult care, so we can ensure that the hard work that went into keeping the pediatric HIV population alive throughout childhood is sustained, and young people with perinatally acquired HIV can thrive as adults.

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### Author contributions

AHS and RH conceptualized and wrote the original draft of the editorial commentary, and critically reviewed, revised, and approved the final version for publication.

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CHAPTER 3

# 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 facilitate 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.

## 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 (e.g., 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 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 devel- oped 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).

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.

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 (e.g., 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 post licensing 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 (e.g., 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

**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 (e.g., 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).

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.

### Author contributions

All authors contributed to the conceptualization of the manuscript. AHS wrote the original draft of the manuscript. MAD supervised the writing of the manuscript. All authors critically reviewed, revised, and approved the final version for publication.

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CHAPTER 4

# The Global Epidemiology of Adolescents Living with HIV: Time for More Granular Data to Improve Adolescent Health Outcomes

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## ABSTRACT

Purpose of review: The aim of this study was to summarize recent evidence on the global epidemiology of adolescents (age 10–19 years) living with HIV (ALHIV), the burden of HIV on the health of adolescents and HIV-associated mortality.

Recent findings: In 2016, there were an estimated 2.1 million (uncertainty bound 1.4–2.7 million) ALHIV; 770 000 younger (age 10–14 years) and 1.03 million older (age 15–19 years) ALHIV, 84% living in sub-Saharan Africa. The population of ALHIV is increasing, as more peri/postnatally infected ALHIV survive into older ages; an estimated 35% of older female ALHIV were peri/postnatally infected, compared with 57% of older male ALHIV. Although the numbers of younger ALHIV deaths are declining, deaths among older ALHIV have remained static since peaking in 2012. In 2015, HIV-associated mortality was the eighth leading cause of adolescent death globally and the fourth leading cause in African low and middle-income countries.

Summary: Needed investments into characterizing and improving adolescent HIV-related health outcomes include strengthening systems for nationally and globally disaggregated data by age, sex and mode of infection; collecting more granular data within routine programmes to identify structural, social and mental health challenges to accessing testing and care; and prioritizing viral load monitoring and adolescent-focused differentiated models of care.


## KEY POINTS

- Among the 2.1 million (uncertainty bound 1.4–2.7 million) adolescents living with HIV (ALHIV) globally in 2016, girls disproportionately account for 61% of older ALHIV and 66% of new infections among older ALHIV. Sixty-five percentage of older female ALHIV were estimated to have been horizontally infected compared with 43% of older male ALHIV.
- HIV is the eighth leading cause of adolescent deaths globally, the fourth leading cause in younger adolescent girls globally and the fourth leading cause of all adolescent mortality in African low and middle-income countries. Despite receiving antiretroviral therapy, ALHIV still experience substantial morbidity and AIDS-related mortality. To better understand mortality in ALHIV in LMICs, we need to collect more detailed data that go beyond the biomedical cause of death to understand contributing structural, social, emotional and mental health factors.
- There is a considerable population of ALHIV unaware of their HIV infection and, once diagnosed, ALHIV experience high rates of loss to follow-up. A priority for

ALHIV must be earlier diagnosis and successful linkage to and retention in care so that they can initiate treatment and achieve sustained viral suppression to prevent avoidable morbidity and mortality.

- Key investments during the turbulent but temporary phase of adolescence that would enhance our ability to track their outcomes so we can develop interventions to address them include systems for nationally and globally disaggregated adolescent data; collection of more granular data within the context of routine care settings to identify structural, social and mental health challenges during adolescence; and prioritizing viral load monitoring and differentiated models of care for ALHIV.

## INTRODUCTION

It is estimated that in 2016, there were almost 2.1 million (uncertainty bounds 1.4– 2.7 million) adolescents (age 10–19 years) living with HIV (1), including 770,000 (uncertainty bounds 520,000–1.01 million) younger adolescents, age 10–14 years and 1.3 million (uncertainty bounds 870,000–1.68 million) older adolescents, age 15–19 years (2). Adolescents living with HIV (ALHIV) are a complex, heterogeneous population of children with peri/postnatally acquired HIV ageing up into adolescence in combination with adolescents newly horizontally infected with HIV during adolescence (3). Peri/postnatally infected ALHIV (pALHIV) often have more advanced HIV disease with related comorbidities and disabilities associated with delayed HIV treatment and lifelong infection (4). They may be highly antiretroviral therapy (ART)-experienced, having commenced ART during infancy or childhood, and are at a higher risk of treatment failure and mortality during adolescence (5). However, horizontally infected ALHIV (hAL-HIV) may experience other social, economic and sexual health risk factors associated with acquiring HIV during adolescence (6).

In common is that both pALHIV and hALHIV are navigating the developmental transition of adolescence while dealing with a chronic disease and sexually transmissible infection. They are a population at a greater risk of being lost to follow-up and dying than younger children and adults living with HIV (7– 10,11). This review summarizes the most recent evidence on the global epidemiology of adolescent HIV, the contribution of HIV to the burden of adolescent disease, underlying causes of HIV-associated mortality and discusses differentiated service delivery as a key investment to improve outcomes for ALHIV.

**BOX 1**. UNAIDS-supported national and global adolescent HIV indicators

UNAIDS assists countries to generate national estimates of key HIV epidemic indicators for monitoring and understanding the HIV epidemic at national and global levels (12). As it is not possible to directly measure the epidemic indicators at a population level in most countries, available national surveillance and complementary research data are fed into the SPECTRUM model to generate estimates, a method used by UNAIDS since the early 2000s (13). Under the guidance of the UNAIDS Reference Group on Estimates, Modelling, and Projections, the model is continuously refined to incorporate the most up to date understanding of the HIV epidemic based on demographic, HIV epidemiologic and programmatic data (http://www.epidem.org/) (14). Estimates are generated on an annual basis and updated for the current and all historic years (15). The UNAIDS modelled estimates for the numbers of adolescents newly HIV-infected, living with HIV and HIV-associated deaths provide a critical global-level resource that can be used to guide policy and programme planning, as well as prioritizing surveillance needs and research agendas. For a detailed description of the methods for the 2017 estimates see reference (12). Current national, regional and global indicator estimates are available at http://aidsinfo.unaids.org..

## GLOBAL DISTRIBUTION OF ADOLESCENTS LIVING WITH, NEWLY INFECTED BY AND DYING WITH HIV

According to the most recent UNAIDS estimates (see Box 1) (12-15), 71% of the estimated 2.1 million ALHIV in 2016 lived in just 10 high-burden countries, including nine in sub-Saharan Africa and India (2). Amongst the 770,000 younger ALHIV, 90% lived in sub-Saharan Africa (2). The estimated number of younger ALHIV has stabilized since 2014, likely corresponding with prevention of mother-to-child HIV transmission (PMTCT) programme expansion that has led to fewer new peri/postnatally infected children annually, while ALHIV are ageing up into older adolescence and young adulthood (Figure 1). There were initial declines in the number of older ALHIV up to 2008 that may have been related to a combination of fewer new older adolescent HIV infections and poor survival of pALHIV. New infections in older adolescents have declined globally by 45% from 470,000 (uncertainty bounds 290,000–600,000) in 2000 to 260,000 (uncertainty bounds 150,000– 340,000) in 2016, with regional variation (2). While decreasing in other regions, annual infections have remained static in Central and South America with 17,000 (uncertainty bounds 8500–32,000) since 2010, and in West and Central Africa with 62,000 (uncertainty bounds 15,000–

130,000) since 2009 (2, 15). Overall, the population of older ALHIV is now increasing with an expanding cohort of pALHIV surviving (Figure 1) (2).

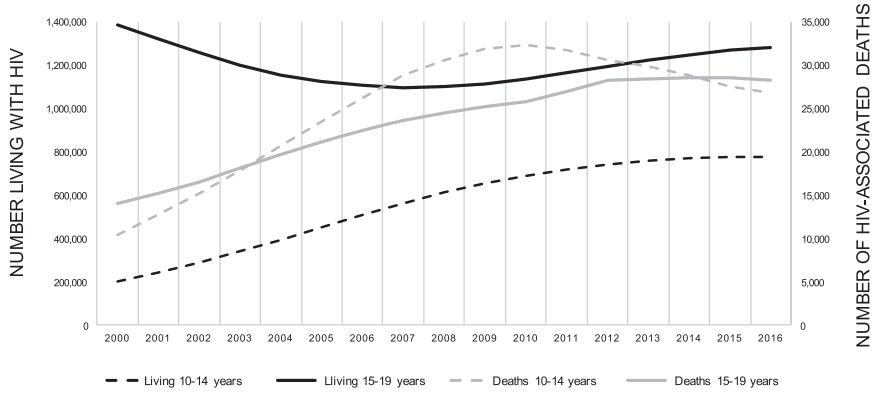


**FIGURE 1.** Trends in numbers of younger (age 10–14 years) and older (age 15–19 years) adolescents living with HIV and HIV-associated deaths between 2000 and 2016 (UNAIDS 2017 Spectrum Model estimates). The primary y-axis (left) displays number of younger (black dashed line) and older (black solid line) adolescents living with HIV. The secondary left axis (right) displays the number of younger (grey dashed line) and older (grey solid line) adolescent deaths.

Although there is little difference in the numbers of younger adolescent males compared with females living with HIV, important sex-based differences are apparent in older ALHIV. In 2016, girls disproportionately accounted for 61% of older ALHIV, and 67% of new infections among older ALHIV (2). Furthermore, where 65% of older female ALHIV were estimated to have been horizontally infected, only 43% of older male ALHIV were horizontally infected (Figure 2) (16). These sex differences are particularly prominent in Eastern and Southern Africa, where 62% of older female ALHIV were estimated to be horizontally infected, compared with 28% of older male ALHIV (Figure 3) (16). Although the numbers of ageing pALHIV are steadily increasing with successful ART, their relative contribution to the global epidemic will depend in large part on our ability to prevent new horizontal adolescent infections.

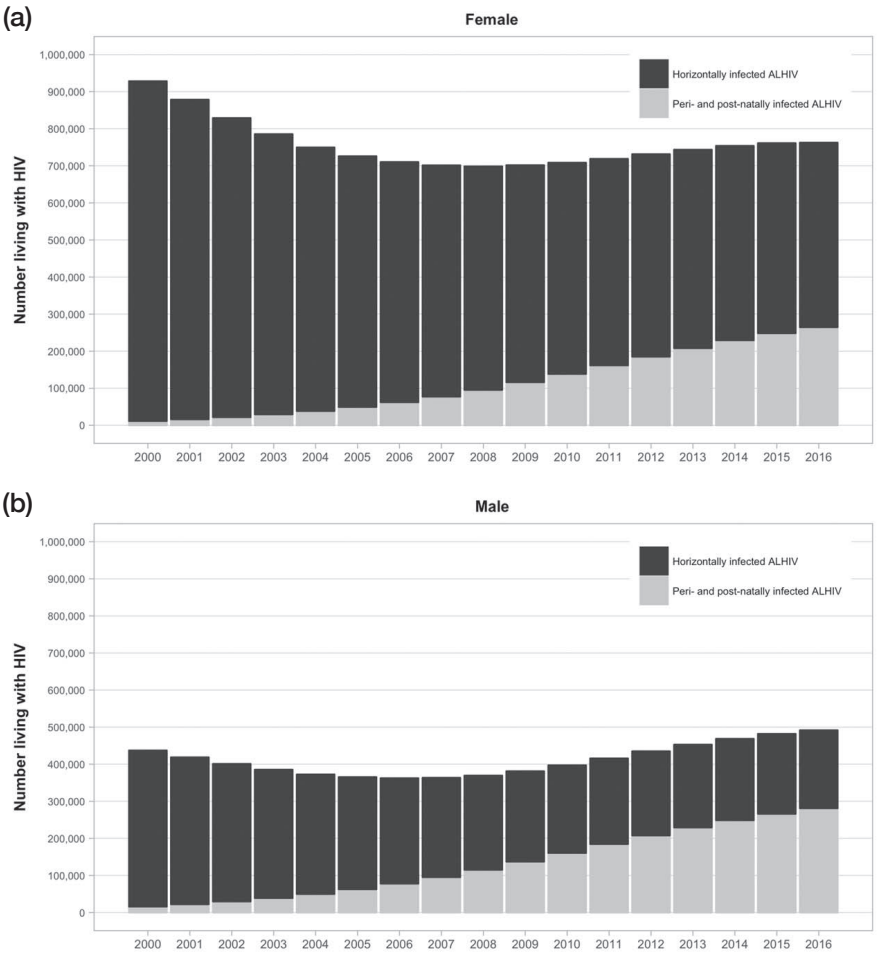


**FIGURE 2.** Numbers of older adolescents (age 15–19 years) living with HIV globally by sex and mode of transmission: 2000–2016 (Additional analysis of UNAIDS 2017 estimates by John Stover). This figure displays the number of female **(a)** and male **(b)** older adolescents (age 15–19 years) globally living with HIV by mode of transmission (peri/postnatally infected in grey and horizontally infected in black).

Absolute numbers of deaths in younger ALHIV appear to be in decline, having peaked in 2010 at 32,000 (24,000–44,000) HIV-associated deaths and reduced to 27,000 (uncertainty bounds 19,000–37,000) in 2016 (Figure 1) (2). Corresponding with the distribution of younger ALHIV, more than half of younger adolescent HIV-associated

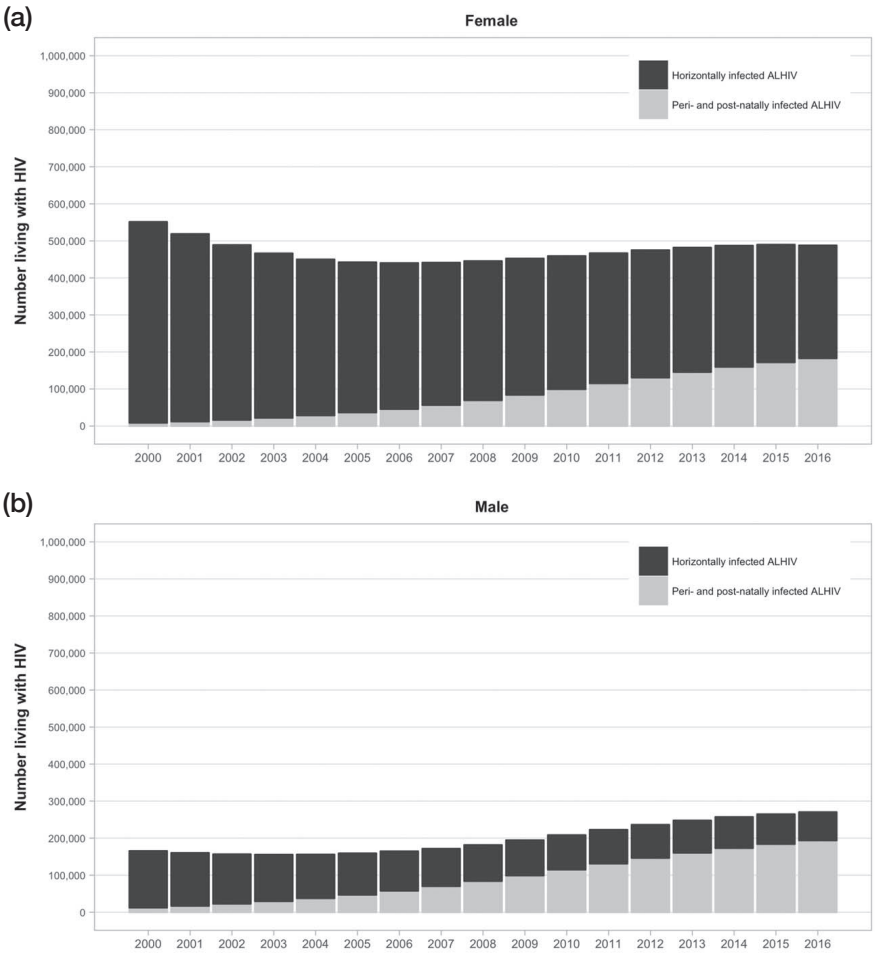


**FIGURE 3.** Numbers of older adolescents (age 15–19 years) living with HIV in Eastern & Southern Africa by sex and mode of transmission: 2000–2016 (Additional analysis of UNAIDS 2017 estimates by John Stover). This figure displays the number of female **(a)** and male **(b)** older adolescents (age 15–19 years) in Eastern & Southern Africa living with HIV by mode of transmission (peri/postnatally infected in grey and horizontally infected in black).

deaths in 2016 occurred in Eastern and Southern Africa (16,000 [uncertainty bounds 12,000–22,000]) and almost 90% in sub-Saharan Africa overall. However, unlike the reduction in absolute numbers of deaths that has been observed in children (0–14 years) and adults (≥15 years), the absolute number of deaths in older adolescents

remained static at 28,000 (uncertainty bounds 20,000–39,000) per year since peaking in 2012 (Figure 1). With the steadily increasing size of the older ALHIV population, mortality rates, rather than absolute numbers, are required to accurately monitor survival trends of older ALHIV. Empiric studies following cohorts of ALHIV in high-income countries have been used to complement and inform the UNAIDS-supported modelled mortality estimates in ALHIV. Comparable studies in high-burden low and middle-income countries (LMICs) will be necessary to provide mortality rate trends to validate the UNAIDS estimates in these regions going forward (3). Strengthening data disaggregated by age, sex and mode of HIV transmission would facilitate more granular monitoring of sub-populations of ALHIV who have differing risks for newly acquiring HIV and HIV-associated mortality, evidence required to develop effective interventions to mitigate these risks.

## THE CONTRIBUTION OF HIV TO THE GLOBAL BURDEN OF ADOLESCENT DISEASE

HIV-associated mortality is an important contributor to global adolescent mortality. The WHO Global Health Estimates for 2015, published in 2016, reported that HIV was the eighth leading cause of death among all adolescents globally (17). In African LMICs, HIV was the fourth leading cause of all adolescent deaths, following lower respiratory tract infections, diarrhoeal disease and meningitis. Globally, in younger adolescent girls, HIV was the fourth leading cause of death, following lower respiratory tract infections, diarrheal disease and meningitis. In older adolescent girls, HIV was the eighth leading cause of death, with maternal causes of death leading in this group. In both younger and older adolescent males, traumatic deaths related to road injury, drowning or interpersonal violence predominated, with HIV being the seventh and 10th leading cause of death in younger and older adolescent boys, respectively (17).

This heterogeneity in causes of adolescent death by age and sex highlights that the need for disaggregated adolescent data is not exclusive to HIV. Reorientation of health system monitoring and service provision that is sensitive to the rapidly changing needs of adolescents will have benefits for the well being of all adolescents, including ALHIV (18). Adolescent-specific health system policy implementation is starting to occur, the recently released South African National Adolescent and Youth Health Policy being one example (19). However, such efforts need to be more widespread to improve the quality of care and outcomes for adolescents, particularly in the global pursuit of Sustainable Development Goal 3 to achieve health for all at all ages (20).

## HIV-ASSOCIATED MORTALITY AND MORBIDITY DURING ADOLESCENCE

To reduce HIV-associated mortality during adolescence, an understanding of the underlying causes of HIV-associated mortality and morbidity is needed to complement estimates of the numbers of deaths and where they are occurring. Evidence from multiple regions and research teams is converging around common findings of poorer outcomes among ALHIV in general, and for older youth in particular.

1. In a study combining 1446 perinatally HIV-infected youth aged 13–30 years in the Pediatric HIV/AIDS Cohort Study (PHACS) Adolescent Master Protocol and International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1074 multicentre cohort studies in the United States (US) between 2007 and 2015, CDC-C and WHO-4 events were more frequent in older than younger youth (0.7, 0.9 and 2.1 events per 100 person-years in those aged 7–12, 13–17 and 18–30 years respectively, P <0.001 for trend) (21). Mental health and neurodevelopmental conditions were amongst the most frequent morbidity events (four events per 100 person-years). Compared with youth of the same age in the general US population, mortality rates in pALHIV were 5.6-fold (95% confidence interval [95% CI] 2.8–11.1) higher in those aged 15–19 years and 12.3-fold (95% CI 8.0–18.9) higher in those aged 20–29 years (21).

2. In the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC), mortality was described in 3526 children and adolescents after initiating ART in Europe and Thailand up until 2013 (22). By the end of the study period, 3% (N=94) of children had died. Despite these ALHIV having received ART, 64% of deaths were due to HIV-related infections, predominantly bacterial infection and/or sepsis and 27% were due to other HIV-related causes. Two suicides, recorded amongst other non-HIV related deaths, may be an unrecognized consequence of the mental health strains of growing up with HIV (23, 24).

3. The International Epidemiology Databases to Evaluate AIDS (IeDEA) Global consortium conducted a multiregional analysis of 164,218 adolescents and youth aged 10–24 years across the Caribbean and Central and South America, sub-Saharan Africa and Asia, and observed that those over 15 years of age had substantially higher incidence of WHO stage 4 events following ART initiation compared with younger ALHIV 10–14 years of age (1.5 [95% CI 1.3–1.7] vs. 0.21 [95% CI 0.9–0.23] per 100 person-years) (25).

4. In the TREAT Asia Pediatric HIV Observational Database (TApHOD) of IeDEA Asia-Pacific, there were 60 deaths (0.80 [95% CI 0.62–1.04] per 100 person-years) among 2416 ALHIV over 7458 person-years of follow-up reported between 2008 and 2012 (26). The incidence of mortality was 1.12 (95% CI 0.75–1.67) and 0.68 (95% CI 0.49–0.94) per 100 person-years in older and younger adolescents, respectively (incidence rate ratio 1.65 [95% CI 0.94–2.84]). Through a standardized cause of death reporting process, 58% of deaths were determined to have been due to underlying infectious causes, of which 46% were AIDS-related opportunistic infections, despite 95% of ALHIV being on ART at the time of death (26).

Even with access to ART, ALHIV across the globe are dying from AIDS-related causes and experiencing substantial mental health and neurodevelopmental morbidity, including in settings wherein second and third-line ART are available. Furthermore, multiregional collaborations have identified that despite expansion of HIV services and access to ART, inequality in survival remains. Mortality of ALHIV on ART living in LMICs remains higher than ALHIV on ART in high-income countries (22, 27, 28). Geographic inequalities in combination with the burden of AIDS-related morbidity and mortality clearly indicate that survival for ALHIV is impacted by factors beyond access to ART (29–31). These may include social and mental health factors such as adherence challenges, treatment fatigue and depression (30, 32). To better understand mortality in ALHIV in LMICs, we need to collect more detailed data that go beyond the biomedical causes of death to understand contributing structural, social, emotional and mental health factors.

## BURDEN OF UNDIAGNOSED AND UNRETAINED ADOLESCENTS LIVING WITH HIV

To realize the UNAIDS 90–90–90 targets for ALHIV, adolescents must first be diagnosed as HIV-infected to achieve the first target (90% know their HIV status) and must be retained in care to achieve the second (90% on ART) and third (90% virologically suppressed) targets. However, there is a considerable population of ALHIV unaware of their HIV infection and, once diagnosed, ALHIV experience high rates of loss to follow-up (LTFU). In a community survey conducted in 2013–2015, following implementation of optimized opt-out provider-initiated counselling and testing at primary healthcare clinics in Harare, Zimbabwe, 38% (95% CI 30–46%) of children and adolescents aged 8–17 years with positive HIV tests had not previously been diagnosed (33). Children were less likely to have been diagnosed if they were over 13 years of age, in good health and with both parents alive. These findings are consistent with population-level estimates from the Population Health Impact

Assessment (PHIA) surveys in Zimbabwe and Swaziland that found youth aged 15–24 years to be less likely to know their HIV status and less likely to be on ART than older adults (34, 35). Late diagnosis of HIV has major implications for the health and survival of these ALHIV (36).

Once diagnosed, ALHIV struggle to remain in care. Older adolescents in Zimbabwe had higher LTFU rates than older children and younger adolescents (adjusted rate ratio 1.6, 95% CI 1.2–2.1) and starting ART during older adolescence was associated with a 1.7 (95% CI 1.1–2.8) times greater risk of LTFU than starting in any younger age group (11). Unlike for adults living with HIV, there are still evidence gaps to understand what proportion of LTFU in ALHIV is due to mortality as compared with other reasons for LTFU, such as undocumented transfer to care elsewhere (37–39). Thus, the accuracy of survival estimates in ALHIV are limited where LTFU is high and mortality may be underestimated as unascertained deaths in those LTFU are often not adjusted for (27). A priority for ALHIV must be earlier diagnosis and successful linkage to and retention in care so that they can initiate treatment and achieve sustained viral suppression to prevent avoidable morbidity and mortality.

## THE PROMISE AND POTENTIAL OF DIFFERENTIATED SERVICE DELIVERY FOR ADOLESCENTS LIVING WITH HIV

Differentiated care is being widely promoted as a way to allow patients greater freedoms in managing their own care, shifting the locus of care into the community, where peer and healthcare worker led adherence clubs offer a more efficient and effective alternative to busy institutional settings (40, 41). It also has the potential to substantially reduce national HIV programme costs and provider burden by decreasing the frequency of clinic visits for stable patients with evidence of viral suppression, when there are reliable supply chains to sustain multimonth medication refills (42, 43). In Rwanda, programme implementers specifically created a visit schedule for virologically suppressed adolescents up to age 19 years that align 3-monthly clinical and medication pick-up visits with school breaks (44). However, full implementation of these models requires routine viral load monitoring, which is infrequently available in much of sub-Saharan Africa (45). There is a strong case to be made for prioritizing routine viral load monitoring for ALHIV, who are in a life stage wherein they are at a high risk for poor outcomes (46).

Optimal approaches for differentiated care for adolescents who struggle with daily adherence, and are more often on second-line regimens, are less clear. Such youth are often given more frequent clinic visits, which can be perceived as punishment

and include stern counselling that may engender guilt rather than encouragement (47). Although the vast majority could benefit from differentiated care and maintain stable HIV disease, greater attention should be focused on studying how to modify care models for the minority of adolescents who need more proactive engagement (48). Although recent achievements in expanding treatment to 21 million people with HIV are to be celebrated, policies and programmes that do not directly address ALHIV struggles with long-term care will limit their chances for future treatment success and sustained health benefits (49).

## CONCLUSION

Adolescence is a turbulent, but temporary phase. Considering that ALHIV, whether peri/postnatally or horizontally infected, are the population that will be living with HIV for the longest span of their lives, strategic targeted investments during this transitional phase are warranted. Priority investments for monitoring ALHIV outcomes include strengthening systems for nationally and globally disaggregated adolescent data by age, sex and mode of transmission to monitor progress in reducing new infections and mortality in high-risk subpopulations of ALHIV; collection of more granular data within the context of routine care settings to identify structural, social and mental health challenges to being diagnosed with HIV, retained in care and maintaining viral suppression; prioritizing viral load monitoring for earlier identification of those with viral nonsuppression and treatment failure; and differentiated models of care to allow flexibility, freedom and independence for the majority of ALHIV that are retained in care and on stable ART.

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ALS has no conflicts of interest to declare. AHS has received programme grants and travel support to her institution from ViiV Healthcare.

### Author contributions

ALS and AHS conceptualized, designed, and conducted the review; performed data curation; wrote the original draft of the manuscript; and critically reviewed, revised, and approved the final version for publication.

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CHAPTER 5

# Mortality and Losses to Follow-up Among Adolescents Living with HIV in the IeDEA Global Cohort Collaboration

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## ABSTRACT

Introduction: We assessed mortality and losses to follow-up (LTFU) during adolescence in routine care settings in the International epidemiology Databases to Evaluate AIDS (IeDEA) consortium.

Methods: Cohorts in the Asia-Pacific, the Caribbean, Central, and South America, and sub-Saharan Africa (Central, East, Southern, West) contributed data, and included adolescents living with HIV (ALHIV) enrolled from January 2003 and aged 10 to 19 years (period of adolescence) while under care up to database closure (June 2016). Follow-up started at age 10 years or the first clinic visit, whichever was later. Entering care at <15 years was a proxy for perinatal infection, while entering care ≥15 years represented infection acquired during adolescence. Competing risk regression was used to assess associations with death and LTFU among those ever receiving triple-drug antiretroviral therapy (triple-ART).

Results: Of the 61,242 ALHIV from 270 clinics in 34 countries included in the analysis, 69% (n=42,138) entered care <15 years of age (53% female), and 31% (n=19,104) entered care ≥15 years (81% female). During adolescence, 3.9% died, 30% were LTFU and 8.1% were transferred. For those with infection acquired perinatally versus during adolescence, the four-year cumulative incidences of mortality were 3.9% versus 5.4% and of LTFU were 26% versus 69% respectively (both p <0.001). Overall, there were higher hazards of death for females (adjusted sub-hazard ratio (asHR) 1.19, 95% confidence interval (CI) 1.07 to 1.33), and those starting treatment at ≥5 years of age (highest asHR for age ≥15: 8.72, 95% CI 5.85 to 13.02), and in care in mostly urban (asHR 1.40, 95% CI 1.13 to 1.75) and mostly rural settings (asHR 1.39, 95% CI 1.03 to 1.87) compared to urban settings. Overall, higher hazards of LTFU were observed among females (asHR 1.12, 95% CI 1.07 to 1.17), and those starting treatment at age ≥5 years (highest asHR for age ≥15: 11.11, 95% CI 9.86 to 12.53), in care at district hospitals (asHR 1.27, 95% CI 1.18 to 1.37) or in rural settings (asHR 1.21, 95% CI 1.13 to 1.29), and starting triple-ART after 2006 (highest asHR for 2011 to 2016 1.84, 95% CI 1.71 to 1.99).

Conclusions: Both mortality and LTFU were worse among those entering care at ≥15 years. ALHIV should be evaluated apart from younger children and adults to identify population-specific reasons for death and LTFU.

## INTRODUCTION

UNAIDS estimates that there were 1.0 million female and 770,000 male adolescents living with HIV in 2017 (aidsinfo.unaids.org). The adolescent age group (10 to 19 years) represents a combination of young people who were perinatally infected with HIV and those more recently infected, often through high-risk behaviours (1). Many adolescents are not accessing HIV treatment or have challenges with adherence and retention in care, with subsequent poor health outcomes (2-5).

Although UNAIDS Global AIDS Monitoring protocols recommend the collection and reporting of data in detailed age groups, only 84 of 178 (47%) countries reported age disaggregated paediatric data (separating 10- to 14- and 15- to 19-year-olds) in 2016 (6). The quality of the strategic information used to monitor the adolescent HIV epidemic and the impact of youth-focused programmatic interventions could be enhanced by including routinely collected observational data from clinical and programme settings that are sufficiently detailed to be analysed by multiple categories (e.g., sex, age) and used to assess predictors of antiretroviral treatment (ART) outcomes. The objective of this analysis was to describe mortality and retention among a mixed population of adolescents living with HIV acquired perinatally as well as later in adolescence in routine care settings in low- and middle-income countries in the International epidemiology Databases to Evaluate AIDS (IeDEA) cohort consortium.

## METHODS

### Study population

IeDEA is a collaboration of clinical centres and research partners across seven global regions which was established in 2006 and is supported through the US National Institutes of Health (https://www.iedea.org/). For this analysis, data from 270 sites were included from six IeDEA regions (Asia-Pacific, Central, East, West, and Southern Africa, the Caribbean and Central and South America [CCASAnet]), with data from Southern Africa separated into South Africa and the rest of Southern Africa due to variations in national paediatric HIV treatment guidelines (e.g. regarding use of protease inhibitors [PIs]) that resulted in differing treatment histories from other countries in that region. The analysis included all patients enrolled in HIV care at participating IeDEA sites from January 2003, and who had at least six months of potential follow-up during adolescence (i.e. 10 to 19 years of age). Patients could have initiated antiretrovirals or remained antiretroviral-naïve. The analysis database included data up to June 2016.

## Ethics review

Each region secured local regulatory approvals for participation in this analysis, including reviews by local research and ethics regulatory bodies and, where required, national-level approvals. Consent and assent requirements and procedures were regulated by the local regulatory bodies, and adherence to those standards was the responsibility of each site while being monitored and managed by regional coordinating centres. (https://www.iedea.org/regions/) (7-9).

## Definitions and measurements

Adolescents were defined as those 10 up to 19 years of age and the analysis focused on this period of life. The beginning of follow-up, referred to as the "baseline" time point, was the date of the 10th birthday for those who entered care before age 10, and the date of the first clinic visit for those who entered care at or after age 10. Follow-up time ended and data were censored at whichever of the following came first: (1) death, (2) transfer out, (3) loss to follow-up (LTFU), (4) turning 19 years of age, or (5) the closing date of the individual regional cohort database. The main outcomes of interest were death, LTFU and transfer that occurred in the year following the last clinic visit during the period of adolescence.

Specifically, adolescents without evidence of contact with the clinic for more than 12 months were classified as LTFU with their follow-up period ending 12 months after their last clinic contact. In addition, if a patient previously considered LTFU was subsequently known to have died or have been transferred (e.g. through updated reporting by their clinic), their outcomes were revised up to 24 months after their last clinic contact (and not beyond turning age 19 or database closure).

HIV disease stage was categorized as asymptomatic (CDC N or WHO 1), mild (CDC A or WHO 2), moderate (CDC B or WHO 3) and severe (CDC C or WHO 4). Weight and height measurements were converted to age- and sex-adjusted z-scores. For weight-for- age z-scores, US National Center for Health Statistics and WHO International Growth Reference standards were used to allow for scoring children >10 years of age (10,11). For height-for-age z-score we used the WHO 2006/2007 Child Growth Standards (12,13). Severe immunodeficiency was defined according to 2006 WHO global guidelines (e.g. <15% or <200 cells/$mm^3$ for children ≥5 years old) (14).

For laboratory and clinical measurements, we used the closest values reported during a window of plus or minus three months from the baseline visit (i.e. at age 10 or the date of the first visit if entering care after age 10), with the pre-baseline measurement used in the case of multiple values. At antiretroviral initiation, we used a testing window of three months before and one week after start (e.g. for CD4, viral load).

## Statistical analysis

The analysis was restricted to assess outcomes during the period of adolescence. Adolescents entering care before age 15 years were compared to those with a first visit at or after age 15. Entry into care before age 15 was considered a proxy for those likely to have been infected perinatally or very early in life compared to those infected in older adolescence, predominantly assumed to be through risk behaviours and called the "late-infected" (15-17). The term "late-infected" was chosen to characterize the timing of HIV infection relative to the stage of adolescence (i.e. between 15 and 19 years of age). The selection of the age threshold is consistent with UNAIDS Global AIDS Monitoring methods where those 10 to 14 years of age are considered to be in early adolescence and those 15 to 19 years in late adolescence. In addition, infections acquired through risk behaviours are not modelled in the UNAIDS Spectrum model to occur among those entering HIV care before the age of 15 years (6). We conducted a sensitivity analysis to examine the impact of differentiating patients by age <10 versus ≥10 years at entry into care as a comparison (18).

To compare proportions, we used chi-square tests, and we compared medians with the Mann–Whitney test. We used a cumulative incidence function to estimate the probabilities of death and LTFU during adolescence. In a subset of adolescents who had received ≥3 antiretrovirals as their initial treatment regimen, we conducted separate competing risks regression analyses based on Fine and Gray's proportional sub-hazards model (19) to identify correlates of death (LTFU as a competing event) and correlates of LTFU (death as a competing event) from the start of triple-drug ART. The following variables were included in the univariate analysis: age and calendar year at first triple-drug ART, sex, facility level and facility setting (as defined by the site). CD4 count and weight-for-age z-scores were included as time-updated variables, and their values were carried forward if no subsequent measurements were recorded. In regression analyses, missing data were modelled as a separate category within each variable. We did not use multiple imputation to model missing data due to the relatively small numbers of covariates available, and the resulting lack of precision in imputation. To assess the robustness of our analyses to missing data, we undertook a sensitivity analysis based on subsets of patients with complete data. Variables were included in the multivariate model if they had a $p < 0.2$ in univariate analysis. We selected the final model using a backward elimination procedure and retained all variables in the model that had a $p < 0.05$. The adjusted subdistribution hazard ratios (asHR) were reported with their 95% confidence intervals (95% CI).

Management of the multiregional aggregated data and statistical analyses were performed at the Kirby Institute, UNSW Australia, using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata (StataCorp, STATA 14.0 for Windows, College Station, TX, USA).

## RESULTS

A total of 61,242 adolescents (61% female) were included from 270 sites in 34 countries (Figure 1): Asia-Pacific (n=2508, 4.1%; 16 sites), Central Africa (n=2143, 3.5%; 15 sites), CCASAnet (n=1728, 2.8%; 12 sites), East Africa (n=10,767, 18%; 47 sites), South Africa (n=15,494, 25%; 12 sites), Southern Africa (n=25,102, 41%; 148 sites) and West Africa (n=3500, 5.7%; 20 sites). Overall, 69% (n=42,138) entered care before 15 years of age (perinatally infected) at a median age at first visit of 9.8 (interquartile range (IQR) 6.8 to 12.0) years (Table 1) and median duration of follow-up during adolescence of 2.9 (IQR 1.4 to 5.0) years. Those entering care at or after age 15 (late-infected) represented 31% (n=19,104) of the adolescents, and had a median age at first visit of 17.5 (IQR 16.4 to 18.3) years and median duration of follow-up during adolescence of 1.0 (IQR 0.9 to 1.6) year. Approximately one-third of adolescents in CCASAnet (33%), and East (34%), South (37%), and Southern Africa (32%) were late-infected, compared to 1.9% in the Asia-Pacific, 13% in Central Africa and 19% in West Africa.

At baseline (age 10 years or first clinic visit if entering care later), antiretrovirals had already been started by 41% of perinatally infected adolescents and 0.9% of late-infected adolescents. The median CD4 count was 435 (IQR 196 to 745) cells/$mm^3$ for those perinatally infected and 329 (IQR 178 to 521) cells/mm3 for the late-infected; higher proportions of perinatally infected were severely underweight (17% vs. 11%, p <0.001) and severely stunted (13% vs. 4.5%, p <0.001) with z-scores <-3 compared to late-infected adolescents. At baseline, HIV viral load was infrequently available in both groups (19% vs. 5.4%). Of those with a viral load measurement at baseline, 38% of the perinatally infected and 22% of the late-infected were undetectable.

### Antiretroviral use

A total of 44,922 adolescents ever initiated any combination of antiretroviral drugs by the end of the follow-up period (84% perinatally vs. 51% late-infected; Table S1). Median CD4 percent at antiretroviral initiation was 12% (IQR 6% to 18%) among the perinatally infected and 14% (IQR 7% to 23%) among late-infected adolescents (p <0.001). Perinatally infected adolescents had a greater degree of severe immunodeficiency (59% vs. 51%; p <0.001) and were more likely to be severely underweight (22% vs. 13%; p <0.001) and stunted (16% vs. 4.6%; p <0.001) at antiretroviral start. The median lifetime duration of antiretroviral use was 4.8 (IQR 2.4 to 7.3) years among those entering care before age 15 years, and 1.1 (IQR 0.8 to 1.8) years for those entering at ≥15 years.

## Patient outcomes

During the adolescent follow-up period, 3.9% died, 30% were LTFU and 8.1% were transferred. Separated by age at cohort entry, among those entering care before age 15 years, 4.0% died, 27% were LTFU, and 9.7% transferred (Table S2). For those entering care at or after age 15 years, 3.8% died, 38% were LTFU and 4.6% were transferred. These data include 62 adolescents living with HIV (ALHIV) who were recategorized from LTFU to dead and 98 recategorized to transferred between 12 and 24 months after most recent clinic contact (and before age 19 or database closure). Among perinatally infected adolescents, the four-year cumulative incidence of death was 3.9% and of LTFU was 26%, while for late-infected adolescents it was 5.4% for death and 69% for LTFU; both outcomes were significantly higher in late-infected adolescents (p <0.001) (Figure 2).

In the sensitivity analysis where age at entry into care was redefined as <10 years versus ≥10 years, the median CD4 at baseline for the group entering care at <10 years of age (n=22,168) was 673 (IQR 429 to 949) cells/mm$^3$. The proportion of adolescents entering care before age 10 years who died was 1.9%, compared to 4.0% using the age 15 threshold, and the proportion who were LTFU was 18% compared to 27% (Table S3). In addition, of the 19,970 adolescents entering care between age 10 and 14 years, 1247 (6.2%) died and 7469 (37%) were LTFU by the age of 19 years.

The multivariate regression model restricted to those who received triple-drug ART as their initial antiretroviral regimen showed that there was an increase in the hazard rate of death for those starting treatment at older ages compared to those <5 years of age (5 to 9 years adjusted subdistribution hazard ratios asHR 2.59, 95% CI 1.74 to 3.85; 10 to 14 years asHR 6.93, 95% CI 4.69 to 10.22; ≥15 years asHR 8.72, 95% CI 5.85 to 13.02) (Table 2). The hazard was higher for females (asHR 1.19, 95% CI 1.07 to 1.33), and those receiving care in mostly urban (asHR 1.40, 95% CI 1.13 to 1.75) and mostly rural settings (asHR 1.39, 95% CI 1.03 to 1.87) compared to urban settings. The hazard of death was lower for those with higher CD4 count, better weight-for-age z-scores, receiving care at a district hospital and in rural settings compared to health centres and in urban settings, with a later year of starting ART, and for cohorts from the Asia-Pacific, Central Africa, East Africa, and South Africa compared to Southern Africa. Hazard rates of death were lowest overall among adolescents with a current CD4 ≥500 cells/mm$^3$ compared to <200 cells/mm$^3$ (asHR 0.12, 95% CI 0.10 to 0.15), a weight-for-age z-score ≥-2 compared to <-3 (asHR 0.22, 95% CI 0.19 to 0.25), initiating ART between 2011 and 2016 compared to 2003 and 2006 (asHR 0.36, 95% CI 0.31 to 0.43), or receiving care in South Africa compared to Southern Africa (asHR 0.45, 95% CI 0.36 to 0.57).

Increased hazard rates of LTFU among adolescents who received triple-drug ART as their initial antiretroviral regimen were associated with female sex (asHR 1.12, 95% CI 1.07 to 1.17), older age at ART start compared to <5 years (5 to 9 years asHR 2.59, 95% CI 2.32 to 2.88; 10 to 14 years asHR 6.11, 95% CI 5.49 to 6.81; ≥15 years asHR 11.11, 95% CI 9.86 to 12.53), receiving care at a district hospital compared to a health centre (asHR 1.27, 95% CI 1.18, 1.37), receiving care in rural compared to urban settings (asHR 1.21, 95% CI 1.13, 1.29), receiving care in East Africa (asHR 1.14, 95% CI 1.01 to 1.28), South Africa (asHR 1.75, 95% CI 1.63 to 1.88), or CCASAnet (asHR 2.99, 95% CI 2.65 to 3.36) compared to Southern Africa, and starting triple-drug ART after 2006 (highest asHR for 2011 to 2016 1.84, 95% CI 1.71 to 1.99) (Table 3). In contrast, lower hazard rates of LTFU were associated with CD4 count ≥350 cells/mm$^3$ (lowest asHR for ≥500 0.65, 95% CI 0.61 to 0.69), receiving care in regional, provincial, or university hospitals compared to health centres (asHR 0.63, 95% CI 0.58 to 0.68), receiving care in mostly urban and mostly rural compared to urban settings (lowest asHR for mostly urban 0.71, 95% CI 0.62 to 0.81), and receiving care in the Asia-Pacific compared to Southern Africa (asHR 0.19, 95% CI 0.14 to 0.25).

The sensitivity analyses excluding missing data gave qualitatively very similar results for most covariates (data not shown). The only exceptions were in mortality analyses, where survival was no longer improved in Central Africa (asHR in sensitivity analysis of 1.10 95% CI 0.71 to 1.70, compared with asHR in main analysis of 0.68 95% 0.48 to 0.95), or in rural settings (asHR in sensitivity analysis of 1.02 95% CI 0.82 to 1.27, compared with asHR in main analysis of 0.76 95% 0.63 to 0.91). Importantly, results for individual-level covariates such as age, sex and CD4 count, were qualitatively the same.

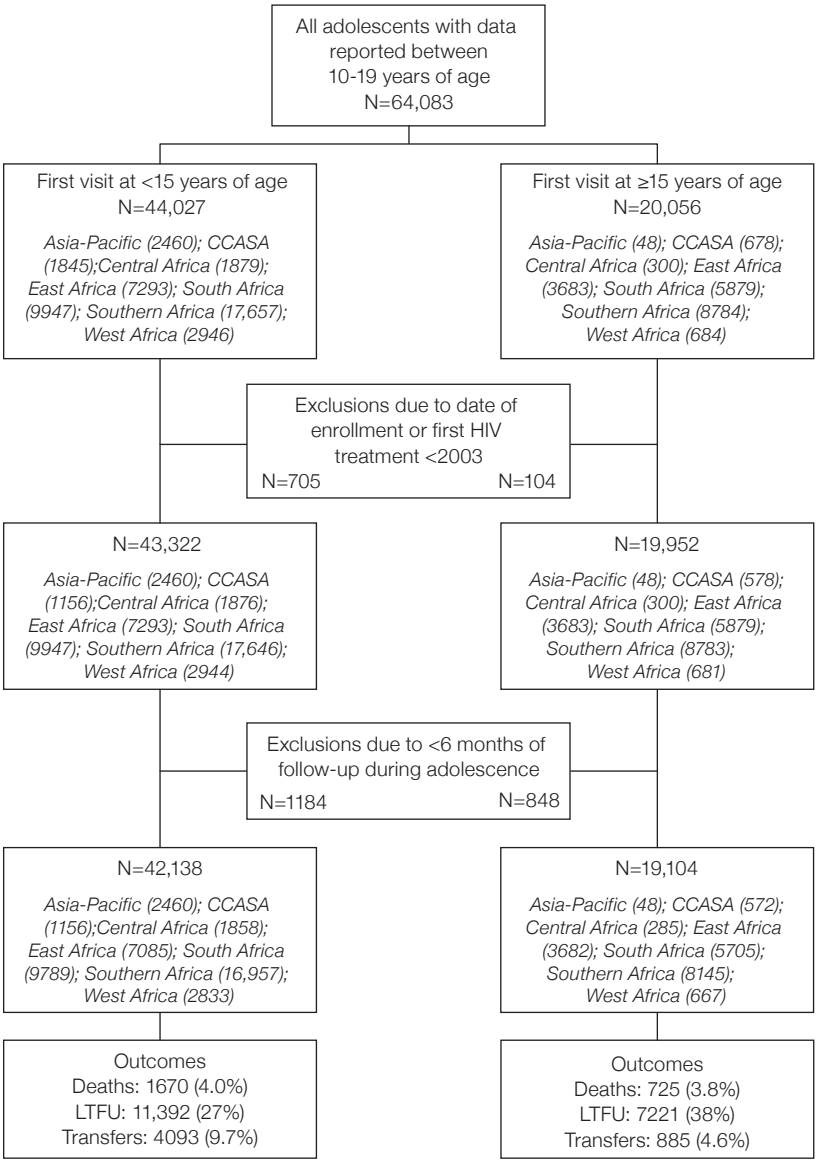



**FIGURE 1.** Flow diagram for analysis cohort by age at entry into HIV care (N = 61,242).

CCASA, Caribbean, Central America, South America; LTFU, lost to follow-up.

**TABLE 1.** Characteristics at analysis baseline[a] for 61,242 patients who had a care visit at 10 to 19 years of age at an IeDEA site between 2003 and 2016.

| Characteristics[b] | At age 10 or first visit if first visit < age 15 N=42,138 (68.8%) | At first visit if first visit ≥ age 15 N=19,104 (31.2%) | *p*-value |
|---|---|---|---|
| **Sex** | | | <0.001 |
| Male | 19,816 (47.0) | 3638 (19.0) | |
| Female | 22,137 (52.5) | 15,420 (80.7) | |
| Unknown | 185 (0.4) | 46 (0.3) | |
| **Age at first clinic visit (years)** | | | N/A |
| Median (IQR) | 9.8 (6.8, 12.0) | 17.5 (16.4, 18.3) | |
| Mean (SD) | 9.3 (3.48) | 17.3 (1.14) | |
| **CD4 count (cells/mm$^3$)** | | | <0.001 |
| <200 | 6447 (15.3) | 3764 (19.7) | |
| 200-349 | 4087 (9.7) | 3360 (17.6) | |
| 350-499 | 3668 (8.7) | 2508 (13.1) | |
| ≥500 | 11,176 (26.5) | 3617 (18.9) | |
| Unknown | 16,760 (39.8) | 5855 (30.7) | |
| Median (IQR) | 435 (196, 745) | 329 (178, 521) | <0.001 |
| Mean (SD) | 513 (405.1) | 377 (274.3) | <0.001 |
| **HIV viral load, copies/mL** | | | <0.001 |
| <50 | 3026 (7.2) | 227 (1.2) | |
| 50-399 | 1535 (3.6) | 132 (0.7) | |
| 400-999 | 472 (1.1) | 42 (0.2) | |
| 1000-9999 | 837 (2.0) | 157 (0.8) | |
| ≥10,000 | 2199 (5.2) | 483 (2.5) | |
| Unknown | 34,069 (80.9) | 18,063 (94.6) | |
| Median $\log_{10}$ (IQR) HIV-RNA | 2.4 (1.6, 4.2) | 3.9 (1.9, 4.9) | <0.001 |
| Mean (SD) | 2.8 (1.6) | 3.6 (1.58) | <0.001 |
| **WHO/CDC clinical stage** | | | <0.001 |
| WHO stage 1/ CDC stage N | 1759 (4.2) | 1808 (9.5) | |
| WHO stage 2/ CDC stage A | 2613 (6.2) | 885 (4.6) | |
| WHO stage 3/ CDC stage B | 2638 (6.3) | 798 (4.2) | |
| WHO stage 4/ CDC stage C | 1872 (4.4) | 267 (1.4) | |
| Not documented | 33,256 (78.9) | 15,346 (80.3) | |

**TABLE 1.** Continued.

| Characteristics[b] | At age 10 or first visit if first visit < age 15 N=42,138 (68.8%) | At first visit if first visit ≥ age 15 N=19,104 (31.2%) | *p*-value |
|---|---|---|---|
| **Weight-for-age z-score** | | | <0.001 |
| <-3 | 7179 (17.0) | 2079 (10.9) | |
| -3 ≤ to <-2 | 6644 (15.8) | 1401 (7.3) | |
| -2 ≤ to <-1 | 9051 (21.5) | 2353 (12.3) | |
| ≥-1 | 7664 (18.2) | 6690 (35.0) | |
| Unknown | 11,600 (27.5) | 6581 (34.5) | |
| Median (IQR) | -1.9 (-2.9, -1.0) | -0.9 (-2.2, -0.1) | <0.001 |
| Mean (SD) | -2.1 (1.63) | -1.3 (1.99) | <0.001 |
| **Height-for-age z-score** | | | <0.001 |
| <-3 | 5254 (12.5) | 851 (4.5) | |
| -3 ≤ to <-2 | 6896 (16.4) | 1348 (7.1) | |
| -2 ≤ to <-1 | 7642 (18.1) | 3138 (16.4) | |
| ≥-1 | 6422 (15.2) | 5136 (26.9) | |
| Unknown | 15,924 (37.8) | 8631 (45.2) | |
| Median (IQR) | -1.9 (-2.8, -1.0) | -1.0 (-1.9, -0.3) | <0.001 |
| Mean (SD) | -1.9 (1.42) | -1.1 (1.35) | <0.001 |
| **Timing of antiretrovirals[c]** | | | <0.001 |
| Started before baseline | 17,420 (41.3) | 164 (0.9) | |
| Started at baseline | 4982 (11.8) | 3232 (16.9) | |
| **Type of regimen[c, d]** | | | <0.001 |
| 3-ART-NNRTI | 18,389 (82.1) | 2822 (83.1) | |
| 3-ART-PI | 1489 (6.7) | 147 (4.3) | |
| 3-ART-NNRTI/PI based | 55 (0.3) | 2 (0.1) | |
| 3-ART-other | 52 (0.2) | 11 (0.3) | |
| Mono/dual | 2417 (10.8) | 414 (12.2) | |

**TABLE 1.** Continued.

| Characteristics[b] | At age 10 or first visit if first visit < age 15 N=42,138 (68.8%) | At first visit if first visit ≥ age 15 N=19,104 (31.2%) | *p*-value |
|---|---|---|---|
| **Most frequent antiretroviral regimen[c]** | | | <0.001 |
| 3TC/d4T/EFV | 4105 (18.3) | 191 (5.6) | |
| 3TC/d4T/NVP | 3759 (16.8) | 265 (7.8) | |
| 3TC/AZT/NVP | 3362 (15.0) | 184 (5.4) | |
| 3TC/AZT/EFV | 2418 (10.8) | 156 (4.6) | |
| ABC/3TC/EFV | 2264 (10.1) | 53 (1.6) | |
| ABC/3TC/NVP | 1344 (6.0) | 16 (0.5) | |
| FTC/EFV/TDF | 313 (1.4) | 1057 (31.1) | |
| 3TC/EFV/TDF | 314 (1.4) | 653 (19.2) | |
| 3TC/NVP/TDF | 47 (0.2) | 153 (4.6) | |
| Others[e] | 4476 (20.0) | 668 ( (19.7) | |
| **Duration on antiretrovirals, years[f]** | | | <0.001 |
| <1 | 3765 (21.6) | 91 (55.5) | |
| 1-2 | 5764 (33.1) | 27 (16.5) | |
| ≥3 | 7891 (45.3) | 46 (28.1) | |
| Median (IQR) | 2.7 (1.2, 4.6) | 0.6 (0.1, 3.9) | <0.001 |
| Mean (SD) | 3.1 (2.29) | 2.1 (2.55) | <0.001 |

Data are presented as n (%) unless otherwise noted. We used the 1977 WHO growth curve for weight-for-age z-score (more recent weight curves are limited to children age ≤10 years) and the 2006/2007 WHO growth curve for height-for-age z-score.

3-ART, antiretroviral therapy regimen of three or more antiretrovirals; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; mono/dual, single or two drugs; SD, standard deviation.

[a] Baseline was the date of the 10th birthday for those who entered care before age 10, and the date of the first clinic visit for those who entered care at or after age 10.

[b] IeDEA regions utilize a common data exchange standard for harmonizing data for use in multiregional analyses that includes formats and categorizations for specific data variables that are available at iedeades.org.

[c] This only includes those who were on antiretrovirals at baseline. Those who started before baseline and stopped before baseline and those who started antiretrovirals after baseline were not included.

[d] 3-ART represents triple-drug regimens. The drug class following that term denotes where one of the drugs included either an NNRTI, PI, or both classes; "other" represents triple-drug regimens without an NNRTI or PI. Non-3-ART represents regimens with fewer than three individual antiretroviral drugs.

[e] Includes other triple-drug and mono/dual antiretroviral combinations.

[f] Duration has been calculated for adolescents who started antiretrovirals before baseline and were still on them at baseline.

**TABLE 2.** Factors associated with death during the adolescent period (10 to 19 years of age) in 39,262 patients who received ≥3 antiretroviral drugs as initial HIV treatment regimens.

| | | | Univariate | | Multivariate | |
|---|---|---|---|---|---|---|
| Characteristics | Total N=39,262 | Deaths N=1518 | asHR (95% CI) | *p*-value | asHR (95% CI) | *p*-value |
| **Sex** | | | | | | |
| Male | 16,475 | 681 | 1.00 | | 1.00 | |
| Female | 22,640 | 832 | 0.99 (0.90, 1.10) | 0.899 | 1.19 (1.07, 1.33) | 0.001 |
| **Age at ≥3-drug ART (years)** | | | | | | |
| <5 | 3006 | 26 | 1.00 | | 1.00 | |
| 5-9 | 11,923 | 248 | 3.05 (2.05, 4.53) | <0.001 | 2.59 (1.74, 3.85) | <0.001 |
| 10-14 | 14,522 | 844 | 11.28 (7.73, 16.45) | <0.001 | 6.93 (4.69, 10.22) | <0.001 |
| ≥15 | 9811 | 400 | 11.26 (7.67, 16.52) | <0.001 | 8.72 (5.85, 13.02) | <0.001 |
| **Current CD4 count (cells/mm$^3$)[a]** | | | | | | |
| <200 | - | 913 | 1.00 | | | |
| 200-349 | - | 162 | 0.20 (0.17, 0.23) | <0.001 | 0.27 (0.23, 0.32) | <0.001 |
| 350-499 | - | 121 | 0.15 (0.13, 0.18) | <0.001 | 0.23 (0.19, 0.28) | <0.001 |
| ≥500 | - | 170 | 0.06 (0.05, 0.07) | <0.001 | 0.12 (0.10, 0.15) | <0.001 |
| **Current weight-for-age z score[a]** | | | | | | |
| <-3 | - | 834 | 1.00 | | 1.00 | |
| -3 ≤ to <-2 | - | 199 | 0.22 (0.19, 0.26) | <0.001 | 0.34 (0.29, 0.40) | <0.001 |
| ≥-2 | - | 325 | 0.12 (0.11, 0.14) | <0.001 | 0.22 (0.19, 0.25) | <0.001 |
| **Facility level** | | | | | | |
| Health centre | 16,068 | 532 | 1.00 | | | |
| District hospital | 6708 | 232 | 1.11 (0.95, 1.30) | 0.174 | 0.76 (0.64, 0.91) | 0.003 |
| Regional, provincial, or university hospital | 13,214 | 635 | 1.31 (1.17,1.47) | <0.001 | 1.02 (0.86, 1.22) | 0.800 |

**TABLE 2.** Continued.

| Characteristics | Total N=39,262 | Deaths N=1518 | Univariate | | Multivariate | |
|---|---|---|---|---|---|---|
| | | | asHR (95% CI) | *p*-value | asHR (95% CI) | *p*-value |
| **Facility setting** | | | | | | |
| Urban | 16141 | 750 | 1.00 | | 1.00 | |
| Mostly urban | 4857 | 241 | 1.10 (0.95, 1.30) | 0.184 | 1.40 (1.13, 1.75) | 0.002 |
| Mostly rural | 2758 | 114 | 1.04 (0.85, 1.26) | 0.723 | 1.39 (1.03, 1.87) | 0.032 |
| Rural | 12,184 | 291 | 0.57 (0.49, 0.65) | <0.001 | 0.76 (0.63, 0.91) | 0.003 |
| **Region** | | | | | | |
| Southern Africa | 11,640 | 528 | 1.00 | | 1.00 | |
| Asia-Pacific | 2295 | 85 | 0.62 (0.49, 0.78) | 0.001 | 0.54 (0.39, 0.75) | 0.001 |
| Caribbean, Central and South America | 1473 | 114 | 1.40 (1.15, 1.72) | 0.001 | 0.96 (0.72, 1.26) | 0.748 |
| Central Africa | 1660 | 54 | 0.59 (0.45, 0.78) | <0.001 | 0.68 (0.48, 0.95) | 0.026 |
| East Africa | 7476 | 303 | 0.90 (0.78, 1.04) | 0.160 | 0.49 (0.37, 0.65) | <0.001 |
| South Africa | 11,574 | 202 | 0.35 (0.29, 0.41) | <0.001 | 0.45 (0.36, 0.57) | <0.001 |
| West Africa | 3144 | 232 | 1.37 (1.18, 1.60) | <0.001 | 1.02 (0.80, 1.30) | 0.859 |
| **Year of first ≥3-drug ART** | | | | | | |
| 2003-2006 | 8560 | 554 | 1.00 | | 1.00 | |
| 2007-2010 | 14,553 | 659 | 0.83 (0.74, 0.92) | 0.001 | 0.69 (0.61, 0.78) | <0.001 |
| 2011-2016 | 16,149 | 305 | 0.49 (0.43, 0.57) | <0.001 | 0.36 (0.31, 0.43) | <0.001 |

Loss to follow-up (n=9131) was a competing event for death in this analysis and death was a competing event for loss to follow-up. Total numbers include missing values (not shown in the table). Missing values were included as a separate category in all analyses.

95% CI, 95% confidence interval; asHR, adjusted subdistribution hazard ratio.

[a] CD4 count and weight-for-age z score were considered time-dependent variables. Total number was not given as adolescents moved between categories.

**TABLE 3.** Factors associated with LTFU during the adolescent period (10 to 19 years of age) in 39,262 patients who received ≥3 antiretroviral drugs as initial HIV treatment regimens.

| | | | Univariate | | Multivariate | |
|---|---|---|---|---|---|---|
| **Characteristics** | **Total N = 39,262** | **LTFU N = 9131** | **asHR (95% CI)** | ***p*-value** | **asHR (95% CI)** | ***p*-value** |
| **Sex** | | | | | | |
| Male | 16,475 | 3753 | 1.00 | | 1.00 | |
| Female | 22,640 | 5374 | 1.33 (1.27, 1.38) | <0.001 | 1.12 (1.07, 1.17) | <0.001 |
| **Age at ≥3-drug ART (years)** | | | | | | |
| <5 | 3006 | 304 | 1.00 | | 1.00 | |
| 5-9 | 11,923 | 2198 | 3.17 (2.84, 3.54) | <0.001 | 2.59 (2.32, 2.88) | <0.001 |
| 10-14 | 14,522 | 4142 | 9.90 (8.91, 11.00) | <0.001 | 6.11 (5.49, 6.81) | <0.001 |
| ≥15 | 9811 | 2487 | 24.54 (21.94, 27.46) | <0.001 | 11.11 (9.86, 12.53) | <0.001 |
| **Current CD4 count (cells/mm$^3$)[a]** | | | | | | |
| <200 | - | 1824 | 1.00 | | 1.00 | |
| 200-349 | - | 1489 | 0.92 (0.86, 0.99) | 0.017 | 1.01 (0.94, 1.08) | 0.777 |
| 350-499 | - | 1143 | 0.57 (0.53, 0.61) | <0.001 | 0.72 (0.67, 0.78) | <0.001 |
| ≥500 | - | 3076 | 0.35 (0.33, 0.37) | <0.001 | 0.65 (0.61, 0.69) | <0.001 |
| **Current weight-for-age z score[a]** | | | | | | |
| <-3 | - | 1448 | 1.00 | | | |
| -3 ≤ to <-2 | - | 1046 | 0.64 (0.59, 0.69) | <0.001 | *0.93 (0.86, 1.01)* | *0.079* |
| ≥-2 | - | 3252 | 0.65 (0.61, 0.69) | <0.001 | *0.94 (0.88, 1.01)* | *0.087* |
| **Facility level** | | | | | | |
| Health centre | 16,068 | 4747 | 1.00 | | 1.00 | |
| District hospital | 6708 | 1527 | 0.84 (0.79, 0.89) | <0.001 | 1.27 (1.18, 1.37) | <0.001 |
| Regional, provincial, or university hospital | 13,214 | 2091 | 0.37 (0.35, 0.39) | <0.001 | 0.63 (0.58, 0.68) | <0.001 |

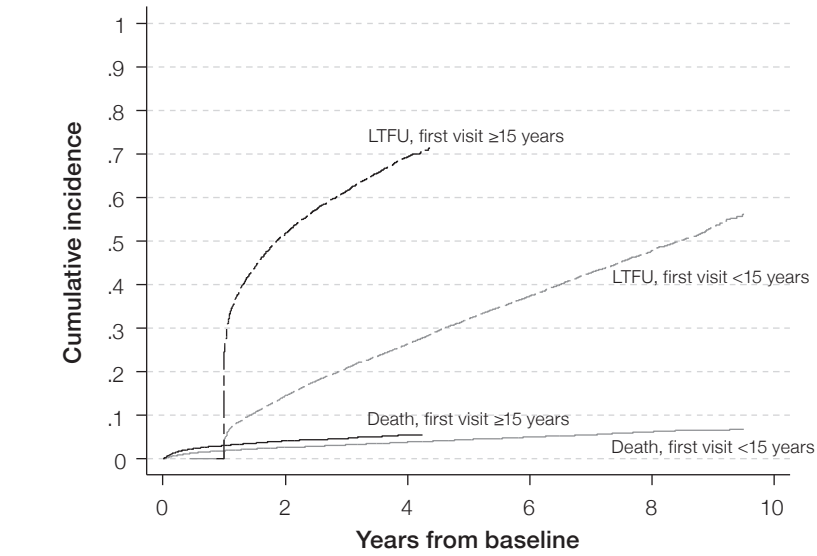
**TABLE 3.** Continued.

| | | | Univariate | | Multivariate | |
|---|---|---|---|---|---|---|
| Characteristics | Total N = 39,262 | LTFU N = 9131 | asHR (95% CI) | *p*-value | asHR (95% CI) | *p*-value |
| **Facility location** | | | | | | |
| Urban | 16,141 | 3185 | 1.00 | | | |
| Mostly urban | 4857 | 545 | 0.58 (0.53, 0.64) | <0.001 | 0.71 (0.62, 0.81) | <0.001 |
| Mostly rural | 2758 | 401 | 0.99 (0.90, 1.10) | 0.914 | 0.75 (0.64, 0.87) | <0.001 |
| Rural | 12,184 | 4223 | 2.70 (2.58, 2.82) | <0.001 | 1.21 (1.13, 1.29) | <0.001 |
| **Region** | | | | | | |
| Southern Africa | 11,640 | 2776 | 1.00 | | 1.00 | |
| Asia-Pacific | 2295 | 49 | 0.04 (0.03, 0.06) | <0.001 | 0.19 (0.14, 0.25) | <0.001 |
| Caribbean, Central and South America | 1473 | 649 | 1.21 (1.12, 1.31) | 0.822 | 2.99 (2.65, 3.36) | <0.001 |
| Central Africa | 1660 | 266 | 0.42 (0.37, 0.47) | <0.001 | 0.93 (0.80, 1.08) | 0.347 |
| East Africa | 7476 | 1152 | 0.61 (0.57, 0.66) | <0.001 | 1.14 (1.01, 1.28) | 0.028 |
| South Africa | 11,574 | 3850 | 1.22 (1.16, 1.28) | <0.001 | 1.75 (1.63, 1.88) | 0.001 |
| West Africa | 3144 | 389 | 0.31 (0.28, 0.35) | <0.001 | 0.93 (0.81, 1.06) | 0.288 |
| **Year of first ≥3-drug ART** | | | | | | |
| 2003-2006 | 8560 | 1940 | 1.00 | | 1.00 | |
| 2007-2010 | 14,553 | 3689 | 2.11 (1.99, 2.24) | <0.001 | 1.24 (1.16, 1.32) | <0.001 |
| 2011-2016 | 16,149 | 3502 | 5.36 (5.03, 5.72) | <0.001 | 1.84 (1.71, 1.99) | <0.001 |

Loss to follow-up (n=9131) was a competing event for death in this analysis and death was a competing event for loss to follow-up. Total numbers include missing values (not shown in the table). Missing values were included as a separate category in all analyses.

95% CI, 95% confidence interval; asHR, adjusted subdistribution hazard ratio.

[a] CD4 count and weight-for-age z score were considered time-dependent variables. Total number was not given as adolescents moved between categories.




**Number at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| <15 years | 42,138 | 27,096 | 15,258 | 6540 | 1705 | 0 |
| ≥15 years | 19,104 | 3274 | 248 | 0 | 0 | 0 |

**FIGURE 2.** Estimated cumulative incidences of death and loss to follow-up using competing risk methods, among adolescents (10 to 19 years) enrolled at 270 IeDEA clinical sites from 2003 to 2016, by age at first clinic visit (n=61,242).

## DISCUSSION

This is the first IeDEA multiregional cohort analysis to reflect the complexity of the mixed adolescent HIV epidemic including both individuals with perinatally acquired HIV and those infected later. Among the 61,242 adolescents in our analysis, 69% entered care before the age of 15 (our proxy for perinatally acquired infection), but not until a median age of 9.8 years.

While the cumulative incidence of both mortality and LTFU were higher among those entering care at ≥15 years (our proxy for infection acquired later during adolescence), the qualitative differences in mortality over this period were small. However, the sensitivity analysis demonstrated a higher burden of mortality among those perinatally infected adolescents who did not enter care until 10 to 14 years of age. Our overall four-year cumulative incidence of death of 4.2% compares to the post-ART mortality incidence rate of 0.97 per 100 person-years among children five to nine years of age

in IeDEA (20), and rates among youth starting ART during the ages of 15 to 24 years from 0.8 per 100 in Nigeria up to 13.5 per 100 in Tanzania in a seven-African country analysis (2).

From our regression model, most factors found to be protective against death among those who started treatment with triple-drug ART were consistent with other studies (e.g. better immune control, higher weight-for-age z-score) (4,21,22). Any CD4 category ≥200 cells/mm$^3$ or weight-for-age z-score better than or equal to -3 was highly protective; as was starting triple-drug ART after 2011, which may reflect scale-up and quality improvement of paediatric HIV programmes and broadening treatment access in our settings (23,24). Among those who had not received treatment, the median duration of follow-up during adolescence was only one year and 52% were LTFU, making reliable ascertainment of mortality difficult in this sub-group. The associations with regional cohort may reflect variations in national infrastructures for HIV and availability of other supportive healthcare services in the context of background country development (2,25-27).

The overall high cumulative incidence of LTFU was concerning. Losses among those presenting to care during late adolescence rose sharply starting in the first year of follow-up, whereas losses among the perinatally infected steadily increased over time. The four-year cumulative incidence of LTFU during adolescence was 26% for the perinatally infected and almost three times that at 69% for the late-infected. This compares to data from adolescents and young adults 15 to 24 years of age at treatment initiation in seven African countries, where LTFU ranged from 7.1% in Uganda to 30% in Tanzania (2). The rapid early losses are also consistent with levels of LTFU, approximately 30%, documented in prevention of mother-to-child HIV transmission Option B+ programmes (28,29). While we did not have access to pregnancy data to confirm whether young women entered HIV care through antenatal care, being female was a risk factor for LTFU. While current universal treatment recommendations may reduce the early LTFU that was previously associated with delays related to CD4 testing (30-32), there are also studies among adolescents and adults reporting greater attrition among those started on ART at higher CD4 counts who have not experienced clinical disease progression (33-35).

The associations between LTFU and older age, as well as later year at cohort entry, may be related to having less time to return to care after an interruption (i.e. patient churn), survival bias among those who started treatment as younger children, or the poorer retention often seen among older adolescents and young adults (2,36-39). Receiving care in rural settings was associated with higher LTFU, but protective against death, which may suggest under ascertainment of mortality in rural areas

where out migration in sub-Saharan Africa has been common (40,41). The reasons for the associations with regional cohort are unclear, and could be due to varying proportions of perinatally infected youth, local patient case mix, or other socio-economic or demographic factors (18,28,42,43). In addition, regional cohorts with sites within areas with a high density of ART programmes may see more "silent transfers," where patients move between clinics without formal referrals.

The median baseline CD4 count for the group entering care between 15 and 19 years was unexpectedly low at 329 cells/$mm^3$, implying that there may have been perinatally infected adolescents mixed into this group who entered care at older ages with advanced HIV disease. This may reflect the health status of older slow progressors among perinatal adolescent survivors or the potential contribution of rapid disease progressors among those infected during adolescence. Age alone may be insufficient to avoid misclassification, and more complex algorithms to assess combinations of routinely available variables (e.g. weight, height and CD4 count) would help to disaggregate data (15).

Our analysis was limited by the use of routinely collected clinical data, which were incomplete. We included children with missing data in analyses using missing value categories in covariates, which has the advantage of maximising the sample size. Sensitivity analyses which excluded missing data gave very similar results, but did result in some changes in differences in survival between regions and facility setting. These site-level covariates should be interpreted especially cautiously. Beyond variations in clinical resources and programme policies, some of the regions had more older female adolescents enrolled, which may have been associated with antenatal care programmes where early LTFU rates have been high (28). Our focus on those 10 to 19 years of age results in a survivor bias, as individuals who were perinatally infected would have had to survive childhood in order to be eligible for inclusion. In addition, our age proxy for perinatally acquired infection may have miscategorized those presenting very late to care as being infected during adolescence. Restricting inclusion in the analysis to those with at least six months of data may have resulted in underreporting of LTFU. While we allowed for randomly collected tracing data to reclassify outcomes, we did not systematically adjust for the risk of unascertained mortality among those LTFU.

## CONCLUSIONS

In this global analysis of adolescent outcomes in IeDEA, 3.9% of ALHIV were reported to have died and 30% were LTFU, with both rates higher in those entering care after age 15. However, those entering care between 10 and 15 years were at higher risk of death than those in care before age 10, reflecting the severe immunodeficiency associated with delayed diagnoses. Greater prioritization of adolescents for clinical and social support is urgently needed to retain youth in HIV treatment programmes as they transition through adolescence into adult life.

### Competing Interests

AHS reports support to her institution for travel and grants from ViiV Healthcare, and ML reports unrestricted grants from Boehringer Ingelhiem, Gilead Sciences, Merck Sharp & Dohme, Bristol-Myers Squibb, Janssen-Cilag, ViiV HealthCare, consultancy fees from Gilead Sciences, and DSMB sitting fees from Sirtex Pty Ltd. Other authors have no conflicts to report.

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### Author contributions

AK, ML, and AHS developed and wrote the analysis concept and analysis plan. AK, ML, MAD, KWW, VL, AE, CM, RV, SA, MY, MP, RH, AHS revised and finalized the concept. AK, ML, MAD, MV, KWW, VL, AE, CM, RV, LF, SA, MY, ET, JP, AA, KM, DMM, and AHS were involved with the collection, preparation, and/or submission of the source data for the analysis. AK and ML conducted the analysis. AK and AHS wrote the paper. All co-authors were involved with revisions of the paper, and read and approved the final version.

## SUPPLEMENTAL INFORMATION

- Tables available at: https://onlinelibrary.wiley.com/action/downloadSupplement?-doi=10.1002%2Fjia2.25215&file=jia225215-sup-0001-TableS1-S3.docx *(direct download of the complete file)*
  - o Table S1. Characteristics at antiretroviral initiation for 44,922 adolescents who had a care visit at 10 to 19 years of age at an IeDEA site between 2003 and 2016
  - o Table S2. Outcomes, by region and age at first clinic visit (Group A, first visit <15 years of age; Group B, first visit ≥15 years of age)
  - o Table S3. Outcomes, by region and age at first clinic visit (Group A, first visit <10 years of age; Group B, first visit ≥10 years of age)
- Appendix A available at: https://onlinelibrary.wiley.com/doi/10.1002/jia2.25215
  - o IeDEA global investigator acknowledgements by region

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PART 2

# ADOLESCENTS LIVING WITH HIV IN ASIA: HOW LIFE-LONG HIV INFECTION IMPACTS CLINICAL AND PROGRAM OUTCOMES

CHAPTER 6

# Identifying Gaps in Adolescent HIV Care and Treatment Delivery in Asia: Results of a Regional Health Provider Survey

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## ABSTRACT

Adolescents living with HIV (ALHIV) have substantial challenges accessing and adhering to HIV care and antiretroviral therapy (ART). We conducted a study to gather data on clinical service practices to support ALHIV-focused care in Asia using a 31-question survey for healthcare providers on care and treatment services, support for adherence and retention, and tracking of risk behaviors. It was generated in Google Forms, available in seven languages (Bahasa Indonesia, Chinese Mandarin, English, Malay, Khmer, Thai, Vietnamese), and hosted via Google Drive. Survey request emails were distributed to individual stakeholders (e.g. HIV clinicians, researchers, policymakers), and via sector listserves. Survey completion denoted consent to participate. Descriptive statistics with median values are provided. Between December 2015 and May 2016, 82 respondents from Cambodia (17%), China (6.1%), India (3.6%), Indonesia (20%), Malaysia (12%), Thailand (23%), and Vietnam (18%) participated. Most were physicians (73%) from tertiary-level hospitals (66%); 16% reported caring for >100 patients, 42% for 21–100, and 31% for <20; 95% of ALHIV in their care were on ART, 20% were on a second-line regimen. ALHIV-specific services were offered by less than half of the respondent clinics, and included 22% with designated adolescent care providers, and 19% with adolescent clinic times. Transition preparation included how to navigate adult care services (82%) and communicate with new health providers (67%), and some used a multidisciplinary team of pediatric and adult providers to coordinate transition (35%). Their most commonly reported challenges in ALHIV care included socio-economic limitations impacting care uptake (e.g. transportation, food insecurity; 44%), difficulty supporting self-disclosure by the adolescent (44%), and poor ART adherence (42%). These study results highlight the variable scope of HIV care offered by pediatric HIV centers to ALHIV in Asia, as well as challenges with service delivery, social support, and engaging adult HIV providers in the transition preparation process

## INTRODUCTION

There has been accelerated growth around research and policy related to global adolescent health that has emphasized the many missed opportunities for prevention and care interventions for this age group and their consequences on morbidity and mortality (Abdul- Razak, Azzopardi, Patton, Mokdad, & Sawyer, 2017; Mokdad et al., 2016; Patton et al., 2016). An increasing focus has been placed on the right to health care, especially around access to sexual and reproductive health by young women and girls (Melgar, Melgar, Festin, Hoopes, & Chandra-Mouli, 2018; WHO, 2018). Among adolescents living with HIV (ALHIV), there are added layers related to the intersection between HIV and local social, cultural, and religious contexts. The estimated 1.8 million ALHIV worldwide have substantial challenges adhering to HIV care and antiretroviral therapy (ART), including often having non-parental caregivers due to orphanhood, facing stigma and discrimination in education and employment, and managing a chronic life-long illness (Bobat, Archary, & Lawler, 2015; Cluver et al., 2016; Kim et al., 2017; UNAIDS, 2017, 2018; Van Dyke et al., 2016).

Outcomes vary by setting, and change over time as these young people are transitioned out of pediatric to adult HIV care and expected to take greater responsibility for their own care (Chokephaibulkit et al., 2014; Hansudewechakul et al., 2015; Kakkar et al., 2016; Ryscavage, Macharia, Patel, Palmeiro, & Tepper, 2016; Westling, Naver, Vesterbacka, & Belfrage, 2016). Those perinatally infected are more likely to have clinical symptoms and complex HIV management issues as a consequence of life-long infection, while those infected later in life are required to cope with a disease that greatly impacts family and other social relationships (Kahana et al., 2016; Neilan et al., 2017).

A range of interventions have been applied to better engage ALHIV during this period of social, emotional, and physical development (Chokephaibulkit et al., 2015; Judd, Sohn, & Collins, 2016; Lee et al., 2016). A key factor affecting whether and how such programs can be successfully implemented is the available programmatic infra-structure to deliver care for ALHIV. Despite calls for “youth-friendly” services (UNICEF, 2015; WHO, 2016), it remains unclear to what degree care specifically designed for ALHIV populations is actually provided in routine health settings. In 2015, Paediatric AIDS Treatment for Africa (PATA) and the World Health Organization (WHO) conducted a survey across sub-Saharan Africa to assess the availability of appropriate adolescent services, and the standards used to guide care (Mark et al., 2017). These findings were used to guide the development of the WHO’s 2016 consolidated HIV treatment and antiretroviral prevention guidelines (WHO, 2016). However, comparative information about program resources and clinical practices were not available for the Asia region.

Although the overall prevalence among both females and males 15–24 years in the region is low at <0.1%, there are an estimated 150,000 adolescents 10–19 years of age and 450,000 15–24-year-old young adults living with HIV in the Asia-Pacific (UNAIDS; aidsinfo.unaids.org). In order to better address the adolescent epidemic in Asia and inform local treatment guidelines, similar types of data are needed that reflect the region's social, cultural, and economic contexts.

Perinatally infected children in Asia are frequently cared for in specialist pediatric HIV clinics rather than the family care settings that are more prevalent in African countries (Nyandiko et al., 2009; Prasitsuebsai et al., 2010). This requires eventual transfer to adult HIV care, which generally involves different health providers, physical spaces and locations for care. In collaboration with PATA, amfAR's (Foundation for AIDS Research) TREAT Asia program adapted the original African survey tool to the Asian setting in order to gather comparable service and transition data, and highlight gaps where future efforts can improve the care for the 190,000 ALHIV in the region (UNAIDS, 2017).

## METHODS

### Study design and participants

TREAT Asia (Therapeutics Research, Education, AIDS Training in Asia) is a regional research, education, and community advocacy and policy organization that works through a network of research and clinical institutions and civil society partners to optimize HIV care and treatment for children, adolescents, and adults living with and at risk for HIV in the Asia-Pacific region (treatasia.org). The Asia study protocol and survey tool were developed with the aim to conduct a simplified version of the original PATA-WHO Africa situational analysis that would be feasible to implement across multiple language contexts, while being sufficiently comparable to the Africa data to allow for regional comparisons. In particular, open-ended questions were replaced with lists of multiple answer options that were based on the results of the Africa survey.

### Survey development

The Africa analysis included two surveys: a 31-item 'high-level' version, and a 61-item 'deep-dive' version (Mark et al., 2017). Instead of continuing this approach, the survey for the Asia study duplicated and merged elements from the two Africa versions into a single survey with 31 questions on clinic characteristics, care and treatment services, support for adherence and retention, sexual and reproductive health (SRH) services, adolescent-specific services, and tracking of risk behaviors (see File 1 – Complete survey tool; Africa survey tools available in reference Mark et al., 2017).

The survey was developed in English and translated into six languages and distributed in Cambodia, China, India, Indonesia, Malaysia, Thailand, and Vietnam; including Bahasa Indonesia, Chinese Mandarin, Malay, Khmer, Thai, and Vietnamese. All translations were reviewed for accuracy by pediatric HIV clinicians within TREAT Asia's pediatric and adolescent research network.

## Survey implementation

The multi-language surveys were converted into a web-based document using Google Forms. Survey links were posted on a publicly available webpage that was accessible using a specific uniform resource locator (URL) located within the Google Forms online application and hosted by Google servers via Google Drive. The survey was pilot-tested in each language to confirm the clarity of the translations, and took approximately 20 minutes to complete.

The survey link was distributed via email from December 2015 until May 2016. Emails were sent by the study investigators to 1) individual stakeholders (e.g. TREAT Asia research network members, WHO national and regional representatives), and 2) sector listserves (e.g. HIV community organization email groups) for completion and further distribution. Three reminders were sent out by email to both of these groups and through phone calls to the first group to request completion and distribution of the surveys.

## Confidentiality and data handling

Survey responses were loaded real time into an online spreadsheet stored on the same Google Drive server as the Google Forms. The Google Drive account that housed the Google Forms and the aggregated responses spreadsheet were password-protected. The data were extracted from the spreadsheet into an Excel file; all files were stored on password-protected computers. Once the survey period was completed, all forms and data from the Google Forms and the Google account were deleted.

Identifying participant information was used to ensure that no duplicate data were collected from the same clinic (none were identified), and if response data were substantially unclear and required follow-up clarification. Thereafter, personal identifiers were deleted. Participants were assured in the consent statement that responses would be anonymized to the degree that data would only be presented at a country level, and no individuals or clinics would be named in presentations or reports.

### Ethical considerations

The study protocol was approved by the Institutional Review Board (IRB) of the coordinating center at TREAT Asia. Individuals accessing the survey online were presented with a consent statement on the online landing page introducing the project. The statement detailed the purpose of the study, clarification of the anonymous nature of their response, potential risks and benefits to participation, and options for not participating. If they did not agree to participate, they were not directed to the survey questions. Those who agreed to participate could stop at any time and withdraw from the study without penalty or further consequence.

### Data analysis

Quantitative data were analyzed using descriptive statistics. All percentages presented are median values for the overall or the country-level responses, as appropriate. Qualitative data from the free text responses for some of the survey questions were categorized into common themes (e.g. social vs. economic barriers to adherence) for further characterization.

## RESULTS

### Respondents and care settings

Between December 2015 and May 2016, 82 respondents from Cambodia, China, India, Indonesia, Malaysia, Thailand, and Vietnam submitted completed surveys (Table 1). Most were physicians (73%) from clinics within tertiary-level hospitals (66%). The sizes of the adolescent populations on ART reported by all respondents varied, with 16% reporting caring for greater than 100 patients, 42% with between 21 and 100, and 31% with fewer than 20 (Supplemental Table 1 – Complete survey results). The majority of clinics (55%) offered care for adolescents together with children, while 27% had integrated care for all ages. A total of 38% of respondent clinics offered some level of adolescent-specific services. These included designated adolescent care providers (22%), adolescent clinic times (19%), and clinic space for adolescent HIV care (6%).

### Treatment, adherence, and retention in care

Almost all adolescents in care at respondent clinics (95%) were on ART, and a median of 20% were on a second-line regimen (Table 2). Survey responses were not mutually exclusive and allowed for selection of multiple interventions to measure and address adherence and retention. The most common methods to measure adherence were self- report by recall of missed doses (70%) and pill counts in clinic (69%). Respondents noted low patient motivation to adhere to ART (80%), insufficient caregiver support

(69%), as well as pill burden (53%) as common challenges to consider when deciding to switch adolescents to second-line ART. While 71% of clinics provided routine viral load monitoring for adolescents, viral load testing was used by one-third for assessing those suspected of poor adherence.

Half of clinics (54%) had formal guidelines for managing adolescents with adherence challenges. Both individual (84%) and family (73%) counseling were commonly used, with an emphasis on detailing the negative consequences of poor adherence (e.g. telling adolescents about their risk of treatment failure) and developing practical strategies with the adolescent on how to improve adherence. Interventions to promote retention in care similarly focused on counseling, while including greater engagement of caregivers and families (69%). When adolescents were lost to follow-up (LTFU), 70% used telephone calls or electronic reminders to try to re-engage them into care, 58% organized home visits by social workers or counselors, and 41% made referrals to community health workers and support organizations for assistance.

## Transition to adult care and special populations

Approximately half of the adolescents in care at the respondent clinics were in specialist pediatric HIV care and would eventually require transition to separate adult HIV clinical care services (Table 2). Half of all clinics offered some transition guidance. Transition preparation included combinations of interventions, including practical support around how to navigate adult care services (82%), communicate with new health providers (67%), and request SRH services (54%). Some clinics took additional steps, such as identifying specific adult providers who would be responsible for caring for transitioned youth (40%), using a multidisciplinary team of both pediatric and adult providers to coordinate transition (35%), and making efforts to educate the adult care team about transition (33%).

Half of the respondent clinics offered screening and treatment for sexually transmitted infections (STIs) and 45% provided family planning support. Few providers reported assessing injection drug use (21%), male-to-male sex (20%), or selling sex (18%). Similar percentages offered specific services for young men who have sex with men (MSM; 23%) or injection drug users (19%), which included 23% offering services such as partner testing or condoms specifically for adolescent MSM, and 19% offering counseling, opiate substitution therapy, or other interventions for young people who inject drugs.

## Key challenges in adolescent care

Respondents noted multiple and often concurrent challenges to providing adolescent HIV care (responses not mutually exclusive; Supplemental Table 1), including socio-

economic limitations impacting adolescent access to and uptake of care and treatment (e.g. transportation, food insecurity; 44%), difficulty disclosing HIV infection to the adolescent and supporting self-disclosure by the adolescent (44%), and poor adherence to ART (42%). Insufficient caregiver support (26%) and limited technical resources at the clinic level (e.g. management guidelines, counseling tools; 26%) were also identified. Respondents highlighted the long-term clinical problems of poor growth and development (43%), ART side effects (38%), and neurocognitive deficits (38%). Despite being on treatment, malnutrition (34%) and opportunistic infections (33%) continued to be encountered.

**TABLE 1.** Description of adolescent care and services survey respondents in seven Asian countries, N=82*.

| | Overall | Thailand | Indonesia | Vietnam | Cambodia | Malaysia | China | India |
|---|---|---|---|---|---|---|---|---|
| | (N=82) N (%) | (N=19) N (%) | (N=16) N (%) | (N=15) N (%) | (N=14) N (%) | (N=10) N (%) | (N=5) N (%) | (N=3) N (%) |
| **Respondents** | | | | | | | | |
| Physician in pediatrics and/or adolescent medicine | 45 (55) | 11 (58) | 12 (75) | 10 (67) | 5 (36) | 7 (70) | 0 (0) | 0 (0) |
| Physician in general medicine | 15 (18) | 0 (0) | 3 (19) | 3 (20) | 2 (14) | 1 (10) | 5 (100) | 1 (33) |
| Counselor | 7 (9) | 4 (21) | 0 (0) | 0 (0) | 2 (14) | 0 (0) | 0 (0) | 1 (33) |
| Clinic administrator | 4 (5) | 1 (5) | 0 (0) | 0 (0) | 3 (21) | 0 (0) | 0 (0) | 0 (0) |
| Clinical nurse or nurse practitioner | 4 (5) | 3 (16) | 0 (0) | 0 (0) | 0 (0) | 1 (10) | 0 (0) | 0 (0) |
| Other | 4 (5) | 0 (0) | 1 (6) | 2 (13) | 0 (0) | 1 (10) | 0 (0) | 0 (0) |
| Social worker | 3 (4) | 0 (0) | 0 (0) | 0 (0) | 2 (14) | 0 (0) | 0 (0) | 1 (33) |
| **Clinic setting** | | | | | | | | |
| Hospital-based clinic within a tertiary-level hospital (e.g., provincial, referral) | 54 (66) | 17 (89) | 5 (31) | 10 (67) | 12 (86) | 5 (50) | 3 (60) | 2 (67) |
| Hospital-based clinic within a primary- or secondary-level hospital | 14 (17) | 1 (5) | 9 (56) | 1 (7) | 0 (0) | 2 (20) | 0 (0) | 1 (33) |
| Specialist clinic (e.g., HIV, infectious diseases, research center), not part of a hospital | 11 (13) | 1 (5) | 0 (0) | 4 (27) | 1 (7) | 3 (30) | 2 (40) | 0 (0) |
| Primary health care clinic, not part of a hospital | 3 (4) | 0 (0) | 2 (13) | 0 (0) | 1 (7) | 0 (0) | 0 (0) | 0 (0) |

**TABLE 1.** Continued.

| | Overall | Thailand | Indonesia | Vietnam | Cambodia | Malaysia | China | India |
|---|---|---|---|---|---|---|---|---|
| | (N=82) N (%) | (N=19) N (%) | (N=16) N (%) | (N=15) N (%) | (N=14) N (%) | (N=10) N (%) | (N=5) N (%) | (N=3) N (%) |
| **Estimated number of adolescents at clinics** | | | | | | | | |
| **Number of respondents** | **71 (87)** | **17 (89)** | **15 (94)** | **11 (73)** | **10 (71)** | **10 (100)** | **5 (100)** | **3 (100)** |
| 1-20 | 22 (31) | 5 (29) | 7 (47) | 3 (27) | 2 (20) | 3 (30) | 1 (20) | 1 (33) |
| 21-100 | 30 (42) | 9 (53) | 3 (20) | 6 (55) | 4 (40) | 6 (60) | 2 (40) | 0 (0) |
| 101-500 | 11 (15) | 3 (18) | 0 (0) | 2 (18) | 3 (30) | 0 (0) | 2 (40) | 1 (33) |
| 501-1000 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| ≥1001 | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (33) |
| Unknown | 3 (4) | 0 (0) | 2 (13) | 0 (0) | 1 (10) | 0 (0) | 0 (0) | 0 (0) |
| No adolescents | 4 (6) | 0 (0) | 3 (20) | 0 (0) | 0 (0) | 1 (10) | 0 (0) | 0 (0) |
| **HIV care and treatment services for adolescents** | | | | | | | | |
| Adolescents are seen with children, but not with adults | 45 (55) | 14 (74) | 5 (31) | 10 (67) | 9 (64) | 6 (60) | 0 (0) | 1 (33) |
| Adolescents, children and adults are all seen together | 22 (27) | 4 (21) | 9 (56) | 4 (27) | 2 (14) | 0 (0) | 2 (40) | 1 (33) |
| Adolescents are seen with adults, but not with children | 10 (12) | 1 (5) | 2 (13) | 1 (7) | 3 (21) | 2 (20) | 0 (0) | 1 (33) |
| Adolescents receive separate services from children and adults | 5 (6) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (20) | 3 (60) | 0 (0) |
| **Routine HIV viral load monitoring** | | | | | | | | |
| **Number of respondents** | **80 (98)** | **18 (95)** | **15 (94)** | **15 (100)** | **14 (100)** | **10 (100)** | **5 (100)** | **3 (100)** |
| Yes | 57 (71) | 18 (100) | 3 (20) | 6 (40) | 14 (100) | 10 (100) | 5 (100) | 1 (33) |
| No | 23 (29) | 0 (0) | 12 (80) | 9 (60) | 0 (0) | 0 (0) | 0 (0) | 2 (67) |

*Number of respondents is 82 out of 82, unless otherwise noted when responses were incomplete.

**TABLE 2.** Treatment, adherence, retention in care, and transition support for adolescents, N=82*.

| | Overall | Thailand | Indonesia | Vietnam | Cambodia | Malaysia | China | India |
|---|---|---|---|---|---|---|---|---|
| | (N=82) N (%) | (N=19) N (%) | (N=16) N (%) | (N=15) N (%) | (N=14) N (%) | (N=10) N (%) | (N=5) N (%) | (N=3) N (%) |
| **Percentage of adolescents on antiretroviral therapy,** median** | 95% | 95% | 60% | 100% | 96% | 95% | 95% | 52% |
| **First-line antiretroviral regimen**, median | 80% | 60% | 85% | 85% | 81% | 50% | 80% | 87% |
| **Second-line antiretroviral regimen**, median | 20% | 30% | 10% | 15% | 14% | 46% | 20% | 12% |
| **Top 5 methods to measure adherence to antiretroviral therapy (Multiple responses allowed)** | | | | | | | | |
| **Number of respondents** | **77 (94)** | **18 (95)** | **13 (81)** | **15 (100)** | **14 (100)** | **9 (90)** | **5 (100)** | **3 (100)** |
| Self-report of how many doses have been missed within the past days or weeks | 54 (70) | 15 (83) | 11 (85) | 12 (80) | 3 (21) | 5 (56) | 5 (100) | 3 (100) |
| Pill counts, in clinic | 53 (69) | 10 (56) | 7 (54) | 12 (80) | 11 (79) | 5 (56) | 5 (100) | 3 (100) |
| Viral load testing for adolescents suspected of non-adherence | 26 (34) | 7 (39) | 0 (0) | 9 (60) | 8 (57) | 2 (22) | 0 (0) | 0 (0) |
| Pill counts, in the home (announced or unannounced) | 19 (25) | 2 (11) | 4 (31) | 4 (27) | 3 (21) | 3 (33) | 2 (40) | 1 (33) |
| Therapeutic drug monitoring for adolescents suspected of non-adherence | 18 (23) | 4 (22) | 1 (8) | 11 (73) | 0 (0) | 0 (0) | 1 (20) | 1 (33) |

**TABLE 2.** Continued.

| | Overall | Thailand | Indonesia | Vietnam | Cambodia | Malaysia | China | India |
|---|---|---|---|---|---|---|---|---|
| | (N=82) N (%) | (N=19) N (%) | (N=16) N (%) | (N=15) N (%) | (N=14) N (%) | (N=10) N (%) | (N=5) N (%) | (N=3) N (%) |
| **Top 5 methods offered to promote adherence (Multiple responses allowed)** | | | | | | | | |
| **Number of respondents** | **79 (96)** | **18 (95)** | **14 (88)** | **15 (100)** | **14 (100)** | **10 (100)** | **5 (100)** | **3 (100)** |
| Individual counseling | 66 (84) | 17 (94) | 11 (79) | 13 (87) | 10 (71) | 8 (80) | 4 (80) | 3 (100) |
| Discussing with them about the negative consequences of poor adherence (for example: treatment failure, illness, death) | 62 (78) | 14 (78) | 11 (79) | 14 (93) | 10 (71) | 7 (70) | 4 (80) | 2 (67) |
| Family counseling | 58 (73) | 11 (61) | 12 (86) | 11 (73) | 8 (57) | 8 (80) | 5 (100) | 3 (100) |
| Discussing with them about what adherence-promoting strategies would work for them (for example: reminders, pill boxes) | 55 (70) | 5 (28) | 10 (71) | 8 (53) | 9 (64) | 7 (70) | 5 (100) | 2 (67) |
| Asking the adolescent to share about their individual challenges in adhering to their medicines | 48 (61) | 8 (44) | 8 (57) | 13 (87) | 10 (71) | 7 (70) | 1 (20) | 1 (33) |
| **Top 5 methods offered to promote retention in care (Multiple responses allowed)** | | | | | | | | |
| **Number of respondents** | **77 (94)** | **16 (84)** | **14 (88)** | **15 (100)** | **14 (100)** | **10 (100)** | **5 (100)** | **3 (100)** |
| Individual counseling | 65 (84) | 14 (88) | 11 (79) | 14 (93) | 11 (79) | 8 (80) | 4 (80) | 3 (100) |
| Family counseling | 56 (73) | 10 (63) | 9 (64) | 13 (87) | 10 (71) | 7 (70) | 5 (100) | 2 (67) |
| Caregiver and family engagement | 53 (69) | 14 (88) | 9 (64) | 13 (87) | 9 (64) | 4 (40) | 3 (60) | 1 (33) |
| HIV health education and treatment literacy | 40 (52) | 9 (56) | 6 (43) | 6 (40) | 9 (64) | 4 (40) | 4 (80) | 2 (67) |
| | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Community health worker and community-based organization engagement | 28 (36) | 6 (38) | 7 (50) | 7 (47) | 3 (21) | 3 (30) | 0 (0) | 2 (67) |
| **Top 5 strategies to re-engage adolescents into care (Multiple responses allowed)** | | | | | | | | |
| **Number of respondents** | **79 (96)** | **18 (95)** | **14 (88)** | **15 (100)** | **14 (100)** | **10 (100)** | **5 (100)** | **3 (100)** |
| Telephone calls and/or electronic reminders | 55 (70) | 15 (83) | 9 (64) | 14 (93) | 4 (29) | 6 (60) | 4 (80) | 3 (100) |
| Home visits by social workers/ counselors | 46 (58) | 11 (61) | 7 (50) | 8 (53) | 9 (64) | 4 (40) | 5 (100) | 2 (67) |
| Referral to community health worker and community-based organization to help adolescents return to clinic | 32 (41) | 7 (39) | 7 (50) | 6 (40) | 6 (43) | 4 (40) | 0 (0) | 2 (67) |
| Peer outreach to encourage adolescents to return to care | 26 (33) | 4 (22) | 6 (43) | 8 (53) | 4 (29) | 1 (10) | 0 (0) | 3 (100) |
| Offer financial incentives – For transportation costs to attend clinic | 13 (16) | 2 (11) | 1 (7) | 4 (27) | 2 (14) | 3 (30) | 1 (20) | 0 (0) |
| **Adult HIV care transition practices** | | | | | | | | |
| **Number of respondents** | **74 (90)** | **18 (95)** | **12 (75)** | **14 (93)** | **13 (93)** | **9 (90)** | **5 (100)** | **3 (100)** |
| Adolescents are transitioned to a new clinic or a different provider, and they are offered the below counseling services. | 40 (54) | 10 (56) | 4 (33) | 10 (71) | 5 (38) | 8 (89) | 1 (20) | 2 (67) |
| Adolescents are not transitioned to a new clinic or a different provider. They continue with the same clinic or provider as they age into adults. | 28 (38) | 7 (39) | 7 (58) | 3 (21) | 6 (46) | 1 (11) | 4 (80) | 0 (0) |

**TABLE 2.** Continued.

| | Overall | Thailand | Indonesia | Vietnam | Cambodia | Malaysia | China | India |
|---|---|---|---|---|---|---|---|---|
| | (N=82) N (%) | (N=19) N (%) | (N=16) N (%) | (N=15) N (%) | (N=14) N (%) | (N=10) N (%) | (N=5) N (%) | (N=3) N (%) |
| **Adult HIV care transition practices (continued)** | | | | | | | | |
| Adolescents are transitioned to a new clinic or a different provider, but they are not offered counseling about this change in their care | 6 (8) | 1 (6) | 1 (8) | 1 (7) | 2 (15) | 0 (0) | 0 (0) | 1 (33) |
| **Routine pre-transition counseling services (Multiple responses allowed)** | | | | | | | | |
| **Number of respondents** | **39 (48)** | **9 (47)** | **5 (42)** | **9 (60)** | **5 (36)** | **8 (80)** | **1 (20)** | **2 (67)** |
| How to navigate the adult HIV care services (for example: where the clinic and pharmacy are located, how to make appointments) | 32 (82) | 9 (100) | 4 (80) | 8 (89) | 3 (60) | 7 (88) | 1 (100) | 1 (50) |
| How to communicate with new healthcare providers | 26 (67) | 6 (67) | 3 (60) | 8 (89) | 1 (20) | 7 (88) | 1 (100) | 1 (50) |
| How to ask their providers about their sexual and reproductive health needs | 21 (54) | 4 (44) | 5 (100) | 6 (67) | 2 (40) | 3 (38) | 1 (100) | 1 (50) |
| Understanding their own eligibility for health benefits and insurance | 19 (49) | 7 (78) | 3 (60) | 6 (67) | 1 (20) | 2 (25) | 1 (100) | 0 (0) |
| How to independently manage their own healthcare needs in the adult HIV clinic | 14 (36) | 5 (56) | 3 (60) | 3 (33) | 0 (0) | 3 (38) | 1 (100) | 0 (0) |
| | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Guidelines or protocols for transition from pediatric clinic into adult HIV care** | | | | | | | | |
| **Number of respondents** | **79 (96)** | **18 (95)** | **14 (88)** | **15 (100)** | **14 (100)** | **10 (100)** | **5 (100)** | **3 (100)** |
| Yes | 40 (51) | 9 (50) | 1 (7) | 11 (73) | 12 (86) | 3 (30) | 1 (20) | 3 (100) |
| No or not applicable | 39 (49) | 9 (50) | 13 (93) | 4 (27) | 2 (14) | 7 (70) | 4 (80) | 0 (0) |
| **Top 5 activities for transition preparation among those with guidelines or protocols (N=40) (Multiple responses allowed)** | | | | | | | | |
| **Number of respondents** | **40 (49)** | **9 (47)** | **1 (6)** | **11 (73)** | **12 (86)** | **3 (30)** | **1 (20)** | **3 (100)** |
| Individual counseling | 35 (88) | 7 (78) | 1 (100) | 10 (91) | 10 (83) | 3 (100) | 1 (100) | 3 (100) |
| Family counseling | 32 (80) | 6 (67) | 1 (100) | 10 (91) | 9 (75) | 3 (100) | 1 (100) | 2 (67) |
| Allow adolescents to express their opinions about the transition process and date of transition | 24 (60) | 5 (56) | 0 (0) | 8 (73) | 5 (42) | 3 (100) | 1 (100) | 2 (67) |
| Disclose HIV status to perinatally infected youth before the transition to adult clinic | 23 (58) | 6 (67) | 0 (0) | 9 (82) | 1 (8) | 3 (100) | 1 (100) | 3 (100) |
| Educate the pediatric HIV care team and staff about the transition process | 20 (50) | 6 (67) | 1 (100) | 6 (55) | 1 (8) | 3 (100) | 1 (100) | 2 (67) |
| **Top 5 routinely sexual and reproductive health services offered to adolescents (Multiple responses allowed)** | | | | | | | | |
| **Number of respondents** | **77 (94)** | **18 (95)** | **14 (88)** | **13 (87)** | **14 (100)** | **10 (100)** | **5 (100)** | **3 (100)** |
| General sexual health counselling and education | 61 (79) | 17 (94) | 12 (86) | 11 (85) | 8 (57) | 5 (50) | 5 (100) | 3 (100) |
| Services for the prevention of mother-to-child HIV transmission (PMTCT) | 51 (66) | 14 (78) | 13 (93) | 8 (62) | 5 (36) | 6 (60) | 2 (40) | 3 (100) |
| STI screening and treatment | 36 (47) | 12 (67) | 8 (57) | 4 (31) | 4 (29) | 2 (20) | 4 (80) | 2 (67) |
| Family planning counseling | 35 (45) | 17 (94) | 6 (43) | 7 (54) | 4 (29) | 1 (10) | 1 (20) | 3 (100) |
| Support for disclosure to partners | 33 (43) | 11 (61) | 7 (50) | 5 (38) | 5 (36) | 1 (10) | 1 (20) | 3 (100) |

**TABLE 2.** Continued.

| | Overall | Thailand | Indonesia | Vietnam | Cambodia | Malaysia | China | India |
|---|---|---|---|---|---|---|---|---|
| | (N=82) N (%) | (N=19) N (%) | (N=16) N (%) | (N=15) N (%) | (N=14) N (%) | (N=10) N (%) | (N=5) N (%) | (N=3) N (%) |
| **Characterizing adolescent risk populations (Multiple responses allowed)** | | | | | | | | |
| **Number of respondents** | **80 (98)** | **17 (89)** | **16 (100)** | **15 (100)** | **14 (100)** | **10 (100)** | **5 (100)** | **3 (100)** |
| Whether they are perinatally infected | 67 (84) | 15 (88) | 8 (50) | 14 (93) | 12 (86) | 10 (100) | 5 (100) | 3 (100) |
| Whether females are pregnant | 27 (34) | 11 (65) | 4 (25) | 3 (20) | 3 (21) | 2 (20) | 3 (60) | 1 (33) |
| Whether they inject drugs | 17 (21) | 4 (24) | 2 (13) | 3 (20) | 1 (7) | 3 (30) | 3 (60) | 1 (33) |
| Whether males have sex with other males | 16 (20) | 5 (29) | 4 (25) | 0 (0) | 1 (7) | 3 (30) | 2 (40) | 1 (33) |
| Whether they sell sex | 14 (18) | 3 (18) | 3 (19) | 2 (13) | 1 (7) | 4 (40) | 0 (0) | 1 (33) |
| None of above | 9 (11) | 1 (6) | 6 (38) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

*Number of respondents is 82 out of 82, unless otherwise noted when responses were incomplete. Overall median values are reported.

**Adolescents in some clinics may have been on regimens other than standard first- or second-line combinations (e.g., holding regimen, third-line).

**TABLE 3.** Comparison between Asia and Africa responses to adolescent services survey questions*.

| | Asia sites | | Africa sites | |
|---|---|---|---|---|
| | N (%) | Denominator | N (%) | Denominator |
| Separate care services for adolescents from adult and/or pediatric patients | 5 (6) | 82 | 75 (35) | 215 |
| Monitoring of viral load testing | 57 (71) | 80 | 92 (43) | 214 |
| Guidelines or protocols for managing adolescents with adherence challenges | 43 (54) | 80 | 22 (39) | 56 |
| Retention support for adolescents (any category)** | 74 (94) | 79 | 132 (61) | 216 |
| · Peer support | 26 (33) | 79 | 45 (34) | 132 |
| · Home visits | 46 (58) | 79 | 41 (31) | 132 |
| Provision of sexual and reproductive health services to adolescents (any category)** | 61 (79) | 77 | 137 (63) | 217 |
| · Family planning and contraception | 16 (21) | 77 | 99 (72) | 137 |
| · Sexually transmitted infection screening and treatment | 36 (47) | 77 | 42 (31) | 137 |
| Guidelines or protocols to guide adolescent transition process | 40 (51) | 79 | 27 (51) | 54 |
| Provision of transition-related counseling | 35 (88) | 40 | 34 (63) | 54 |

*Denominators for each row may vary due to the type of questions asked and incomplete responses. The Africa survey was divided into a general high-level survey for a broad group of sites and a detailed deep-dive survey for a limited group of clinical sites. (Mark, et al, 2017)

**Selected responses are provided in the table. For more detailed information of all responses provided, please see File 1 and Mark, et al, 2017.

## DISCUSSION

Our survey results reflect a diverse picture of adolescent clinical resources and service delivery within a limited sample from seven Asian countries. The results differ in notable ways from the prior survey conducted in Africa (Table 3) (Mark et al., 2017). Many of these differences were expected a priori and are related in part to the relative sizes of the ALHIV and general HIV epidemics in the Asia region compared to Africa, with epidemics in Asia being largely concentrated in urban areas and among key populations (UNICEF, 2015). For example, while few of the respondent Asia clinics cared for adolescents separately from other ages (6% in Asia vs. 35% in Africa), about one-third offered some kind of adolescent-specific clinical support (Mark et al., 2017). The Asia clinics more often provided advanced medical services, including second-line ART and viral load monitoring (71% in Asia vs. 43% in Africa). However, few in either region assessed risk behaviors specific to young key populations (Asia 18–21% vs. Africa 14–18%), this despite the higher relative proportion of people living with HIV among most at-risk groups in Asia.

The majority of Asia respondents were hospital-based, pediatric HIV referral clinics, with adolescent populations under 100 people. Given their prioritization of poor growth and development, and neurocognitive deficits as common challenges to providing adolescent HIV care, it is likely that the respondents' patient base was predominantly perinatally infected. Perinatal infection would be a key factor influencing the range of services offered as well as clinical outcomes, such as the 10–46% estimated to already be on second-line regimens while still in pediatric care.

Asia survey respondents almost equally highlighted poor adherence (42%), socio-economic difficulties such as clinic travel costs and family food security (44%), and disclosure to the patient and others (44%) as challenges to adolescent HIV care. Most offered individual counseling around the negative consequences of poor adherence and strategies to support adherence, and employed some range of interventions to promote retention in care. If patients were LTFU, 70% of clinics used telephone calls or electronic messaging to bring patients back into care.

There is untapped potential for electronic health (eHealth) interventions to support adolescent HIV care in the region. The Asia-Pacific has high regional rates of social media and Internet usage, representing almost half of all Internet users and one-third of all global Facebook users (Internet World Stats, 2017). Thailand currently has a greater than 100% mobile user penetration rate (i.e. more than one mobile device per person). (Anand et al., 2017). Efforts to use online methods to reach high-risk MSM and transgender individuals have been successful in the context of HIV testing and

prevention in Southeast Asia (amfAR, 2014; Anand et al., 2017, 2017). eHealth platforms have become more sophisticated, allowing for counselor interaction and group chat functions, features that could facilitate more efficient and effective peer support and outreach for young people in the Asian context (Anand et al., 2017; Anand, Nitpolprasert, & Phanuphak, 2017).

Although the patients cared for by the pediatric specialty clinics in our sample would need to be transitioned to adult HIV care, half of the clinics reported having no formal guidelines to standardize that process, as was reported in the Africa analysis. Almost all clinics with a transition protocol provided individual and family counseling which preferentially emphasized the logistics of how to access adult HIV care over some of the associated psychosocial challenges and responses. However, few reported activities that involved adult providers as part of the transition process. Almost half (43%) started the process itself one to three years in advance, and the actual transfer happened around the age of 18, which is similar to the Africa survey and other cohorts in Canada, the Netherlands, and the United Kingdom (Collins et al., 2017; Kakkar et al., 2016; Weijsenfeld et al., 2016), but younger than what has been reported in some cohorts in the United States (Tanner et al., 2016).

A recognized weakness of pediatric HIV care delivery is the frequent lack of support for SRH services (S. Kim, Kim, McDonald, Fidler, & Foster, 2016), which are generally more often offered within adult-focused care in Asia. There were also notable gaps in the care targeted to young key populations. Although almost half of the respondent Asia clinics offered family planning and prevention of mother-to-child HIV transmission (PMTCT), only one-fifth offered services to young MSM or those who injected drugs.

The major limitation of our study was our low response rate leading to a small sample size relative to our geographic distribution across diverse care settings. Most respondents were from urban referral centers, preventing generalizability to rural or primary care clinics. Importantly, we had few clinics from India, where the largest numbers of people living with HIV in the region reside. While the survey was available in seven languages, we did not offer versions in non-English official Indian languages, which likely impacted our Indian response rate. In addition, we were unable to accurately assess the denominator of those who received the survey request emails, as they were sent out through listserves with unknown numbers of members and email opening rates, and the potential for secondary forwarding beyond the initial distribution. Because of the smaller numbers of responses per country, we were unable to compare country-level responses in order to avoid over generalizing the results. We also did not capture variations in social contextual issues such as consent laws that may have impacted management of adolescent care and transition to adult HIV care.

## CONCLUSIONS

These study results highlight the variable scope of HIV care that can be offered by Asian pediatric HIV centers to their adolescent patients, as well as gaps in service delivery, social support within the community, and the transition preparation process. In addition, the survey results help to illustrate differences between the Asian and African youth epidemics, emphasizing the importance of region-specific solutions to addressing gaps in care and retention. As more adolescents age out of pediatric care, providers will need technical and financial resources to prepare them to successfully move on to adult life.

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### Disclosure statement

Pharma Company as a potential conflict of interest was reported by the authors.

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### Author contributions

All authors conceptualized and designed the study. AHS, PB, and CA performed data curation and contributed to data collection and coordination of the study. AHS, CA, and DM designed the methodology of the study. CA conducted the formal analysis. AHS obtained funding, and AHS and DM supervised the conduct of the study. AHS wrote the original draft of the manuscript. All authors critically reviewed, revised, and approved the final version for publication.

## SUPPLEMENTAL INFORMATION

- Complete results: TREAT Asia-PATA Adolescent HIV Care and Treatment Survey (release version 14 July 2017).
  - o Available at: https://www.tandfonline.com/doi/suppl/10.1080/17450128.2019.1576958/suppl_file/rvch_a_1576958_sm0896.pdf

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CHAPTER 7

# Determining Standardized Causes of Death of Infants, Children, and Adolescents Living with HIV in Asia

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## ABSTRACT

Objective: To implement a standardized cause of death reporting and review process to systematically disaggregate causes of HIV-related deaths in a cohort of Asian children and adolescents.

Design: Death-related data were retrospectively and prospectively assessed in a longitudinal regional cohort study.

Methods: Children under routine HIV care at sites in Cambodia, India, Indonesia, Malaysia, Thailand, and Vietnam between 2008 and 2017 were followed. Causes of death were reported and then independently and centrally reviewed. Predictors were compared using competing risks survival regression analyses.

Results: Among 5918 children, 5523 (93%; 52% male) had ever been on combination antiretroviral therapy. Of 371 (6.3%) deaths, 312 (84%) occurred in those with a history of combination antiretroviral therapy (crude all-cause mortality 9.6 per 1000 person-years; total follow-up time 32 361 person-years). In this group, median age at death was 7.0 (2.9–13) years; median CD4 cell count was 73 (16–325) cells/ml. The most common underlying causes of death were pneumonia due to unspecified pathogens (17%), tuberculosis (16%), sepsis (8.0%), and AIDS (6.7%); 12% of causes were unknown. These clinical diagnoses were further grouped into AIDS-related infections (22%) and noninfections (5.8%), and non-AIDS-related infections (47%) and noninfections (11%); with 12% unknown, 2.2% not reviewed. Higher CD4þ cell count and better weight-for-age z-score were protective against death.

Conclusion: Our standardized cause of death assessment provides robust data to inform regional resource allocation for pediatric diagnostic evaluations and prioritization of clinical interventions, and highlight the continued importance of opportunistic and nonopportunistic infections as causes of death in our cohort.

## INTRODUCTION

Infants and children with perinatally acquired HIV are extremely vulnerable to opportunistic infection. Delaying combination antiretroviral therapy (cART) for even a few months after birth has been associated with a 76% increased risk of death (1). It is challenging to tease out causes of pediatric HIV-associated mortality because of the limited range of and access to diagnostic testing for this population in low-income and middle-income countries (LMICs). It has been simpler to consider all early deaths among infants and children with HIV due to AIDS (2). In addition, although pediatric deaths may be more thoroughly ascertained than those of adults (3), available approaches to death reporting are not specific to children with HIV. This limits the ability of providers and implementers to use cause of death data to guide selection of diagnostic evaluations, or prioritize clinical resources to address preventable causes of death.

When the TREAT Asia Pediatric HIV Observational Database (TApHOD) study was established in 2008, a systematic approach to describing and determining causes of death was instituted to address this evidence gap (4). The Coding Causes of Death (CoDe) model, originally developed for the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study in adults with HIV, was already in use in parallel adult cohort studies in the Asia- Pacific and Australia (5,6). Informed by prior experience with the 'adult CoDe' process, we used a 'pediatric CoDe' process to allow for the addition of key data variables without changing the structure of the original method. We conducted an analysis of the pediatric CoDe results to characterize the process and describe the deaths reported over the first 10 years of our regional cohort study.

## METHODS

### Study population

The study was conducted within TApHOD, a member cohort of IeDEA Asia-Pacific (4). The database was established in 2006 and includes routinely collected, patient-level data from more than 6500 infants, children, and adolescents with HIV who have ever been followed at 16 network sites in Cambodia (n=1), India (n=1), Indonesia (n=2), Malaysia (n=4), Thailand (n=5), and Vietnam (n=3). Network sites are pediatric referral clinics within larger healthcare facilities (n=12) or free-standing pediatric hospitals (n=4); all but one (a research clinic) are public HIV treatment centers. National HIV treatment guidelines were based on WHO global guidelines and updated over time based on CD4-specific and age-specific criteria (7–9). Individuals of any age taking or naïve to cART with a pediatric HIV clinic visit on or after January 2008 were eligible for study inclusion. The analysis database included data up to September 2017.

All network sites, the coordinating center (TREAT Asia/ amfAR, Thailand), and the data management and biostatistics center (Kirby Institute, UNSW Australia) have local institutional review board (IRB) approval to participate in the cohort study. Consent by parents or legal guardians and assent of the children and adolescents under care are not routinely obtained unless required by an IRB (i.e. in some sites in India, Malaysia, and Thailand).

## Clinical and laboratory data

Baseline values for laboratory (e.g. CD4) and clinical measurements (e.g. weight) were based on a single measure in the 6 months prior and closest to the baseline date. At cART initiation, we used a window of 6 months before and 1 week after start. For the last available clinic visit, we used the closest value that fell within 12 months prior. To calculate height-for-age z-score, we used the WHO 2006/2007 child growth standards (3,10,11). For weight-for-age z-score, we used the WHO 1977 standards because the 2006/2007 standards are limited to children of 10 years or less (12,13). Second-line ART was defined as the second triple-drug regimen with an antiretroviral class switch (e.g. nonnucleoside reverse transcriptase inhibitor (NNRTI) to protease inhibitor), excluding those exposed to mono/dual nucleoside reverse transcriptase inhibitor therapy and known to have been switched without failure of first-line therapy.

## Cause of death ascertainment

Causes of death were reported by local providers using standardized CoDe forms originally developed for the D:A:D study (5,6,14). The CoDe process captures patient data leading up to and around the time of death, and site provider comments and determinations about the specific immediate (one diagnosis), contributing (up to four diagnoses), and underlying (one diagnosis) causes of death. Immediate causes are diseases or injuries directly leading to death (e.g. cardiorespiratory failure), contributing causes are those that contributed to death but are not considered the main reasons for death, and underlying causes are those that initiated the train of events leading directly or indirectly to death. The forms were revised for use in our pediatric population with the modification of some variables (e.g. full date of birth rather than year) and the addition of others (e.g. birth weight). Additional details and the data collection tool are provided as an Appendix. The primary objective of the process is to use all available data (including immediate and contributing causes) to inform the identification of a single underlying cause of death.

Sites were asked to provide additional information (e.g. birth weight) for infants and young children in their narrative comments. Forms were completed in English by local site staff and reviewed by the site's study Principal Investigator, if they were not written by them. Deaths were assessed retrospectively for those that occurred prior to the site data being added to the database, and prospectively thereafter.

The CoDe forms were independently reviewed by two regional pediatric HIV experts and site investigators from within the network to concur with or present differing conclusions regarding reported causes of death; reviewers were blinded to each other's assessments. Provider and reviewer forms were then centrally reviewed. In the standard adult CoDe process, deaths in which the reviewers do not concur undergo secondary review by a central committee. In the pediatric CoDe process, all deaths underwent secondary review by an unblinded adjudication committee of three network investigators, one of whom (A.H.S.) chaired all review meetings, to arrive at consensus over the final immediate, contributing, and underlying causes of death. The committee further determined whether deaths were AIDS-related on the basis of the contributing and underlying causes (by US Centers for Disease Control and Prevention (CDC) clinical staging criteria (15)). Deaths with insufficient clinical information were classified as due to unknown causes. All provider, reviewer, and committee forms were then submitted to the data management and biostatistics center for analysis.

## Statistical analysis

The beginning of study follow-up (baseline) was 1 January 2008, the first reported clinic visit, or the date of cART initiation, whichever occurred later. Data were censored at loss to follow-up (LTFU), transfer out of the clinic, death, the 24th birthday, or database closure, whichever occurred first. LTFU was defined as having no clinic contact (visit, lab test) in the 12 months prior to the site-specific database closure date, with the date of LTFU defined as 12 months following the last clinic contact. Treatment failure was defined as having at least one HIV viral load test over 1000 copies/ml before regimen change or a 50% or more decline in CD4 cell count from its peak value, or a fall in CD4 before the baseline (pre- cART) value.

The underlying cause assigned to each death was considered the primary outcome for the analysis. These were grouped into: AIDS, infection; AIDS, noninfection; non-AIDS, infection; and non-AIDS, noninfection. These categorizations were made on the basis of the individual clinical diagnosis and their inclusion in US CDC AIDS staging criteria by age (16,17). Consequently, some pathogens could appear in both AIDS and non-AIDS categories depending on the age at diagnosis, severity (e.g. local vs. disseminated disease), or chronicity (e.g. one-time or recurrent condition).

The percentages and rates (per 1000 person-years) of death attributed to each group and to each specific underlying cause of death were calculated overall and by sex. Age at death was evaluated for trend over calendar time. We used a cumulative incidence function to estimate the probabilities of different categories of death during follow-up. We assessed independent predictors of AIDS vs. non-AIDS mortality, and

infection-related vs. noninfection-related mortality using four separate competing risks survival regression analyses based on Fine and Gray's proportional sub-hazards model (18). In this analysis, we used an alternate classification in which contributing causes of death were taken into account to distinguish AIDS and non-AIDS deaths on the basis of whether those contributing causes met CDC Stage C criteria. For example, a child whose underlying cause of death was pneumonia of unknown cause (CDC Stage B) and who had severe malnutrition and wasting (CDC Stage C) as contributing causes of death would have been categorized in the 'AIDS, infection' group.

Sex, calendar year at first cART, and facility level were considered in the analyses. Age, history of AIDS diagnosis, CD4 cell count, weight-for-age z-score, and receiving second-line ART were included as time-updated variables. CD4 cell count and weight-for-age z-score were lagged by 6 months so that the most recent value was less likely to be the consequence of a clinical event leading to death. For these two variables, missing data were imputed by carrying forward values from the nearest previous visit for up to 6 months if no subsequent measurement was recorded. We created a category for missing observations and considered them as a separate group in the analyses. Potential predictors with P less than 0.20 in univariable analyses were included in multivariable analyses. The final model included variables with P less than 0.05. The adjusted subdistribution hazard ratios (asHR) were reported with their 95% confidence intervals (95% CI).

Data management and analyses were performed at the Kirby Institute, UNSW Australia, using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) and Stata (StataCorp, STATA 14.0 for Windows, College Station, Texas, USA).

## RESULTS

There were 6567 children and adolescents enrolled in the cohort at database closure (up to September 2017), of whom 5918 had a clinic visit during or after January 2008 and 91% acquired HIV perinatally. Over the follow-up period, 5523 (93%; 52% male) had ever been on cART, with 394 (6.7%) never starting antiretrovirals; one received only mono/dual therapy and was excluded from further analysis. Overall, there were 371 (6.3%) deaths; 312 in those who had ever been on cART, 58 among those who had not started any antiretrovirals, and one who had been on mono/dual therapy. CoDe forms were available for 363 (98%) of the deaths.

The primary analyses were conducted among the 5523 who ever received cART, which included 84% of all deaths (Table 1). The total follow-up time available was

32,361 person-years; 16,482 person-years for males and 15,879 for females. At cART start, median age was 5.4 (interquartile range 2.5–8.6) years, median CD4 percentage was 11% (4–18%), and 90% started cART with an NNRTI-based regimen (Supplemental Table 1, http://links.lww.com/QAD/B755). At the analysis baseline, the overall median age was 6.7 (3.3–10.5) years, median weight-for-age z-score was -2.0 (-3.2 to -1.0), height-for-age z-score was -2.1 (-3.0 to -1.2), and 25% had a history of meeting WHO stage 3 or 4 criteria. Median CD4 was 510 (193–917) cells/ml, CD4 percentage was 18% (9–26%), and the median time on cART was 2.2 (1.0–4.2) years.

## Causes of death among those with a history of combination antiretroviral therapy

Of the 5523 who had been on cART, 312 (5.6%) died during follow-up, representing a crude all-cause mortality rate of 9.6 per 1000 person-years (males 10.3; females 8.9). Over time, this decreased from 19.8 from 2008 to 2010, to 8.8 in 2011 to 2013, to 4.0 per 1000 person-years in 2014–2017 (Supplemental Figure 2, http://links.lww.com/QAD/B755). The median age at death was 7.0 (2.9–13) years: males 6.4 (2.9–13) years, females 7.7 (2.8–13) years. This increased by calendar year from 3.9 (2.7–7.8) years in 2008 to 15 (10–20) years by 2017 (Supplemental Figure 1, http://links.lww.com/QAD/B755). Of the 88% with an available CD4 cell count at death, the median value was 73 (16–325) cells/ ml. The most common individual underlying causes of death were pneumonia due to unspecified pathogens (17%), tuberculosis (TB) (16%), sepsis (8.0%), and AIDS (6.7%); 12% of deaths were due to unknown causes, and 2.2% did not have CoDe forms to review (Table 2, Supplemental Table 2, http://links.lww.com/QAD/B755).

The underlying causes were grouped into AIDS-related infections (22%) and noninfection (5.8%) causes, and non-AIDS-related infections (47%) and noninfections (11%), with 12% due to unknown and 2.2% to unreviewed causes. Non-AIDS-related infections were consistently the most common underlying causes of death (Figure 1). The cumulative incidence of non-AIDS, noninfection-related deaths exceeded that of AIDS, noninfection-related deaths during recent years of follow-up. Median time on cART at last visit prior to death was 5.7 (1.6–7.9) years for non-AIDS, noninfections, and ranged from 0.3 to 0.4 years for all other categories.

There were 228 contributing causes of death reported for 161 children (52%), of which the most common were wasting with or without severe malnutrition (n=114), anemia (n=36), and pneumonia (n=12). When the contributing causes of death were taken into account in the alternate classification, the proportions of AIDS-related deaths in those whose underlying causes were infections increased to 52%; the noninfection category remained stable.

**TABLE 1.** Characteristics of children and adolescents with a history of starting combination antiretroviral therapy at analysis baseline[a], by vital status and underlying cause of death.[b]

| | Alive (N=5211) | Deaths (N=305)[a] | | | | |
|---|---|---|---|---|---|---|
| | | AIDS, infection N=66 | AIDS, non-infection N=18 | Non-AIDS, infection N=148 | Non-AIDS, non-infection N=35 | Unknown N=38 |
| **Sex, female** | 2532 (49) | 28 (42) | 8 (44) | 74 (50) | 11 (31) | 16 (42) |
| **Age (years)** | | | | | | |
| <1 | 469 (9.0) | 10 (15) | 1 (5.6) | 23 (16) | 5 (14) | 6 (16) |
| 1-4 | 1471 (28) | 20 (30) | 6 (33) | 56 (38) | 6 (17) | 14 (37) |
| 5-9 | 1793 (34) | 20 (30) | 6 (33) | 43 (29) | 11 (31) | 6 (16) |
| 10-14 | 1231 (24) | 11 (17) | 2 (11) | 21 (14) | 9 (26) | 11 (29) |
| ≥15 | 247 (4.7) | 5 (7.6) | 3 (17) | 5 (3.4) | 4 (11) | 1 (2.6) |
| Median (IQR) | 6.8 (3.4, 10.6) | 5.6 (2.7, 9.9) | 5.4 (1.8, 10.9) | 4.6 (1.9, 8.6) | 7.0 (3.5, 12.5) | 4.7 (1.9, 10.2) |
| **CD4 count (cells/mm$^3$)** | | | | | | |
| <200 | 1034 (20) | 38 (58) | 7 (39) | 93 (62) | 10 (29) | 15 (39) |
| 200-349 | 561 (11) | 3 (4.6) | 1 (5.6) | 7 (4.7) | 2 (5.7) | 6 (16) |
| 350-499 | 515 (9.9) | 4 (6.1) | - | 11 (7.4) | 4 (11) | 3 (7.9) |
| ≥500 | 2339 (45) | 8 (12) | 4 (22) | 15 (10) | 15 (43) | 4 (11) |
| Unknown | 762 (15) | 13 (20) | 6 (33) | 22 (15) | 4 (11) | 10 (26) |
| Median (IQR) | 534 (217, 934) | 36 (10, 246) | 96 (35, 530) | 47 (12, 220) | 486 (64, 846) | 189 (36, 369) |
| **HIV viral load (copies/mL)** | | | | | | |
| <50 | 793 (15) | 7 (11) | 3 (16) | 3 (2.0) | 6 (17) | 2 (5.3) |
| 50-399 | 275 (5.3) | 1 (1.5) | 0 | 2 (1.4) | 1 (2.9) | 0 |
| 400-999 | 45 (0.9) | 0 | 0 | 1 (0.7) | 0 | 0 |
| 1000-9999 | 128 (2.5) | 1 (1.5) | 0 | 2 (1.4) | 2 (5.7) | 0 |
| >10,000 | 779 (15) | 16 (24) | 2 (11) | 18 (12) | 8 (23) | 8 (21) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Unknown | 3191 (61) | 41 (62) | 13 (72) | 122 (82) | 18 (51) | 28 (74) |
| Median log 10 (IQR) | 2.4 (1.7, 5.0) | 4.7 (1.7, 5.4) | 1.7 (1.7, 4.2) | 4.9 (3.2, 5.4) | 3.8 (1.7, 5.5) | 5.0 (4.0, 6.9) |
| **Weight-for-age z-score** | | | | | | |
| <-3 | 1178 (23) | 35 (53) | 10 (56) | 83 (56) | 13 (37) | 20 (53) |
| -3 ≤ to <-2 | 1008 (19) | 11 (17) | 0 | 25 (17) | 7 (20) | 7 (18) |
| -2 ≤ to <-1 | 1160 (22) | 6 (9.1) | 3 (17) | 7 (4.7) | 4 (11) | 7 (18) |
| ≥ -1 | 1163 (22) | 4 (6.1) | 1 (5.6) | 8 (5.4) | 4 (11) | 1 (2.6) |
| Unknown | 702 (13) | 10 (15) | 4 (22) | 25 (17) | 7 (20) | 3 (7.9) |
| Median (IQR) | -1.9 (-3.1, -1.0) | -3.9 (-5.6, -2.4) | -5.1 (-5.7, -1.7) | -3.8 (-6.4, -2.6) | -2.9 (-4.0, -1.5) | -3.2 (-4.4, -2.1) |
| **Height-for-age z-score** | | | | | | |
| <-3 | 982 (19) | 23 (35) | 6 (33) | 49 (33) | 11 (31) | 17 (45) |
| -3 ≤ to <-2 | 1157 (22) | 13 (20) | 2 (11) | 25 (17) | 6 (17) | 8 (21) |
| -2 ≤ to <-1 | 1173 (23) | 6 (9.1) | 2 (11) | 14 (9.5) | 3 (8.6) | 5 (13) |
| ≥ -1 | 950 (18) | 3 (4.6) | 1 (5.6) | 8 (5.4) | 6 (17) | 2 (5.3) |
| Unknown | 949 (18) | 21 (32) | 7 (39) | 52 (35) | 9 (26) | 6 (16) |
| Median (IQR) | -2.0 (-2.9, -1.3) | -3.1 (-3.7, -2.3) | -3.0 (-3.4, -1.6) | -3.1 (-4.3, -2.2) | -2.5 (-3.5, -1.20) | -3.0 (-3.8, -2.3) |
| **WHO clinical stage** | | | | | | |
| Stage 1 | 494 (9.5) | 1 (1.5) | 0 | 2 (1.4) | 1 (2.9) | 2 (5.3) |
| Stage 2 | 555 (11) | 7 (11) | 1 (5.6) | 6 (4.1) | 0 | 5 (13) |
| Stage 3 | 824 (16) | 17 (26) | 3 (17) | 60 (41) | 7 (20) | 5 (13) |
| Stage 4 | 337 (6.5) | 14 (21) | 7 (39) | 42 (28) | 9 (26) | 8 (21) |
| Unknown | 3001 (58) | 27 (41) | 7 (39) | 38 (26) | 18 (51) | 18 (47) |
| **Age at cART (years)** | | | | | | |
| <1 | 612 (12) | 12 (18) | 1 (5.6) | 23 (16) | 6 (17) | 8 (21) |
| 1-4 | 1793 (34) | 21 (32) | 7 (39) | 66 (45) | 9 (26) | 12 (32) |
| 5-9 | 1935 (37) | 26 (39) | 6 (33) | 42 (28) | 11 (31) | 9 (24) |
| 10-14 | 784 (15) | 7 (11) | 4 (22) | 15 (10) | 8 (23) | 8 (21) |
| ≥15 | 87 (1.7) | 0 | 0 | 2 (1.4) | 1 (2.9) | 1 (2.6) |
| Median (IQR) | 5.5 (2.6, 8.6) | 5.0 (2.6, 7.4) | 5.4 (1.8, 8.5) | 3.6 (1.9, 7.5) | 5.5 (2.9, 10.1) | 4.7 (1.6, 9.1) |

**TABLE 1.** Continued.

| | Alive (N=5211) | Deaths (N=305)[a] | | | | |
|---|---|---|---|---|---|---|
| | | AIDS, infection N=66 | AIDS, non-infection N=18 | Non-AIDS, infection N=148 | Non-AIDS, non-infection N=35 | Unknown N=38 |
| **Year of cART start** | | | | | | |
| <2008 | 2270 (44) | 24 (36) | 7 (39) | 34 (23) | 18 (51) | 15 (39) |
| 2008-2010 | 1304 (25) | 36 (55) | 9 (50) | 73 (49) | 14 (40) | 19 (50) |
| 2011-2013 | 1002 (19) | 6 (9.1) | 2 (11) | 36 (24) | 2 (5.7) | 3 (7.9) |
| 2014-2017 | 635 (12) | 0 | 0 | 5 (3.4) | 1 (2.9) | 1 (2.6) |
| **CD4 count at cART (cells/mm3)** | | | | | | |
| <200 | 1713 (33) | 46 (70) | 10 (56) | 89 (60) | 14 (40) | 20 (53) |
| 200-349 | 688 (13) | 5 (7.6) | 0 | 10 (6.8) | 3 (8.6) | 5 (13) |
| 350-499 | 448 (8.6) | 4 (6.1) | 0 | 8 (5.4) | 4 (11) | 1 (2.6) |
| ≥500 | 1376 (26) | 3 (4.6) | 2 (11) | 12 (8.1) | 9 (26) | 3 (7.9) |
| Unknown | 986 (19) | 8 (12) | 6 (33) | 29 (20) | 5 (14) | 9 (24) |
| Median (IQR) | 288 (72, 644) | 39 (10, 117) | 40 (11, 138) | 40 (11, 208) | 276 (27, 508) | 98 (12, 257) |
| **Type of therapy** | | | | | | |
| cART-NNRTI | 4711 (90) | 58 (88) | 18 (100) | 134 (91) | 28 (80) | 36 (95) |
| cART-PI | 377 (7.2) | 6 (9.1) | 0 | 5 (3.4) | 4 (11) | 1 (2.6) |
| cART-NNRTI/PI | 40 (0.8) | 0 | 0 | 0 | 0 | 1 (2.6) |
| cART-other | 83 (1.6) | 2 (3.0) | 0 | 9 (6.1) | 3 (8.6) | 0 |
| **Duration on cART, years[c]** | | | | | | |
| <1 | 632 (26) | 6 (23) | 2 (25) | 13 (33) | 2 (10.5) | 7 (47) |
| 1-2 | 900 (36) | 8 (31) | 2 (25) | 12 (30) | 11 (58) | 6 (40) |
| ≥3 | 945 (38) | 12 (46) | 4 (50) | 15 (38) | 6 (32) | 2 (13) |
| Median (IQR) | 2.2 (1.0-4.2) | 2.7 (1.2, 4.0) | 2.8 (1.4, 4.5) | 1.5 (0.9, 3.8) | 1.9 (1.4, 4.6) | 1.2 (0.9, 1.9) |
| | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Facility level** | | | | | | |
| Health center | 907 (16) | 11 (17) | 1 (5.6) | 26 (18) | 5 (14) | 6 (16) |
| Regional, provincial or University hospital | 4616 (84) | 55 (83) | 17 (94) | 122 (82) | 30 (86) | 32 (84) |
| **Facility setting** | | | | | | |
| Urban | 3444 (62) | 41 (62) | 13 (72) | 111 (75) | 17 (49) | 33 (87) |
| Mostly urban | 1682 (31) | 23 (35) | 4 (22) | 24 (16) | 13 (37) | 4 (11) |
| Mostly rural | 397 (7.2) | 2 (3.0) | 1 (5.6) | 13 (8.8) | 5 (14) | 1 (2.6) |

cART, combination antiretroviral therapy; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Analysis baseline is defined as 1 January 2008, first clinic visit, or date of first cART, whichever occurred later. Data on the seven deaths without review forms are not presented.

[b]Values are N (%) unless otherwise specified.

[c]Duration was given for 2585 patients who started cART before baseline.

**TABLE 2.** Underlying causes of death and mortality rates of children and adolescents with a history of combination antiretroviral therapy, 2008– 2017.

| | Numbers (%) of deaths) | Rates of death[a], all patients (95% CI) | Rates of death[a], males (95% CI) | Rates of death[a], females (95% CI) |
|---|---|---|---|---|
| **Total deaths** | **312 (100%)** | **9.64 (8.63-10.77)** | **10.31 (8.87-11.99)** | **8.94 (7.59-10.54)** |
| **AIDS-related infections[b]** | **66 (21.8)** | **2.04 (1.60-2.60)** | **2.31 (1.68-3.17)** | **1.76 (1.22-2.55)** |
| AIDS | 21 (6.7) | 0.65 (0.42-1.00) | 0.85 (0.50-1.43) | 0.44 (0.21-0.92) |
| Tuberculosis | 11 (3.5) | 0.34 (0.19-0.61) | 0.49 (0.24-0.97) | 0.19 (0.06-0.59) |
| Cytomegalovirus | 6 (1.9) | 0.19 (0.08-0.41) | 0.12 (0.03-0.49) | 0.25 (0.09-0.67) |
| Cryptococcal infection | 8 (2.6) | 0.25 (0.12-0.49) | 0.30 (0.13-0.73) | 0.19 (0.06-0.59) |
| Pneumocystis pneumonia | 8 (2.6) | 0.25 (0.12-0.49) | 0.24 (0.09-0.65) | 0.25 (0.09-0.67) |
| Penicilliosis | 5 (1.6) | 0.15 (0.06-0.37) | 0.06 (0.01-0.43) | 0.25 (0.09-0.67) |
| Pneumonia | 3 (1.0) | 0.09 (0.03-0.29) | 0.18 (0.06-0.56) | - |
| Mycobacteria Avium Complex | 2 (0.6) | 0.06 (0.02-0.25) | - | 0.13 (0.02-0.25) |
| Other[c] | 2 (0.6) | 0.06 (0.02-0.25) | 0.06 (0.01-0.43) | 0.06 (0.01-0.45) |
| **AIDS-related non-infections** | **18 (5.8)** | **0.56 (0.35-0.88)** | **0.61 (0.33-1.13)** | **0.50 (0.25-1.00)** |
| Severe malnutrition/wasting | 11 (3.5) | 0.34 (0.19-0.61) | 0.30 (0.13-0.73) | 0.38 (0.17-0.84) |
| Encephalopathy | 4 (1.3) | 0.12 (0.05-0.33) | 0.18 (0.06-0.56) | 0.06 (0.01-0.45) |
| Other[d] | 3 (1.0) | 0.09 (0.03-0.29) | 0.12 (0.03-0.49) | 0.06 (0.01-0.45) |
| **Non-AIDS-related infections** | **148 (47.4)** | **4.57 (3.89-5.37)** | **4.49 (3.58-5.64)** | **4.66 (3.71-5.85)** |
| Pneumonia | 49 (15.7) | 1.51 (1.14-2.00) | 1.21 (0.78-1.88) | 1.83 (1.27-2.63) |
| Tuberculosis | 40 (12.8) | 1.24 (0.91-1.69) | 1.46 (0.98-2.17) | 1.01 (0.62-1.64) |
| Sepsis | 25 (8.0) | 0.77 (0.52-1.14) | 0.61 (0.33-1.13) | 0.94 (0.57-1.57) |
| Diarrhea | 13 (4.2) | 0.40 (0.23-0.69) | 0.42 (0.20-0.89) | 0.38 (0.17-0.84) |
| Meningitis/encephalitis | 11 (3.5) | 0.34 (0.19-0.61) | 0.49 (0.24-0.97) | 0.19 (0.06-0.59) |
| Cytomegalovirus | 2 (0.6) | 0.06 (0.02-0.25) | 0.06 (0.01-0.43) | 0.06 (0.01-0.45) |
| Other[e] | 8 (2.6) | 0.25 (0.12-0.49) | 0.24 (0.09 -0.65) | 0.25 (0.09-0.67) |
| | | | | |

| | | | | |
|---|---|---|---|---|
| **Non-AIDS-related non-infections** | **35 (11.2)** | **1.08 (0.78-1.51)** | **1.46 (0.98-2.17)** | **0.63 (0.34-1.17)** |
| Physical trauma | 10 (3.2) | 0.31 (0.17-0.57) | 0.49 (0.24-0.97) | 0.13 (0.03-0.50) |
| Cancer | 5 (1.6) | 0.15 (0.06-0.37) | 0.24 (0.09-0.65) | 0.06 (0.01-0.45) |
| Hematologic | 4 (1.3) | 0.12 (0.05-0.33) | 0.24 (0.09-0.65) | - |
| Other central nervous system | 3 (1.0) | 0.09 (0.03-0.29) | 0.12 (0.03-0.49) | 0.06 (0.01-0.45) |
| Other cardiovascular | 3 (1.0) | 0.09 (0.03-0.29) | 0.06 (0.01-0.43) | 0.06 (0.01-0.45) |
| Renal failure | 2 (0.6) | 0.06 (0.02-0.25) | - | 0.13 (0.03-0.50) |
| Other[f] | 8 (2.6) | 0.25 (0.12-0.49) | 0.30 (0.13-0.73) | 0.19 (0.06-0.59) |
| **Unknown/not reviewed[g]** | **45 (14.4)** | **1.39 (1.04-1.86)** | **1.46 (0.98-2.17)** | **1.32 (0.86-2.03)** |

95% CI, 95% confidence interval; CDC, Centers for Disease Control and Prevention; TB, tuberculosis. Text in bold represents major categories.

[a]AIDS-related clinical diagnoses were defined by US CDC clinical staging criteria (16,18). Some diagnoses meet AIDS criteria by the age at diagnosis, level of invasiveness, or chronicity, and may appear in both AIDS and non-AIDS categories (e.g. pulmonary tuberculosis in children <13 years of age is considered a non-AIDS diagnosis).

[b]Death rate per 1000 person-years.

[c]Includes: brain abscess (1), progressive multifocal leukoencephalopathy (1).

[d]Includes: bronchiectasis (1), non-Hodgkin lymphoma (2).

[e]Includes: cryptococcal pneumonia (1), disseminated mycosis (1), disseminated sporotrichosis (1), invasive aspergillosis (1), mastoiditis (1), necrotizing fasciitis (1), toxoplasmosis (1), unknown infection (1).

[f]Includes: aspiration (1), asthma (1), drug side effect (1), glomerulonephritis (1), lactic acidosis (1), neurogenic bladder (1), psychiatric disease (suicide by poisoning; 1), systemic lupus erythematosus (1).

[g]Seven of the 45 did not have a completed cause of death form.

## Factors associated with AIDS-related and infection-related underlying causes of death

In multivariable analysis, higher CD4 cell count, and better weight-for-age z-score were protective against mortality, regardless of whether or not the underlying cause was AIDS-related (Table 3). Receiving care in mostly rural vs. urban settings and cART initiation between 2014 and 2017 compared with less than 2010 were protective against AIDS-related mortality. Across age subgroupings, increased hazard rates of AIDS-related death were associated with younger age compared with 5–9 years (asHR for <1 year 5.09, 95% CI 2.80–9.23; for 1–4 years 1.82, 95% CI 1.24–2.67), and increased hazard rates of non-AIDS-related death were associated with age less than 1 year (asHR 3.79, 95% CI 1.62–8.84) and age 15–19 years (asHR 2.03, 95% CI 1.06–3.91) compared with age 5–9 years.

CD4 cell count more than 200 cells/ml, weight-for-age z-score at least -3, and cART initiation during 2014–2017 compared with less than 2010 were protective against infection-related mortality (Table 4). For noninfection-related mortality, CD4 cell count at least 500 cells/ml and weight-for-age z-score at least -2 were protective. In contrast, higher hazard rates of infection-related mortality were associated with age less than 5 years compared with 5–9 years (highest asHR for age <1 year 7.46, 95% CI 4.48–12.42), and being on second-line cART. A prior AIDS diagnosis was associated with infection-related (asHR 5.60 [3.30–9.30]) and noninfection-related mortality (asHR 4.13 [1.80–9.50]).

## Underlying causes of death among those without prior antiretroviral therapy

Among 394 children (52% male) who did not receive cART during follow-up, 58 (15%) died (62% male); these deaths were not included in the detailed risk factor analyses. Deaths were due to underlying AIDS-related infections (17%) and noninfections (6.9%), and non- AIDS-related infections (60%) and noninfections (3.4%), with 10% of deaths due to unknown causes and one death not reviewed. When the contributing causes were taken into account for the alternate categorization, the proportion of those with AIDS-related deaths whose underlying causes were infections increased to 59%. The most common underlying causes of death overall were pneumonia (21%), sepsis (16%), and TB (16%).

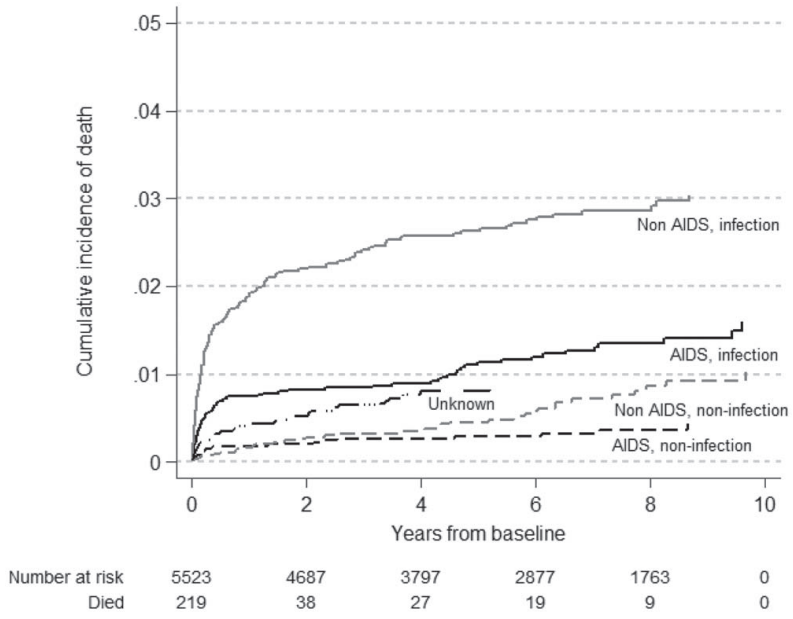


**FIGURE 1.** Cumulative incidence of death by underlying causes using competing risk regression for children and adolescents with a history of combination antiretroviral therapy (N=312).

**TABLE 3.** Factors associated with AIDS-related and non-AIDS-related underlying causes of death among children and adolescents who received combination antiretroviral therapy.

| Characteristics | | AIDS-related | | | Non-AIDS-related | | |
|---|---|---|---|---|---|---|---|
| | Follow-up time (32,361 person-years) | Deaths (n=183) | asHR (95% CI) | p-value | Deaths (n=84) | asHR (95% CI) | p-value |
| **Sex** | | | | | | | |
| Male | 16,482 | 95 | - | - | 51 | | |
| Female | 15,879 | 88 | - | - | 33 | 0.75 (0.48-1.17) | 0.207 |
| **Current age (years)[a]** | | | | <0.001 | | | 0.002 |
| <1 | 173 | 18 | 5.09 (2.80-9.23) | <0.001 | 7 | 3.79 (1.62-8.84) | 0.002 |
| 1-4 | 3894 | 64 | 1.82 (1.24-2.67) | 0.002 | 18 | 1.15 (0.63-2.11) | 0.647 |
| 5-9 | 10,031 | 46 | 1.00 | | 23 | 1.00 | |
| 10-14 | 10,982 | 29 | 0.89 (0.56-1.41) | 0.609 | 14 | 0.67 (0.34-1.31) | 0.244 |
| 15-19 | 6201 | 20 | 1.62 (0.92-2.84) | 0.094 | 20 | 2.03 (1.06-3.91) | 0.034 |
| 20-24 | 10,788 | 6 | 2.17 (0.88-5.34) | 0.093 | 2 | 1.04 (0.20-5.51) | 0.959 |
| **Current CD4 count (cells/mm$^3$)[a]** | | | | <0.001 | | | 0.005 |
| <200 | 1629 | 116 | 1.00 | | 23 | 1.00 | |
| 200-349 | 1478 | 11 | 0.20 (0.10-0.38) | <0.001 | 13 | 1.27 (0.62-2.61) | 0.519 |
| 350-499 | 7223 | 20 | 0.15 (0.09-0.26) | <0.001 | 19 | 0.59 (0.29-1.19) | 0.141 |
| ≥500 | 17,628 | 4 | 0.02 (0.01-0.05) | <0.001 | 20 | 0.35 (0.17-0.73) | 0.005 |
| Missing | 4403 | 32 | | | 9 | | |
| **Current weight-for- age z-score[a]** | | | | 0.029 | | | <0.001 |
| <-3 | 4327 | 127 | 1.00 | | 41 | 1.00 | |
| -3 ≤ to <-2 | 6005 | 17 | 0.23 (0.14-0.39) | <0.001 | 11 | 0.36 (0.18-0.73) | 0.005 |
| ≥-2 | 17,636 | 20 | 0.14 (0.08-0.24) | <0.001 | 21 | 0.29 (0.17-0.52) | <0.001 |
| Missing | 4392 | 19 | | | 11 | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **History of AIDS diagnosis** | | | | | | | |
| No | 14,796 | 14 | 1.00 | | 10 | 1.00 | |
| Yes | 17,565 | 169 | 5.35 (3.04-9.42) | <0.001 | 74 | 4.67 (2.35-9.25) | <0.001 |
| **Currently on second-line cART[a]** | | | | | | | |
| No | 27,453 | 158 | 1.00 | | 67 | 1.00 | |
| Yes | 4908 | 25 | 1.41 (0.87.2.30) | 0.163 | 17 | 1.75 (1.00-3.09) | 0.051 |
| **Facility setting** | | | | 0.021 | | | 0.145 |
| Urban | 19,909 | 136 | 1.00 | | 46 | 1.00 | |
| Mostly urban | 10,436 | 37 | 0.74 (0.52-1.07) | 0.106 | 27 | 1.43 (0.88-2.32) | 0.146 |
| Mostly rural | 2016 | 10 | 0.43 (0.22-0.85) | 0.015 | 11 | 1.73 (0.90-3.31) | 0.101 |
| **Year of first cART** | | | | <0.001 | | | 0.101 |
| <2008 | 17409 | 48 | 1.00 | | 35 | 1.00 | |
| 2008-1010 | 8898 | 96 | 1.49 (1.02-2.18) | 0.041 | 36 | 1.42 (0.80-2.50) | 0.230 |
| 2011_2013 | 4696 | 35 | 0.90 (0.56-1.45) | 0.665 | 11 | 0.77 (0.37-1.60) | 0.479 |
| 2014-2017 | 1358 | 4 | 0.26 (0.09-0.76) | 0.014 | 2 | 0.36 (0.08-1.62) | 0.182 |

Deaths due to non-AIDS-related underlying causes (n=84) and those for which causes were unknown or not reviewed (n=45) were competing events for deaths due to AIDS-related underlying causes (n=183). Similarly, deaths due to AIDS-related underlying causes and those for which causes were unknown or not reviewed were competing events for death due to non-AIDS-related causes. 95% CI, 95% confidence interval; asHR, adjusted sub distribution hazard ratio; cART, combination antiretroviral therapy of three or more antiretrovirals.

[a]Current age, CD4 cell count, weight-for-age z-score, second-line, and AIDS were considered time-dependent variables.

**TABLE 4.** Factors associated with infection and non-infection causes of death in children and adolescents who received combination antiretroviral therapy.

| | | Infection-related | | | Non-infection-related | | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Follow-up time (32,361 person-years)** | **Deaths (n=214)** | **asHR (95% CI)** | **p-value** | **Deaths (n=53)** | **asHR (95% CI)** | **p-value** |
| **Sex** | | | | | | | |
| Male | 16.482 | 112 | - | | 34 | 1.00 | |
| Female | 15.879 | 102 | - | | 19 | 0.64 (0.36-1.13) | 0.125 |
| **Current age (years)[a]** | | | | <0.001 | | | 0.049<br>0.050 |
| <1 | 173 | 24 | 7.46 (4.48-12.42) | <0.001 | 1 | 0.91 (0.12-6.88) | 0.925 |
| 1-4 | 3894 | 70 | 1.73 (1.21-2.47) | 0.003 | 12 | 1.56 (0.71-3.46) | 0.271 |
| 5-9 | 10,031 | 57 | 1.00 | | 12 | 1.00 | |
| 10-14 | 10,982 | 34 | 0.77 (0.50-1.18) | 0.234 | 9 | 0.80 (0.33-1.94) | 0.628 |
| 15-19 | 6201 | 24 | 1.36 (0.81-2.31) | 0.246 | 16 | 2.79 (1.26-6.22) | 0.012 |
| 20-24 | 1079 | 5 | 1.22 (0.45-3.36) | 0.695 | 3 | 2.51 (0.62-10.24) | 0.198 |
| **Current CD4 count (cells/mm$^3$)[a]** | | | | <0.001 | | | 0.033 |
| <200 | 1629 | 124 | 1.00 | | 15 | 1.00 | |
| 200-349 | 1478 | 18 | 0.31 (0.18-0.53) | <0.001 | 6 | 0.84 (0.33-2.19) | 0.731 |
| 350-499 | 7223 | 28 | 0.18 (0.11-0.29) | <0.001 | 11 | 0.47 (0.20-1.14) | 0.095 |
| ≥500 | 17,628 | 11 | 0.05 (0.02-0.09) | <0.001 | 13 | 0.29 (0.13-0.67) | 0.004 |
| Missing | 4403 | 33 | | | 8 | | |
| **Current weight-for-age z score[a]** | | | | <0.001 | | | 0.020 |
| <-3 | 4327 | 146 | 1.00 | | 22 | 1.00 | |
| -3 ≤ to <-2 | 6005 | 19 | 0.21 (0.13-0.34) | <0.001 | 9 | 0.56 (0.25-1.29) | 0.173 |
| ≥-2 | 17,636 | 26 | 0.15 (0.10-0.24) | <0.001 | 15 | 0.38 (0.19-0.75) | 0.005 |
| Missing | 4392 | 23 | | | 7 | | |
| | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **History of AIDS diagnosis** | | | | | | | |
| No | 14,796 | 17 | 1.00 | | 7 | 1.00 | |
| Yes | 17,565 | 197 | 5.60 (3.30-9.30) | <0.001 | 46 | 4.13 (1.80-9.50) | <0.001 |
| **Currently on second-line cART[a]** | | | | | | | |
| No | 27,453 | 182 | 1.00 | | 43 | 1.0 | |
| Yes | 4908 | 32 | 1.64 (1.08-2.50) | 0.020 | 10 | 1.21 (0.56-2.62) | 0.624 |
| **Facility setting** | | | 0.212 | | | | |
| Urban | 19,909 | 152 | 1.00 | | 30 | - | |
| Mostly urban | 10,436 | 47 | 0.89 (0.64-1.23) | 0.476 | 17 | - | |
| Mostly rural | 2016 | 15 | 0.61 (0.35-1.09) | 0.096 | 6 | - | |
| **Year of first cART** | | | | <0.001 | | | 0.100 |
| <2008 | 17,409 | 58 | 1.00 | | 25 | 1.00 | |
| 2008-1010 | 8898 | 109 | 1.51 (1.05-2.18) | 0.028 | 23 | 1.58 (0.82-3.06) | 0.171 |
| 2011_2013 | 4696 | 42 | 1.01 (0.66-1.55) | 0.978 | 4 | 0.52 (0.17-1.60) | 0.256 |
| 2014-2017 | 1358 | 5 | 0.27 (0.10-0.71) | 0.008 | 1 | 0.37 (0.05-2.84) | 0.280 |

Deaths due to noninfection underlying causes (n=53) and those for which causes were unknown or not reviewed (n=45) were competing events for deaths due to infection-related underlying causes (n=214). Similarly, deaths due to infection-related underlying causes and those for which causes were unknown or not reviewed were competing events for deaths due to noninfection causes. 95% CI, 95% confidence interval; asHR, adjusted sub distribution hazard ratio; cART, combination antiretroviral therapy of three or more antiretrovirals.

[a]Current age, CD4 cell count, weight-for-age z-score, second-line, and AIDS were considered time-dependent variables.

## DISCUSSION

This analysis is the first conducted in Asia to systematically evaluate causes of death by applying standardized criteria to routinely collected clinical data among children and adolescents with HIV. By making minor, pediatric- specific modifications to the 'adult' CoDe process, we were able to extract and harmonize the available data to develop robust characterizations of morbidity and mortality in our network of primarily urban, public referral centers in LMIC contexts. Our results represent a valuable benchmark for this population that can be used to guide prioritization of diagnostic testing and clinical care interventions in the region

In the late 2000s, early infant diagnostic testing and cART were not widely available across our cohort (19), as evidenced by the median age of over 5 years at treatment initiation. Notably, severe malnutrition and wasting were associated with 40% of all deaths, outcomes that developing infants and children are especially vulnerable to. Although subsequent widespread HIV program scale-up, changes in global cART guidelines to higher CD4-based thresholds and ultimately universal treatment, and improvements in care quality have led to lower mortality among those recently starting cART, infections continue to represent the most common causes of death (68%). Our crude mortality rates substantially declined over time as access to cART and diagnostic testing expanded. These trends were also seen earlier in cohorts in the United States and Europe (20), such as in the PACTG 219 study, in which deaths fell from 72 to eight per 1000 person-years from 1994 to 2004 (21), the CHIPS study in which deaths fell from 82 to six per 1000 person-years from 1997–2006 (22), and the EPPICC cohort, in which deaths peaked at 17.7 per 1000 person-years in 2003 and fell to 3.6 per 1000 person-years by 2006 (23).

We did observe increasing numbers of noninfection causes of death with age and over time, as more children and adolescents survived beyond the immediate post-cART period. This has been reported in the US pediatric-to-adolescent HIV cohort studies PHACS and IMPAACT P1074, in which deaths due to HIV-related kidney and cardiac disease have become more common than opportunistic infections in older youth (24,25). In our study, the most common non-AIDS, noninfection causes of death were related to trauma; largely due to drowning (six of 10) and head injuries (three of 10), which are major causes of pediatric death worldwide, and reflect that those with HIV additionally face the main risks of mortality experienced by other children (2). However, we were unable to determine whether these deaths could have been related to mental health or neurodevelopmental issues known to be more common among those with perinatally acquired HIV (26–28). Data from cohorts with longer term follow-up in the United States and United Kingdom have emphasized that mental healthcare must be part of comprehensive HIV care for youth (29,30).

In these and other high-income countries, detailed data on causes of death are often available through registries and insurance databases. Although these resources are available in some LMICs (31,32), deaths among those with HIV are more often attributed only to HIV or AIDS (3). Although such data are useful on a population level (2,33,34), broad generalizations are insufficient to guide local clinicians or policy makers to understand how health interventions or systems can be implemented and improved to prevent deaths. For example, pneumonias and sepsis of unknown cause represented 25% of underlying reasons why children in our cohort died. Limited laboratory capacity is likely to have impacted microbiologic confirmation of pathogens that could have been more effectively targeted. Improving laboratory infrastructure could reduce empiric treatment and improve clinical outcomes. In addition, whereas severe malnutrition and wasting represented 3.5% of underlying causes of death, they were noted as contributing causes in 36% of deaths, and represent easily diagnosable and treatable conditions (35).

We found that hallmarks of advanced HIV disease (e.g. immunodeficiency, wasting) were associated with higher risk of infection-related deaths. However, there were more similarities between factors associated with AIDS and non-AIDS deaths than we anticipated, which may have been due to misclassification of the non-AIDS underlying causes, such as if comprehensive diagnostic testing was not available. In fact, when contributing causes of individual deaths were considered in our alternate categorization, the proportion of overall deaths that were AIDS-related in the context of underlying infectious cases increased from 21 to 52%. There was an unexpected protective association between sites in mostly rural settings and AIDS-related death. This may be because sites in that category are referral centers with higher levels of resources and lower patient volumes, despite having a majority of patients who live in rural areas.

In addition to the potential for misclassification of causes of death, a key limitation of our study was that the CoDe method was not developed nor validated for use in children. Although we added pediatric-specific variables to improve the utility of the report forms and instituted an adjudication process to review all deaths, the process was still reliant on medical records and provider reports. It did not include formal interviews with families or caregivers, which could be especially valuable in contexts that have limited diagnostic capacity. Although the CoDe review process uses the US CDC staging system, our cohort tracks clinical disease progression using WHO staging, which is reflected in our risk factor analyses. The risk of subjectivity in the clinical categorization of the causes of death for the purposes of our analysis could have increased the risk of misclassification. Incomplete data on HIV-related parameters (e.g. HIV viral load) and the predominance of patients in care at urban referral centers also could have biased our risk factor analysis, limiting the generalizeability of our findings.

## CONCLUSION

The standardized assessment of causes of death in children with HIV in Asia highlights emerging challenges to pediatric and adolescent care, and the continued importance of infections as causes of death in those with and without AIDS. To maintain public health gains, we must adjust to the needs of our 'aging' populations who have survived beyond childhood. Using rigorous methods like the CoDe process to assess deaths in adolescents and young adults would provide useful data around chronic treatment failure leading to pre-ART levels of immunodeficiency and opportunistic infections, as well as emerging mental health concerns like suicide. Greater emphasis on surveillance of noninfection-related causes of morbidity and mortality will also better prepare national programs to integrate HIV care within models of chronic disease management and guide prioritization of limited clinical resources and targeted interventions.

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### Conflicts of interest

There are no conflicts of interest.

### Author contributions

AHS and AK developed the concept for the study, and drafted and finalized the article. PL, NK, KL, VCD, LVN, KHT, DKW, PO, TP, TS, PSL, NKNY, SMF, TJM, RN, and NK collected and managed patient-level data and completed death reporting forms. AZ and ML conducted the analysis. All co-authors participated in the cause of death review process at the site and/or central levels, and reviewed and approved the article.

## SUPPLEMENTAL INFORMATION

- Tables and figures available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7487212/bin/NIHMS1617555-supplement-Supplemental_Material_1.pdf
  - o Supplemental Table 1. Characteristics of children and adolescents in the study cohort (N=5523)
  - o Supplemental Table 2. Underlying causes of death of children and adolescents with a history of cART, by age at death, 2008-2017 (N=312)
  - o Supplemental Figure 1. Median age at death by year among children and adolescents with a history of combination antiretroviral therapy (N=312)
  - o Supplemental Figure 2. Crude mortality rates per 1000 person-years by calendar period among children and adolescents with a history of combination antiretroviral therapy (N=312)
- Note that the Appendix was not published in the original manuscript in error and is provided below.
  - o **Asia Pediatric Version of the Cause of Death (CoDe) Form**
    - Variables modified from the original CoDe form
      a. Date of birth rather than year of birth
      b. Date that height was measured
      c. Hospice rather than nursing home
      d. Prior cardiac disease could include congenital heart disease
    - Variables added to the original CoDe form
      a. Whether the child had perinatally acquired HIV
      b. Birthweight (closest to birth) and date when measured
      c. Location where death occurred
      d. Added risk factors in the year prior to death: prolonged poor adherence to ART, malnutrition
      e. Added co-morbidities: chronic respiratory diseases, HIV encephalopathy, global developmental delay
      f. History of mental health disorder and type
      g. Signature of the site Principal Investigator

Original form developed by the D:A:D Study Group
Kowalska JD, Friis-Moller N, Kirk O, Bannister W, Mocroft A, Sabin C, et al. The Coding Causes of Death in HIV (CoDe) Project: initial results and evaluation of methodology. Epidemiology. 2011;22(4):516-23.

For more information: https://chip.dk/Studies/DAD

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CHAPTER 8

# Risk Factors for Human Papillomavirus Infection and Abnormal Cervical Cytology Among Perinatally Human Immunodeficiency Virus-Infected and Uninfected Asian Youth

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## ABSTRACT

Background: Infection with high-risk human papillomavirus (HR-HPV) may be higher in perinatally human immunodeficiency virus (HIV)-infected (PHIV) than HIV-uninfected (HU) adolescents because of long-standing immune deficiency.

Methods: PHIV and HU females aged 12–24 years in Thailand and Vietnam were matched by age group and lifetime sexual partners. At enrollment, blood, cervical, vaginal, anal, and oral samples were obtained for HPV-related testing. The Wilcoxon and Fisher exact tests were used for univariate and logistic regression for multivariate analyses.

Results: Ninety-three PHIV and 99 HU adolescents (median age 19 [18–20] years) were enrolled (June 2013–July 2015). Among PHIV, 94% were currently receiving antiretroviral therapy, median CD4 count was 593 (392–808) cells/$mm^3$, and 62% had a viral load <40 copies/mL. Across anogenital compartments, PHIV had higher rates of any HPV detected (80% vs 60%; P = .003) and any HR-HPV (60% vs 43%, P = .02). Higher proportions of PHIV had abnormal Pap smears (e.g., atypical squamous cells of unknown significance [ASC-US], 12% vs 14%; low-grade squamous intraepithelial neoplastic lesions, 19% vs 1%). After adjusting for ever being pregnant and asymptomatic sexually transmitted infections (STI) at enrollment, PHIV were more likely to have HR-HPV than HU (odds ratio, 2.02; 95% confidence interval, 1.09–3.77; P = .03).

Conclusions: Perinatal HIV infection was associated with a higher risk of HR-HPV and abnormal cervical cytology. Our results underscore the need for HPV vaccination for PHIV adolescents and for prevention and screening programs for HPV and other STIs.

## INTRODUCTION

Human immunodeficiency virus (HIV) treatment coverage of the estimated 190,000 adolescents aged 10–19 years living with HIV in the Asia-Pacific has been low, with less than one-third accessing appropriate antiretroviral therapy (ART) (1). There is a growing generation of perinatally infected adolescents transitioning into adult life and at risk for other sexually transmitted infections (STIs) (2, 3). One of the world's most commonly acquired STIs is human papillomavirus (HPV), the primary cause of cervical and anal cancers, which has been shown to be more persistent and pathogenic in HIV-infected younger and older women (4–6).

Younger women may be more vulnerable to HPV due, in part, to immaturity of the cervical tissue as it transitions from meta-plastic to squamous epithelium during that period of life (7). While HIV-uninfected (HU) adolescents and young women frequently have regression of low-grade squamous intraepithelial neoplastic lesions (LSIL), HIV alters the dynamics of HPV infection, leading to prolonged infection and more frequent precancerous lesions. These risks remain even after immunologic recovery while on ART (8, 9) and may be greater in the current generation of perinatally HIV-infected young women, who were more likely to start ART later in childhood, compromising immune system development (10–12).

However, while vaccination now offers an effective prevention intervention in higher-income settings, most Asian countries lack a national policy to support HPV vaccination (13). We conducted an observational study to assess the impact of perinatally acquired HIV (PHIV) on HPV coinfection and cervical cytologic and histologic outcomes among young Asian women.

## METHODS

The HPV in Adolescents Study is a longitudinal, observational, cohort study in Thailand and Vietnam to compare patterns of acquisition and clearance of HPV infection among PHIV and HU females and males, and associated cervical cytology and histologic squamous intraepithelial neoplasia in females. The methods for the female component of this study are described below.

### Study Participants

PHIV and HU female adolescents and young adults aged 12–24 years with a history of vaginal intercourse were recruited at 5 study sites: Thailand - HIV-NAT-Thai Red Cross AIDS Research Centre, and Siriraj Hospital Mahidol University both in Bangkok, and Chiang Rai Prachanukroh Hospital in Chiang Rai, and Vietnam - Children's

Hospital 1 and Hung Vuong Hospital, both in Ho Chi Minh City. All Thai sites and Children's Hospital 1 were providing routine HIV care to the PHIV youth invited to participate in the study. PHIV and HU participants were matched by age group (12–15, 16–18, 19–21, 22–24 years) and number of lifetime partners (≤3 or >3). Participants were excluded if they were pregnant at the screening visit, if they had an untreated symptomatic STI (except genital warts), or had received prior doses of HPV vaccine and if they were unable to independently complete the study's audio computer-assisted self-interview. Individuals were excluded if they were behaviorally HIV infected or if they were HIV uninfected with other chronic diseases or were using medications associated with compromised immune function.

## Study Procedures

Potential study participants provided consent and were then screened at the local study sites. Eligible nonpregnant PHIV and HU females proceeded with baseline study visits that included clinical and sexual behavior assessments, blood testing (complete blood count, alanine transaminase, creatinine, fasting lipids, rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL) tests with confirmatory test, CD4 and HIV RNA for PHIV, HIV antibody for HIV uninfected, urine collection (pregnancy), oral rinse, and anogenital evaluation.

Vaginal, cervical, and anal samples were obtained and placed in separate liquid-based cytology (LBC) containers (ThinPrep PAP test, Hologic, Inc., Massachusetts) for processing. Oral wash and cytology fluid were stored at –20°C to –70°C prior to shipment to the study's central laboratory at the Thai Red Cross AIDS Research Centre. Other routine blood, urine pregnancy, and HIV-related testing (antibody, CD4, HIV RNA) were performed at study site laboratories.

## HPV and Other STI Testing

Cervical cytology and histology were evaluated at Chulalongkorn University, Bangkok, Thailand. Chlamydia and gonorrhea (Abbott RealTime CT/NG assay, Abbott Molecular Inc., Illinois; Cobas4800 CT/NG test, Roche Molecular Systems, Inc., New Jersey), herpes simplex virus 2 (HSV-2; HSV I & II Typing Real Time PCR kit, Shanghai ZJ Bio-Tech Co. Ltd.), syphilis serology screening (RPR, Becton, Dickinson and Company, Maryland; confirmation testing TP-PA, Fujirebio Inc., Tokyo, Japan), and HPV-related testing were conducted at the central laboratory.

LBC fluid from the 3 anogenital compartments and oral rinses were tested using the LINEAR ARRAY test (LA HPV GT, Roche Molecular Systems, Inc.) to identify 13 high-risk HPV (HR-HPV) DNA genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and 24 other genotypes (6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 73 [MM9], 81, 82 [MM4], 83 [MM7], 84 [MM8], IS39, CP6108). Cervical

LBC fluid samples were used to detect E6 and E7 mRNA by flow cytometric analysis (HPV OncoTect E6, E7 mRNA test, incellDx, CA) for 14 HR-HPV types (16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73).

## Cytology and Histology

Cervical cytology results were classified using the 2001 Bethesda system as normal, atypical squamous cells of unknown significance (ASC-US), atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H), LSIL, high-grade squamous intraepithelial lesion (HSIL), or carcinoma (14). Histology results were categorized as atypia, cervical intraepithelial neoplasia (CIN) 1, CIN 2, CIN 3, carcinoma in situ, and invasive carcinoma.

Participants meeting colposcopy referral criteria were scheduled for additional follow-up. Specifically, this included those with ASC-US and concomitant infection with a HR-HPV type or detection of E6/E7 mRNA, LSIL, ASC-H, HSIL, and atypical glandular cells or carcinoma on cervical cytology. Cervicovaginal abnormalities identified during a colposcopy visit were biopsied for histologic analysis.

## Ethics Reviews

The study protocol and informed consent and assent documents were approved by the institutional review boards at the coordinating center (amfAR/TREAT Asia) and at each participating study site. Consent procedures were conducted in the local language (Thai or Vietnamese) by trained study staff. Guardian consent and adolescent assent procedures were followed for participants aged <18 years who could not legally consent for themselves. These participants were formally consented for ongoing study participation after turning 18 or otherwise reaching the age of maturity according to local law.

## Statistical Methods

Power calculations were based on the prevalence of vaginal HPV in HIV-positive (73%) and HU (43%) female adolescents in the US REACH (Reaching for Excellence in Adolescent Care and Health) cohort (15). Assuming a baseline prevalence of 40% in the HU adolescents, with 90 participants in each group we would have 80% power to detect a 21% difference in prevalence between groups, with 80% power at a 2-sided significance level of 5%. Categorical covariates were compared between study groups using a Wilcoxon test for continuous covariates and Fisher exact test for categorical covariates. Logistic regression was used to assess the association between demographic and behavioral characteristics and the presence of any cervical, vaginal, or anal HR-HPV. Factors with $P < .1$ in univariate models were adjusted for in a multivariate analysis. Statistical analysis was performed with Stata, version 14 (Statacorp LP, College Station, Texas).

## RESULTS

### Participant Characteristics

Ninety-three PHIV and 99 HU adolescents with a median age of 19 (18–20) years were enrolled between June 2013 and July 2015. PHIV participants were less likely to live with biological parents (26% vs 62%) and more likely to be single or double orphans (81% vs 24%). Approximately equal proportions of both groups were living with a partner or husband (26% vs 19%) and working to support themselves (45% vs 31%). The majority were currently in or had completed secondary school (77% vs 70%). Among PHIV participants, 94% were currently receiving first- or second-line ART, with a median duration from ART start of 4.1 (interquartile range [IQR], 2.5–6.5) years. The median CD4 cell count at enrollment was 593 (392–808) cells/mm$^3$, and 62% had a viral load <40 copies/mL. One- third (37%) reported some difficulties with adherence, and the median adherence rate in the previous month was 97%.

### Sexual Behaviors and Substance Use

In both groups, the median (IQR) number of lifetime partners was 2 (1–3), and partners in the previous 6 months was 1 (1–1); 4% of PHIV and 1% of HU participants reported ever having receptive anal sex, and approximately 22% of both groups reported ever having receptive oral sex (Table 1). More PHIV than HU participants reported consistently using condoms with vaginal sex in the past 6 months (33% vs 11%); the majority in both groups reported sometimes or never (65% vs 85%) using condoms. One-third of PHIV and 44% of HU adolescents reported previous pregnancies.

Fewer PHIV participants had tried alcohol (77% vs 90%), cigarettes (29% vs 44%), or other drugs (8% vs 19%); 1 PHIV participant reported ever having injected drugs (Supplementary Table 1). Similar proportions (17% vs 20%) reported having unsafe sex after using alcohol or other substances.

### HPV and Asymptomatic STI at Study Entry

Infection with *Chlamydia trachomatis* was the most common prevalent asymptomatic STI, present in 26% of PHIV and 20% of HU adolescents. A significantly higher proportion of PHIV participants had gonorrhea (5% vs 0%, P = .03), 2% of both groups had a reactive VDRL (confirmed by *Treponema pallidum* hemagglutination assay testing), and no PHIV but 3% of HU participants had HSV-2 infection.

Cervical HPV infection of any type was more prevalent in the PHIV group than in the HU group: 62% vs 40% had any HPV detected (P = .003), and 43% vs 29% had at least 1 HR-HPV genotype detected (P = .05). Similar levels of HR-HPV detection were found in samples collected from the vagina (49% vs 35%), but a significantly

higher proportion of PHIV participants had HR-HPV detected in the anus (42% vs 23%, P = .008; Table 1). In any anogenital compartment, PHIV participants had significantly higher rates of any HPV detected (80% vs 60%; P = .003) and any HR-HPV (60% vs 43%, P = .02) than HU participants. HPV infection in the oral cavity was present in 11% of PHIV and 8% of HU adolescents (P = .64). The most commonly detected HR-HPV genotypes in the cervix, vagina, and anus included types 16, 18, 52, and 59 (Figure 1).

## Cervical Cytology

Normal cervical cytology was present in 67% of PHIV participants and 84% of HU participants (Figure 2). Higher proportions of PHIV participants had abnormal Pap smears compared to HU participants (ASC-US, 12% vs 14%; LSIL, 19% vs 1%; HSIL, 1% vs 1%; ASC-H, 1% vs 0; P < .001). Of the 40 (28 PHIV, 12 HU) participants who met criteria for referral, 23 (58%; 19 PHIV, 4 HU) underwent colposcopic examination with or without biopsy within 24 weeks of their baseline cytology visit (Supplementary Table 2). Among those who did not have colposcopies, 9 were PHIV (5 with ASC-US; 1 with ASC-H; 3 with LSIL) and 8 were HU (7 with ASC-US; 1 with HSIL). Reasons for missed colposcopies included delayed referrals (29%) and temporary or permanent loss to follow-up (42%). The colposcopic findings among the PHIV participants included 42% with normal evaluations, 26% with condyloma acuminata, 16% with changes consistent with HPV infection, and 11% with CIN 1. Three (75%) of the 4 HU participants with colposcopies had HPV-related changes. Of the 9 (39%) participants who had biopsies taken, 3 had CIN 1 and 1 had CIN 3; all were PHIV.

## Association Between Participant Demographic and Behavioral Characteristics and HR-HPV in Anogenital Compartments

We used logistic regression to assess associations between participant characteristics and behaviors and any detected HR-HPV infection in the cervix, vagina, or anus (Table 2). In a univariate analysis, HIV status, increasing number of life- time partners, and having an asymptomatic STI diagnosed at enrollment were associated with a significantly higher odds of having HR-HPV, while ever being pregnant was associated with a reduced odds. After adjusting for ever having been pregnant and having an asymptomatic STI at enrollment in a multivariate model, PHIV participants were more likely to have HR-HPV than HU adolescents (odds ratio [OR], 2.02; 95% confidence interval [CI], 1.09–3.77; P = .03). Overall, compared to those with 1 lifetime partner, those with ≥2 partners had an increased odds of HR-HPV infection (OR, 3.46; 95% CI, 1.78–6.71; P < .001). In a subgroup analysis of HIV-specific characteristics in PHIV participants, we found no associations between HR-HPV and current or nadir CD4 count or current viral load.

**TABLE 1.** Participant Characteristics at Study Entry (N=192).

| Characteristic | Total (n=192) | Perinatally HIV-infected (n=93) | HIV-uninfected (n=99) | P |
|---|---|---|---|---|
| Age, years | 19 (18 to 20) | 19 (17 to 20) | 19 (18 to 20) | 0.36 |
| Ethnicity | | | | 1.0 |
| Thai | 177 (92%) | 86 (92%) | 91 (92%) | |
| Vietnamese | 15 (8%) | 7 (8%) | 8 (8%) | |
| Living situation | | | | <0.001 |
| One or both parents | 84 (44%) | 24 (26%) | 60 (61%) | |
| Relatives | 44 (23%) | 33 (35%) | 11 (11%) | |
| Partner | 43 (22%) | 24 (26%) | 19 (19%) | |
| Alone | 15 (8%) | 8 (9%) | 7 (7%) | |
| Other, did not answer | 6 (3%) | 4 (4%) | 2 (2%) | |
| Orphan status | | | | <0.001 |
| Not an orphan | 87 (45%) | 13 (14%) | 74 (75%) | |
| Maternal or paternal orphan | 55 (29%) | 34 (37%) | 21 (21%) | |
| Double orphan | 44 (23%) | 41 (44%) | 3 (3%) | |
| Unknown | 6 (3%) | 5 (5%) | 1 (1%) | |
| Current/highest education | | | | 0.36 |
| Primary school | 20 (10%) | 10 (11%) | 10 (10%) | |
| Secondary school | 141 (73%) | 72 (77%) | 69 (70%) | |
| Beyond secondary school | 30 (16%) | 11 (12%) | 19 (19%) | |
| Employment/School | | | | 0.003 |
| Currently working | 73 (38%) | 42 (45%) | 31 (31%) | |
| In school | 78 (41%) | 41 (44%) | 37 (37%) | |
| Neither | 40 (21%) | 10 (11%) | 30 (30%) | |
| Type of sexual relationships | | | | |
| Female-Male | 184 (99%) | 88 (100%) | 96 (99%) | 1.00 |
| Female-Female | 13 (7%) | 8 (9%) | 5 (5%) | 0.39 |
| Did not answer | 7 (4%) | 5 (5%) | 2 (2%) | |
| Prior sexual activity by route | | | | |
| Anal receptive | 5 (3%) | 4 (4%) | 1 (1%) | 0.20 |
| Oral receptive | 42 (22%) | 19 (21%) | 23 (23%) | 0.73 |

**TABLE 1.** Continued.

| Characteristic | Total (n=192) | Perinatally HIV-infected (n=93) | HIV-uninfected (n=99) | P |
|---|---|---|---|---|
| Lifetime partners | 2 (1 to 3) | 2 (1 to 3) | 2 (1 to 3) | 0.76 |
| Partners in past 6 months | 1 (1 to 1) | 1 (1 to 1) | 1 (1 to 1) | 0.74 |
| Monthly frequency of sex in past 3 months | | | | 0.34 |
| ≤5 times | 107 (56%) | 56 (60%) | 51 (52%) | |
| 6-10 times | 32 (17%) | 11 (12%) | 21 (21%) | |
| 11-20 times | 13 (7%) | 5 (5%) | 8 (8%) | |
| >20 times | 21 (11%) | 11 (12%) | 10 (10%) | |
| Did not answer | 19 (10%) | 10 (11%) | 9 (9%) | |
| Condom use with vaginal sex in past 6 months | | | | <0.001 |
| Always | 42 (22%) | 31 (33%) | 11 (11%) | |
| Sometimes | 93 (48%) | 50 (54%) | 43 (43%) | |
| Never | 52 (27%) | 10 (11%) | 42 (42%) | |
| No recent sex | 5 (3%) | 2 (2%) | 3 (3%) | |
| Ever been pregnant | 75 (39%) | 31 (33%) | 44 (44%) | 0.14 |
| Asymptomatic STI at baseline | | | | |
| *Chlamydia trachomatis* | 44 (23%) | 24 (26%) | 20 (20%) | 0.39 |
| *Neisseria gonorrhoea* | 5 (3%) | 5 (5%) | 0 (0%) | 0.03 |
| Syphilis | 4/190 (2%) | 2/92 (2%) | 2/98 (2%) | 1.0 |
| HSV-2 | 3 (2%) | 0 (0%) | 3 (3%) | 0.25 |
| Any cervical HPV | 98 (51%) | 58 (62%) | 40 (40%) | 0.003 |
| Any cervical HR-HPV | 69 (36%) | 40 (43%) | 29 (29%) | 0.05 |
| Any vaginal HPV | 110/190 (58%) | 62/91 (68%) | 48 (48%) | 0.01 |
| Any vaginal HR- HPV | 80/190 (42%) | 45/91 (49%) | 35 (35%) | 0.06 |
| Any anal HPV | 94/191 (49%) | 54 (58%) | 40/98 (41%) | 0.02 |
| Any anal HR-HPV | 62/191 (32%) | 39 (42%) | 23/98 (23%) | 0.008 |
| Any anogenital HPV | 133 (69%) | 74 (80%) | 59 (60%) | 0.003 |
| Any anogenital HR-HPV | 99 (52%) | 56 (60%) | 43 (43%) | 0.02 |
| Any oral HPV | 18/190 (9%) | 10/91 (11%) | 8 (8%) | 0.62 |
| Any oral HR-HPV | 9/190 (5%) | 5/91 (5%) | 4 (4%) | 0.74 |

Characteristics are described as median (interquartile range or N [%]). Percentages are rounded and may not total 100%. Where test results were invalid or not performed, the denominator is shown.
Abbreviations: HIV, human immunodeficiency virus; HPV, human papillomavirus; HR, high risk.

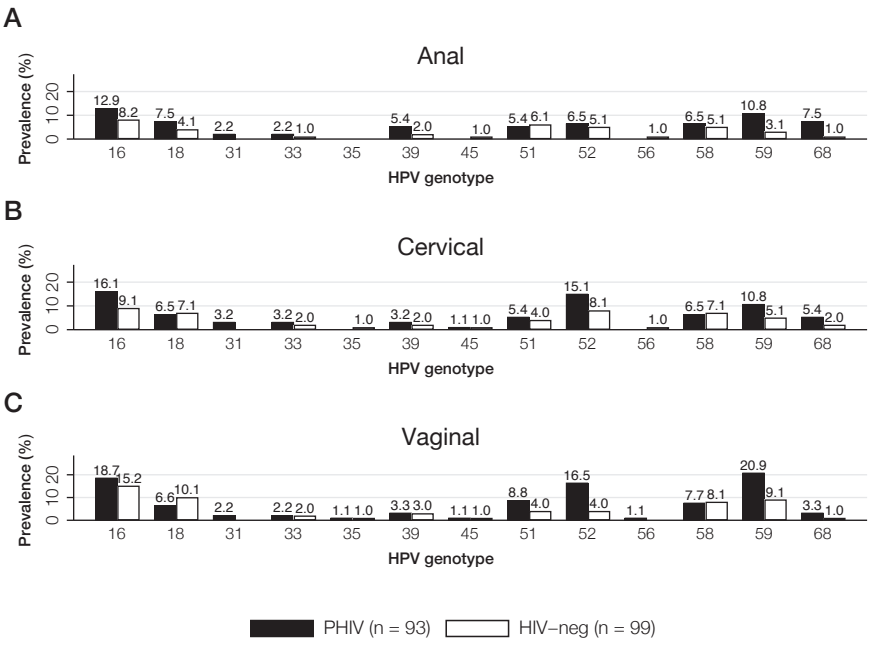


**FIGURE 1.** Prevalence of individual high-risk human papillomavirus subtypes by anatomical site.

Abbreviations: HIV, human immunodeficiency virus; HIV-neg, HIV uninfected; HPV, human papillomavirus; PHIV, perinatally HIV infected.

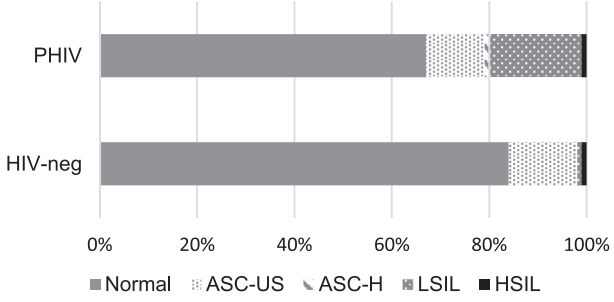


**FIGURE 2.** Cervical cytology results. P for difference between groups <0.001.

Abbreviations: ASC-H, atypical squamous cells, cannot exclude HSIL; ASC-US, atypical squamous cells of unknown significance; HIV, human immunodeficiency virus; HIV-neg, HIV uninfected; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; PHIV, perinatally HIV infected.

**TABLE 2.** Factors Associated With Any High-Risk Human Papillomavirus Genotype at Baseline Study Visit.

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| Characteristic | OR (95%CI) | P | OR (95%CI) | P |
| Study group | | 0.02 | | **0.03** |
| HIV-uninfected | 1 (ref) | | 1 (ref) | |
| Perinatally HIV-infected | 1.97 (1.11-3.50) | | 2.02 (1.09-3.77) | |
| Age (years) | | 0.83 | | |
| 13-16 | 1.34 (0.52-3.43) | | | |
| 17-19 | 1.12 (0.61-2.05) | | | |
| 20-24 | 1 (ref) | | | |
| Orphan status | | 0.57 | | |
| Not an orphan | 1 (ref) | | | |
| Maternal orphan | 1.79 (0.71-4.51) | | | |
| Paternal orphan | 0.68 (0.29-1.56) | | | |
| Double orphan | 2.07 (0.98-4.39) | | | |
| Unknown | 0.21 (0.02-1.91) | | | |
| Highest education | | 0.55 | | |
| Primary school | 1 (ref) | | | |
| Secondary school | 1.28 (0.50-3.27) | | | |
| Beyond secondary school | 1.83 (0.58-5.76) | | | |
| Condom use with vaginal sex in past 6 months | | 0.45 | | |
| Always/no sex in past 6 months | 1 (ref) | | | |
| Sometimes/Never | 1.29 (0.67-2.49) | | | |
| Employment/school status | | 0.48 | | |
| In school | 1 (ref) | | | |
| Working | 1.48 (0.78-2.82) | | | |
| Neither | 1.27 (0.59-2.74) | | | |
| Used alcohol in past 3 months | 1.03 (0.58-1.82) | 0.92 | | |
| Smoked in past 3 months | 1.02 (0.42-2.43) | 0.97 | | |
| Used other drugs in past 3 months | 1.91 (0.46-7.89) | 0.36 | | |
| Lifetime number of sexual partners | | <0.001 | | **<0.001** |
| 1 | 1 (ref) | | 1 (ref) | |
| ≥2 | 3.90 (2.09-7.28) | | 3.46 (1.78-6.71) | |

**TABLE 2.** Continued.

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| **Characteristic** | **OR (95%CI)** | **P** | **OR (95%CI)** | **P** |
| Sexual partners in past 6 months | | 0.28 | | |
| None | 1 (ref) | | | |
| 1 | 0.73 (0.24-2.20) | | | |
| ≥2 | 1.88 (0.39-9.01) | | | |
| Ever had unsafe sex after using alcohol or other drugs | 1.59 (0.76-3.34) | 0.21 | | |
| Ever been pregnant | 0.61 (0.34-1.09) | 0.09 | 0.61 (0.32-1.15) | 0.12 |
| Asymptomatic STI at week 0 visit | 2.72 (1.38-5.36) | 0.003 | 1.99 (0.96-4.14) | 0.06 |
| ***HIV-specific covariates (PHIV only)*** | | | | |
| HIV-RNA >40 copies/mL | 1.77 (0.73 – 4.28) | 0.20 | | |
| Current CD4 count (cells/mm$^3$) | | 0.31 | | |
| ≤350 | 1 (ref) | | | |
| 351-500 | 0.48 (0.12 – 1.98) | | | |
| >500 | 1.18 (0.40 – 3.50) | | | |
| Nadir CD4 count (cells/mm$^3$) | | 0.25 | | |
| <200 | 1 (ref) | | | |
| 201-500 | 0.51 (0.17 – 1.57) | | | |
| >500 | 0.41 (0.13 – 1.22) | | | |

Human papillomavirus detected at cervix, vagina, and/or anus.
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

## DISCUSSION

Half of our cohort had prevalent HR-HPV infection, and PHIV adolescent females were more frequently infected with HR-HPV across anogenital compartments and had greater cervical dysplasia on Pap smear than HU adolescents (60% vs 43%). Although our rate of anogenital HR-HPV infection among PHIV participants is similar to those reported among older HIV-infected women and behaviorally HIV-infected youth from other countries (16–19), it is 2–3 times that observed in older HIV-infected Thai women (19%–35% at median ages of 25–40 years) (20–22). The scale of this difference emphasizes the greater vulnerability of Asian PHIV adolescents to long-term cancer risk. One-third of our adolescents had abnormal cervical cytology,

which was consistent with an earlier US PHIV cohort (30%; mean age 19 years) (23) but higher than a parenterally infected Romanian cohort (25%; mean age 23 years) (24). Furthermore, on colposcopy, condyloma acuminata and CIN 1 and CIN 3 on either visual inspection or biopsy were only detected among PHIV participants (42% vs 0% of those evaluated), raising concerns about the relative severity of disease they experience.

Although recognized as the world's most common STI, the global impact of HPV infection is largely hidden until it causes anogenital and oral cancers decades later. Younger women are more likely to acquire initial and multiple genotype infections due, in part, to cervical ectopy (15, 25). However, these early infections generally self-resolve, which has led to recommendations to screen them less frequently and to avoid aggressive management for less advanced dysplasia (26). However, HIV's weakening of cellular immunity is considered a key reason why it is associated with more rapid HPV acquisition after new HIV infection and a 2- to 22-fold higher incidence of invasive cervical cancer (27, 28). Perinatally acquired HIV and its associated life-long impact on the immune system may consequently put infected adolescents and young women at greater risk of HPV-related diseases.

PHIV youth have been reported to have slower pubertal maturity, later sexual debut, and higher condom use than HU youth (29–31). This has made comparisons to sexual health outcomes of the uninfected or the behaviorally infected more complicated, and STI frequencies have been reported to be lower among the perinatally infected (32). However, when matched for behavior, PHIV females in our study had higher baseline HPV and asymptomatic gonorrhea infection than HU females, despite reporting more regular condom use and less frequent substance use.

There are varying data on how ART impacts the natural history of HPV infection in terms of acquisition, persistence, and disease progression. Studies examining associations with any or longer durations of therapy are confounded by adherence patterns, but ART that effectively controls HIV and leads to immune recovery appears to be beneficial (16, 27, 32). Although we observed no positive or negative association with ART outcomes, almost all of our PHIV participants were on ART and had high levels of immune reconstitution (median CD4, 593 cells/mm$^3$), although HIV control in terms of viral suppression was moderate (63%). The small numbers of patients with immune deficiency may have prevented us from being able to detect an association.

HPV vaccination using the quadrivalent vaccine has been shown in the IMPAACT P1085 study to be 90%–100% immunogenic in PHIV children and young adolescents aged 7–12 years with CD4 levels above 15%, but other studies have reported that

responses may be reduced in the context of unsuppressed HIV (33–35). Current recommendations of the Advisory Committee on Immunization Practices are to use a 3-dose series in those with HIV (36). Unfortunately, the vaccines that can prevent the consequences of HPV are less accessible in the regions where most PHIV youth reside and often do not include catch-up vaccine programs for older adolescents (37). Thailand started a national HPV vaccination program in August 2017 that provides access to females aged 10–12 years and enrolled in primary school (grade 5) (38, 39). While an important step forward, this misses the vast majority of PHIV adolescents who have already aged out of this group, such as in our cohort where the majority had evidence of current HR-HPV infection. In addition to implementation of early vaccination programs, supplemental approaches to offer catch-up vaccine to older adolescents, such as Malaysia's program that includes 18-year-olds, are essential if those at greater risk for HPV-related cancers are to be protected (13).

There were limitations in both the conduct of the study and the interpretation of our results. We were unable to enroll younger adolescents, which restricts the generalizability of our findings. Since consent for legal minors aged <18 years required admission of sexual activity, the social and cultural stigma against premarital sexual debut was viewed by site investigators as a deterrent. Social desirability bias could have impacted the reliability of our self-reported sexual behavior risks. We did not evaluate 42% of those meeting colposcopy referral criteria within 24 weeks of their cytology visit. In our routine clinical care settings, colposcopy referrals are even less consistently completed, further emphasizing the importance of preventive vaccination. Importantly, cross-sectional studies of HPV infection do not indicate the duration of infection, which plays a key role in the development of dysplasia. While we attempted to capture risk factors known to be related to both infections in sufficient detail, and our regression analysis adjusted for potential confounders derived from a careful review of the HPV and HIV literature, there remains a risk of unmeasured confounding. Given our pilot data and previous studies demonstrating associations in adults, we believe there is sufficient rationale for the associations we have observed, but additional follow-up to monitor for persistence vs clearance will facilitate further interpretation of the natural history of HPV in this cohort.

Our study showed that PHIV participants in Thailand and Vietnam had higher rates of HR-HPV infection and cervical dysplasia than HU adolescents and young women after matching for age and sexual behavior. While HPV vaccination is the optimal solution to prevent anogenital cancers, the lack of access to HPV vaccines in low- and middle-income countries makes screening to identify those in need of intervention an essential component of comprehensive HIV care for young women. Our results underscore the need for prevention and screening for HPV and other STIs in Asian PHIV adolescents.

## Notes

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## Author contributions

AHS, SJK, RH, KC, HLDD, DNHT, JA, NT, AC, MT, TS, WT, SC, and NP conceptualized and designed the study. RH, SG, KC, HLDD, DNHT, JA, NT, AC, MT, and SC conducted clinical study visits; together with TP and TS, they performed data curation and contributed to data collection and coordination of the study. AHS, SJK, and NP designed the methodology of the study, and SJK conducted the formal analysis. AHS and NP obtained funding and supervised the conduct of the study. AHS wrote the original draft of the manuscript. All authors critically reviewed, revised, and approved the final version for publication.

## SUPPLEMENTAL INFORMATION

- Tables available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7190885/bin/ciy144_suppl_supplemental-tables.pdf *(direct download of complete file)*
  - o Supplemental Table 1. Substance use among study participants
  - o Supplemental Table 2. Cytology and histology findings for adolescents with colposcopies within 24 weeks of their baseline study visits (N=23)

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CHAPTER 9

# Increased Burden of Concordant and Sequential Anogenital Human Papillomavirus Infections Among Asian Young Adult Women With Perinatally Acquired HIV Compared With HIV-Negative Peers

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## ABSTRACT

Background: Youth with perinatally acquired HIV (YPHIV) are at higher risk for anogenital human papillomavirus (HPV) infection.

Methods: We enrolled a cohort of YPHIV and HIV-negative youth in Thailand and Vietnam, matched by age and lifetime sex partners, and followed them up for 144 weeks (to 2017). Participants had annual pelvic examinations with samples taken for HPV genotyping. Concordant infection was simultaneous HPV detection in multiple anogenital compartments (cervical, vaginal, anal); sequential infection was when the same type was found in successive compartments (cervicovaginal to/from anal). Generalized estimating equations were used to assess factors associated with concordant infection, and Cox regression was used to assess factors associated with sequential infection.

Results: A total of 93 YPHIV and 99 HIV-negative women were enrolled, with a median age of 19 years (interquartile range, 18–20 years). High-risk anogenital HPV infection was ever detected in 76 (82%) YPHIV and 66 (67%) HIV-negative youth during follow-up. Concordant anogenital high-risk HPV infection was found in 62 (66%) YPHIV versus 44 (34%) HIV-negative youth. Sequential cervicovaginal to anal high-risk HPV infection occurred in 20 YPHIV versus 5 HIV-negative youth, with an incidence rate of 9.76 (6.30–15.13) versus 2.24 (0.93–5.38) per 100 person-years. Anal to cervicovaginal infection occurred in 4 YPHIV versus 0 HIV-negative women, with an incidence rate of 1.78 (0.67–4.75) per 100 person-years. Perinatally acquired HIV was the one factor independently associated with both concordant and sequential high-risk HPV infection.

Conclusions: Children and adolescents with perinatally acquired HIV should be prioritized for HPV vaccination, and cervical cancer screening should be part of routine HIV care for sexually active YPHIV.

## INTRODUCTION

Adolescents and youth with perinatally acquired HIV (YPHIV) have lived their lives in varying states of immunodeficiency. Although antiretroviral therapy (ART) has helped them to control their infections and prevent HIV disease progression, many Asian youth sustained substantial early damage to their immune systems leading to low nadir CD4 levels. This was largely due to their starting ART in childhood rather than during infancy, when ART can have the most impact on early mortality and morbidity (1–4). Even when their HIV is controlled (e.g., suppressed viral loads and stable CD4 levels), this health history may put them at greater risk for the high-risk human papillomavirus (HPV) infections associated with cervical cancer among older women with HIV (5,6). High-risk HPV also is associated with noncervical anogenital dysplasias (7), about which there are limited data in YPHIV in low- and middle-income countries (8–10).

Concordant HPV infection, defined as HPV infections of the same genotype in >1 anogenital compartment, may occur through autoinoculation between the cervix and the anus (11–13). Sequential infection may also occur when HPV infection at a single compartment is followed by infection with the same HPV genotype at another compartment. The establishment of infection is the first step toward persistence associated with cellular transformation. We aimed to describe patterns of concordant and sequential high-risk anogenital HPV infection among YPHIV and compare them with controls to better understand patterns of HPV acquisition that could put YPHIV at risk for cellular transformation.

## MATERIALS AND METHODS

### Participants and Study Procedures

We conducted a prospective cohort study among YPHIV and HIV-negative female participants 12–24 years of age in Thailand and Vietnam, matched by age (12–15, 16–18, 19–21, 22–24 years) and number of lifetime sex (vaginal intercourse) partners. Detailed methods have previously been published (14,15). Participants were enrolled between 2013 and 2015 in Thailand (Thai Red Cross AIDS Research Centre, Siriraj Hospital Mahidol University, Chiangrai Prachanukroh Hospital) and Vietnam (Children's Hospital 1, Hung Vuong Hospital), and followed up for 144 weeks (to June 2017).

Participants had annual study visits including complete pelvic examinations with evaluations via vaginal speculum by study physicians who collected samples for HPV genotyping and screening for other sexually transmitted infections (STIs). Cervical,

vaginal, and anal samples were separately obtained using sterile swabs placed in liquid-based cytology fluid (ThinPrep PAP test; Hologic, Inc, Bedford, MA) for testing of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (Abbott RealTime CT/ NG Assay [Abbott Molecular Inc, Des Plaines, IL], Cobas4800 CT/NG Test [Roche Molecular Systems, Inc, Branchburg, NJ]), herpes simplex virus 2 (HSV-2; HSV I and HSV II Typing Real Time PCR Kit; Shanghai ZJ Bio-Tech Co Ltd, Shanghai, China), syphilis serology screening (rapid plasma reagin [Becton, Dickinson and Company, Sparks, MD], confirmation testing TP-PA [Fujirebio Inc, Tokyo, Japan]), and HPV. Study nurses collected midyear vaginal samples without speculum placement using swabs that were tested for HPV. Cytology fluid was stored at –20°C to –80°C at local sites. Testing for HPV and other STIs was done at the Thai Red Cross AIDS Research Centre, Bangkok. Samples not already stored in Bangkok were shipped to the central laboratory for testing. The interval between collection and testing was up to 3 months.

All HPV genotyping was done using the LINEAR ARRAY test (LA HPV GT'; Roche Molecular Systems, Inc), which identifies 37 HPV DNA genotypes, including identification of 13 high-risk DNA genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68). When the HPV and the β-globin gene were negative, the results were reported as inadequate. Detection of HPV-52 was only reported when there was no detection of HPV-33 or HPV-35 or HPV-58 from the same sample. Behavioral risk assessments regarding sexual activity and substance use were conducted annually through an audio computer-assisted self-interview (16).

## Ethics Committee Reviews

The institutional review boards of each participating study site and the study coordinating center (TREAT Asia/amfAR) approved the study protocol and consent/ assent documents. Consent procedures were conducted in local languages of participants at least 18 years of age or parents/guardians of those younger than 18 years, who were asked for their assent and were subsequently consented after reaching the age of 18 years.

## Definitions and Analysis

Concordant infection was when the same high-risk HPV genotype was detected in multiple anogenital compartments at the same visit. For example, if HPV-16 was detected in both the cervical and the anal samples but not the vaginal sample, the participant was categorized as having concordant cervicoanal HPV infection at that visit. Sequential infection was when a high-risk HPV infection at any single site was followed by a new/incident infection with the same HPV genotype at another site(s). Human papillomavirus infections from the cervix and/or vagina (cervicovaginal) to the anus (anal) or vice versa were considered. For example, if HPV-52 was detected in

the cervical sample but not in the anal sample at the baseline visit, and then HPV-52 was detected in the anal sample at the 1-year follow-up visit, that participant was considered to have sequential HPV infection. Non–high-risk types were not included in these analyses.

We summarized the frequency of high-risk HPV subtypes by site, and the frequency of concordant infections of the same high-risk HPV subtype in adjacent compartments by HIV exposure group and study week. We used generalized estimating equations with a logit link and exchangeable correlation matrix to calculate odds ratios (OR) and 95% confidence intervals to assess factors associated with concordant infection, and Cox regression to assess factors associated with sequential infection. Covariates assessed included HIV status, pregnancy history, and time-updated covariates, including age, body mass index, alcohol use, smoking, substance use, sexual behaviors, and STI diagnosis. Covariates with P <0.10 in univariate analysis were adjusted for in multivariate models. Sequential incidence rates were calculated by dividing the total number of sequential high-risk HPV infections by the total number of person-years of follow-up. Median values are presented with interquartile ranges. Statistical analyses were performed with SAS version 9.4 and Stata version 14.

## RESULTS

A total of 93 YPHIV and 99 HIV-negative female participants were enrolled: 176 (92%) were Thai, median age was 19 (18–20) years, and the median number of lifetime sex partners was 2 (1–3). Among YPHIV, the median CD4 was 593 (392–808) cells/$mm^3$ and 58 (62%) had HIV-RNA <40 copies/mL. During follow-up, 159 (83%) completed all scheduled study visits, 29 (15%) were lost to follow-up, and 3 (1.6%) died (1 each: pneumocystis pneumonia, septic shock, meningitis).

Across multiple follow-up visits, YPHIV had sex at median of 1 time/wk overall. During follow-up, 91 (98%) had vaginal sex and 7 (8%) had receptive anal sex. HIV-negative female participants reported having sex at a median of 1 to 2 times/wk, all of which was vaginal sex. Almost all reported 1 partner in the previous 6 months from baseline and week 144 (PHIV: 93%, 94%; HIV-negative: 92%, 95%). An STI was diagnosed among 26 YPHIV (28%) at baseline, which increased to 46 (49%) by week 144 (cumulative): chlamydia, 26% to 47%; gonorrhea 5% to 11%; and syphilis, 2% to 4%. Among HIV-negative female participants, there were 25 (25%) with STIs at baseline, increasing to 33 (33%) by week 144 (cumulative): chlamydia, 20% to 29%; both chlamydia and gonorrhea diagnosed at the same study visit (4 at baseline, 1 at week 48, 1 at week 96), whereas 1 HIV-negative female participant had both infections at week 48; all dual cases occurred in different individuals.

## Overall HPV Infections

Between study enrollment up to week 144 (cumulative), those ever detected to have anogenital infections with high-risk HPV types went from 56 (60%) to 76 (82%) among YPHIV and 43 (43%) to 66 (67%) among HIV-negative youth (Table 1). Human papillomavirus types 16 and 52 were the most commonly detected types at each annual follow-up time point in all compartments, and for concurrent and sequential infections. Between week 0 and week 144, 13% to 27% of YPHIV ever had HPV-16 detected at the cervix, 16% to 29% at the vagina, and 18% to 34% at the anus. Among HIV-negative youth, HPV-16 was ever detected at the cervix in 8% to 17%, at the vagina in 9% to 18%, and at the anus in 15% to 25%.

## Concordant Infections

Overall, 62 (66%) YPHIV ever had simultaneous, concordant anogenital high-risk HPV infection detected compared with 44 (34%) of HIV-negative youth. By individual annual study visit, infection with 1 or more individual high-risk sub-types and concordant infection were higher among YPHIV than among HIV-negative youth (Table 1). Although concordance declined over time for both groups, the magnitude of the decline was smaller among YPHIV, who had higher numbers of female participants with concordant infections between all compartments by 48 weeks. Factors independently associated with concordant infection in multivariate analysis (Table 2) included perinatally acquired HIV (adjusted OR [aOR], 2.55 [1.55–4.17]), a lower body mass index (<18 vs. ≥18 kg/m2; aOR, 1.61 [1.03–2.53]), higher lifetime number of sex partners (3–5: aOR, 2.08 [1.22–3.55]; ≥6: aOR, 2.01 [1.06–3.82] versus ≤2), and chlamydia and gonorrhea infections diagnosed during the study (aOR, 2.1 [1.51–2.91]).

## Sequential Infections

Sequential cervicovaginal to anal high-risk HPV infection occurred in 20 YPHIV versus 5 HIV-negative female participants, for an incidence rate of 9.76 (6.30–15.13) versus 2.24 (0.93–5.38) per 100 person-years (Table 3). Anal to cervicovaginal infection occurred in 4 YPHIV versus 0 HIV-negative female participants, for an incidence rate of 1.78 (0.67–4.75) per 100 person-years. For HPV-16, the incidence rate of sequential cervicovaginal to anal infection was higher for YPHIV at 2.71 (1.22–6.93) versus 0.89 (0.22–3.55) per 100 person-years. In multivariate analysis, being YPHIV (adjusted hazard ratio, 4.12 [1.55–10.99]) was independently associated with sequential cervicovaginal to anal infection.

**TABLE 1.** Frequency of Single and Concordant Anogenital High-Risk HPV Infections of the Same Subtype Among Asian Young Adult Women With and Without Perinatally Acquired HIV.

| | Week 0 | | Week 48 | | Week 96 | | Week 144 | |
|---|---|---|---|---|---|---|---|---|
| **Frequency of HR-HPV subtypes detected*** | YPHIV N=93 | HIV-negative N=99 | YPHIV N=84 | HIV-negative N=83 | YPHIV N=79 | HIV-negative N=75 | YPHIV N=77 | HIV-negative N=72 |
| Anal infection | | | | | | | | |
| 0 | 54 | 76 | 46 | 61 | 47 | 63 | 50 | 60 |
| 1 | 23 | 15 | 24 | 16 | 18 | 8 | 14 | 11 |
| 2 | 10 | 6 | 8 | 4 | 10 | 4 | 8 | 1 |
| >2 | 6 | 2 | 6 | 2 | 4 | 0 | 5 | 0 |
| Cervical infection | | | | | | | | |
| 0 | 53 | 70 | 44 | 57 | 42 | 55 | 48 | 57 |
| 1 | 19 | 17 | 22 | 19 | 20 | 12 | 18 | 10 |
| 2 | 15 | 7 | 12 | 5 | 14 | 8 | 7 | 4 |
| >2 | 6 | 5 | 6 | 2 | 3 | 0 | 4 | 1 |
| Vaginal infection | | | | | | | | |
| 0 | 48 | 64 | 50 | 56 | 38 | 56 | 41 | 51 |
| 1 | 17 | 20 | 14 | 20 | 23 | 12 | 19 | 17 |
| 2 | 22 | 10 | 12 | 7 | 15 | 7 | 10 | 4 |
| >2 | 6 | 5 | 8 | 0 | 3 | 0 | 7 | 0 |
| Vaginal and cervical concordant infection | n=35† | n=24 | n=31† | n=16 | n=33 † | n=12 | n=27 † | n=13 |
| 1 | 17 | 15 | 16 | 13 | 20 | 7 | 16 | 12 |
| 2 | 16 | 7 | 10 | 2 | 11 | 5 | 7 | 1 |
| >2 | 2 | 2 | 5 | 1 | 2 | 0 | 4 | 0 |

**TABLE 1.** Continued.

| | Week 0 | | Week 48 | | Week 96 | | Week 144 | |
|---|---|---|---|---|---|---|---|---|
| **Frequency of HR-HPV subtypes detected*** | YPHIV N=93 | HIV-negative N=99 | YPHIV N=84 | HIV-negative N=83 | YPHIV N=79 | HIV-negative N=75 | YPHIV N=77 | HIV-negative N=72 |
| Vaginal and anal concordant infection | n=27 | n=18 | n=28† | n=15 | n=23† | n=8 | n=21† | n=7 |
| 1 | 13 | 15 | 19 | 13 | 16 | 4 | 12 | 7 |
| 2 | 12 | 2 | 7 | 2 | 7 | 4 | 5 | 0 |
| >2 | 2 | 1 | 2 | 0 | 0 | 0 | 4 | 0 |
| Cervical and anal concordant infection | n=27 | n=17 | n=32† | n=15 | n=25† | n=7 | n=21† | n=8 |
| 1 | 15 | 13 | 22 | 11 | 17 | 4 | 12 | 8 |
| 2 | 11 | 2 | 7 | 3 | 8 | 3 | 7 | 0 |
| >2 | 1 | 2 | 3 | 1 | 0 | 0 | 2 | 0 |
| Vaginal, cervical, and anal concordant infection | n=24 | n=16 | n=27† | n=12 | n=21† | n=6 | n=20† | n=6 |
| 1 | 12 | 14 | 18 | 10 | 15 | 3 | 11 | 6 |
| 2 | 11 | 1 | 7 | 2 | 6 | 3 | 7 | 0 |
| >2 | 1 | 1 | 2 | 0 | 0 | 0 | 2 | 0 |

*0, no HR-HPV detected; 1–1, HR-HPV type detected; 2–2, HR-HPV types detected; >2, HR-HPV types detected.
†P <0.05 by $\chi 2$ test.
HR-HPV indicates high-risk human papillomavirus; YPHIV, youth with perinatally acquired HIV.

**TABLE 2.** Factors Associated With Concordant Anogenital High-Risk HPV Infection Among Asian Young Adult Women With and Without Perinatally Acquired HIV.

| Covariate | Concordant HR-HPV at >1 site | | | |
|---|---|---|---|---|
| | Univariate | P | Multivariate | P |
| | OR (95%CI) | | aOR (95%CI) | |
| **HIV status** | | <0.001 | | <0.001 |
| - HIV-negative | ref | | ref | |
| - Perinatally acquired HIV | 2.41 (1.51-3.84) | | 2.55 (1.55-4.17) | |
| **Current age (years)** | | 0.044 | | 0.51 |
| - <18 | 2.30 (1.19-4.42) | | 2.01 (0.96-4.24) | |
| - 18-22 | 1.58 (0.94-2.65) | | 1.61 (0.90-2.87) | |
| - ≥23 | ref | | ref | |
| **BMI (kg/m$^2$)** | | 0.008 | | 0.038 |
| - <18 | 1.79 (1.16-2.75) | | 1.61 (1.03-2.53) | |
| - ≥18 | ref | | ref | |
| **Highest level of education** | | 0.67 | | |
| - Primary school or secondary school | 1.01 (0.67-1.51) | | | |
| - Vocational school/pre-University | 0.72 (0.41-1.27) | | | |
| - University | 0.87 (0.52-1.44) | | | |
| - Non-formal education | 1.42 (0.66-3.05) | | | |
| - Lower than primary school | ref | | | |
| **Pregnancy history** | | 0.39 | | |
| - Never been pregnant | ref | | | |
| - Ever been pregnant | 0.81 (0.51-1.3) | | | |
| **Alcohol use, ever** | | 0.53 | | |
| - Yes | 1.15 (0.74-1.78) | | | |
| - No | ref | | | |
| **Alcohol use, past 6 months** | | 0.041 | | 0.07 |
| - Yes | 1.41 (1.01-1.97) | | 1.41 (0.97-2.05) | |
| - No | ref | | ref | |
| **Cigarette smoking, ever** | | 0.34 | | |
| - Yes | 1.20 (0.83-1.73) | | | |
| - No | ref | | | |
| **Cigarette smoking, past 6 months** | | 0.31 | | |
| - Yes | 1.33 (0.77-2.31) | | | |
| - No | ref | | | |

**TABLE 2.** Continued.

| Covariate | Concordant HR-HPV at >1 site | | | |
|---|---|---|---|---|
| | Univariate | P | Multivariate | P |
| | OR (95%CI) | | aOR (95%CI) | |
| **Substance use, ever** | | 0.01 | | 0.12 |
| - Yes | 1.87 (1.16-3.01) | | 1.52 (0.87-2.63) | |
| - No | ref | | ref | |
| **Number of sex partners, past 6 months** | | 0.024 | | 0.093 |
| - <3 | ref | | ref | |
| - ≥3 | 3.88 (1.2-12.53) | | 3.34 (0.82-13.59) | |
| **Lifetime number of sex partners** | | 0.002 | | 0.005 |
| - <3 | ref | | ref | |
| - 3-5 | 2.13 (1.27-3.56) | | 2.08 (1.22-3.55) | |
| - ≥6 | 2.52 (1.31-4.83) | | 2.01 (1.06-3.82) | |
| **Condom use with vaginal sex, past 6 months** | | 0.56 | | |
| - Always | ref | | | |
| - Sometimes/Never | 1.06 (0.74-1.51) | | | |
| - Not applicable/Not having vaginal sex | 1.42 (0.74-2.72) | | | |
| **Laboratory diagnosis of chlamydia and/or gonorrhea during study follow-up** | | <0.001 | | <0.001 |
| - Yes | 2.48 (1.82-3.38) | | 2.1 (1.51-2.91) | |
| - No | ref | | ref | |

Covariates with univariate P values <0.10 were included in the multivariate model.
*Concordant infection was defined as having the same high-risk HPV genotype detected in multiple anogenital compartments at the same study visit. BMI indicates body mass index; HR-HPV, high-risk human papillomavirus infection; STI, sexually transmitted infection

**TABLE 3.** Incidence Rate of Sequential High-Risk HPV Infection Among Asian Young Adult Women With and Without Perinatally Acquired HIV by HIV Status (n=178).

| Cervical and/or vaginal HR-HPV infection to anal infection | PHIV (n=89)* | | HIV-negative (n=89)* | | Total (n=178) | | P |
|---|---|---|---|---|---|---|---|
| **Any HR-HPV** | **20** | **9.76 (6.30-15.13)** | **5** | **2.24 (0.93-5.38)** | **25** | **1.79 (0.90-3.58)** | **0.001** |
| 16 | 6 | 2.71 (1.22-6.03) | 2 | 0.89 (0.22-3.55) | 8 | 1.79 (0.90-3.58) | |
| 18 | 3 | 1.32 (0.43-4.10) | 0 | 0 | 3 | 0.66 (0.21-2.05) | |
| 31 | 1 | 0.44 (0.06-3.10) | 0 | 0 | 1 | 0.22 (0.03-1.56) | |
| 33 | 1 | 0.44 (0.06-3.13) | 0 | 0 | 1 | 0.22 (0.03-1.57) | |
| 51 | 2 | 0.88 (0.22-3.51) | 1 | 0.44 (0.06-3.14) | 3 | 0.66 (0.21-2.05) | |
| 52 | 8 | 3.64 (1.82-7.28) | 0 | 0 | 8 | 1.79 (0.90-3.59) | |
| 58 | 1 | 0.44 (0.06-3.11) | 2 | 0.89 (0.22-3.57) | 3 | 0.66 (0.21-2.06) | |
| 59 | 1 | 0.44 (0.06-3.13) | 0 | 0 | 1 | 0.22 (0.03-1.57) | |
| 68 | 1 | 0.44 (0.06-3.13) | 0 | 0 | 1 | 0.22 (0.03-1.57) | |
| **Anal HR-HPV infection to cervical and/or vaginal infection** | | | | | | | |
| **Any HR-HPV** | **4** | **1.78 (0.67-4.75)** | **0** | **0** | **4** | **0.89 (0.33-2.37)** | **0.045** |
| 16 | 1 | 0.44 (0.06-3.13) | 0 | 0 | 1 | 0.22 (0.03-1.57) | |
| 52 | 2 | 0.88 (0.22-3.54) | 0 | 0 | 2 | 0.44 (0.11-1.77) | |
| 58 | 1 | 0.44 (0.06-3.1) | 0 | 0 | 1 | 0.22 (0.03-1.56) | |

*Four PHIV and 10 HIV-negative female participants only had HPV testing done at the baseline visit and were excluded from this analysis.
HR-HPV indicates high-risk human papillomavirus; PHIV, perinatally acquired HIV.

## DISCUSSION

Concordant, multicompartment, anogenital high-risk HPV infections were found in two-thirds of female Asian YPHIV and one-third of youth without HIV. The incidence of sequential cervicovaginal to anal infections was 4 times higher among YPHIV. The increased odds of concordant infections and increased incidence of sequential infections observed in YHPIV are at least partly due to more frequent infection with single and multiple sub-types in this group. In addition, the highly oncogenic type 16 was among the most commonly detected HPV types in YPHIV. Given that the YPHIV enrolled were only a median of 19 years of age at the start of our 3-year study, the results emphasize the need to begin screening these youth for HPV and cervical dysplasia earlier and more often. The study's annual testing schedule may not have been sufficient to fully capture all HPV infections, so the rapidity of sequential spread across anogenital compartments remains unclear. Our testing method for HPV-52 also may have led to underreporting of this type, as additional cross-reacting probe tests were not done. Nevertheless, the consistent associations observed between HR-HPV infection and perinatally acquired HIV demonstrate the hidden impact of lifelong HIV infection and the need to increase the stringency of cervical cancer screening guidelines in the region (17).

Our data build on studies demonstrating that women with nonperinatally acquired HIV are at greater risk for cervical dysplasia and cancer (18). Although a primary focus of HIV care is on achieving viral suppression to maintain health and prevent onward transmission, the current generation of YPHIV in Asia and other global regions have had extended periods in early childhood without treatment, and higher current rates of viremia and treatment failure than adults (1,2,19,20). Most are also living in countries with limited access to HPV vaccination or are too old for the free immunization programs that do exist (21–23). Two-dose and catch-up vaccination schedules for older adolescents are under study (22,24) and could be critical to expanding cervical cancer prevention across the Asia-Pacific. However, most Asian YPHIV women today will not benefit from this primary prevention, yet are not traditionally screened for HPV until they are older. The current cohorts of largely unvaccinated YPHIV require more proactive screening and monitoring for HPV-associated cancers.

The study results should be considered in the context of sexual practices of our patient population and limitations of self-reported data. Although we conducted the study in 2 countries, almost all of the participants were from Thailand because of challenges recruiting Vietnamese adolescents younger than 18 years who were required by local law to have caregiver consent to participate in research. The fear of disclosing sexual activity is related to social stigmas around sex outside of marriage

or for reasons other than reproduction. These barriers to adolescent sexual and reproductive health are common in our region and have been factors in reduced access to related health services, including contraception and testing for HIV, HPV, and other STIs (25,26).

With regard to the data on frequency of sex and numbers of partners, we did not capture whether these were new or old partners, which could impact risk of acquisition of HPV and other STIs. Notably, both the PHIV and HIV-negative partners most of- ten had only 1 sex partner in the previous 6 months of every study visit. Our findings may consequently not be generalizable to populations with higher numbers of concurrent or serial partners. Our results also may not apply to settings where pediatric HIV treatment was started at younger ages or HPV epidemiology varies.

In terms of the completeness of our HPV detection, results were subject to sampling variation and the reliability of the LINEAR ARRAY assay itself and test performance. The imperfect sensitivity of the assay in biological samples may have impacted our ability to distinguish sequential from concordant infections in our study.

In conclusion, our findings that YPHIV were at increased risk for concordant and sequential high-risk anogenital HPV infections emphasize the public health importance of HPV vaccination in children and access to adolescent catch-up vaccination. Combined with other analyses from our cohort showing increased rates of high-risk HPV persistence among YPHIV (14), there is clear evidence for prioritizing children and youth with HIV for HPV and cervical dysplasia testing as well. Cervical cancer screening should be part of routine HIV care for sexually active YPHIV female individuals during adolescence.

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**Conflict of Interest**

AHS has received grant and travel support to her institution from ViiV Healthcare. JA has received honoraria for participating in advisory meetings for Gilead, ViiV Healthcare, Merck, Roche, and Abbvie. PR's institution, outside of the scope of the current study, has received independent scientific grant support from Gilead, Janssen, Merck, and ViiV, and PR has served on scientific advisory boards for Gilead, ViiV, Merck, and Teva, for which honoraria were all paid to his institution.

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### Author contributions

AHS, AC, RH, SG, KC, HLDD, DNHT, JA, NT, MT, NP, and SJK conceptualized and designed the study. AC, RH, SG, KC, HLDD, DNHT, JA, NT, and MT conducted clinical study visits; together with ST, they performed data curation and contributed to data collection. AHS, SJK, and NP designed the methodology of the study, and ST and SJK conducted the formal analysis. AHS and NP obtained funding and supervised the conduct of the study. AHS wrote the original draft of the manuscript. All authors critically reviewed, revised, and approved the final version for publication.

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CHAPTER 10

# Peritransition Outcomes of Southeast Asian Adolescents and Young Adults With HIV Transferring From Pediatric to Adult Care

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## ABSTRACT

Purpose: The aim of this article was to study the clinical and social outcomes of health care transition among Asian adolescents and young adults with HIV (AYHIV).

Methods: AYHIV who transferred from a pediatric to an adult clinic within the past year across five sites in Malaysia, Thailand, and Vietnam had clinical and laboratory evaluations and completed questionnaires about their health, socioeconomic factors, and transition experiences. Multiple logistic regression was used to assess associations with HIV viremia.

Results: Of 93 AYHIV enrolled between June 2016 and April 2017, 56% were female, 87% acquired HIV through perinatal exposure, median age was 20 years (interquartile range [IQR] 18.521). Two-thirds were in a formal education program, 43% were employed, 43% of females and 35% of males were sexually active. Median lifetime antiretroviral therapy duration was 6.2 years (IQR 3.3-10.7); 45% had received second-line therapy. Median CD4 was 601 cells/mm3 (IQR 477-800); 82% had HIV-RNA <40 copies/mL. Being in a relationship, a shorter posttransition duration, self-reported adherence of ≥95%, and higher CD4 were inversely associated with HIV viremia. Half felt very prepared for the transfer to adult care, and 20% frequently and 43% sometimes still met with pediatric providers. Two-thirds reported needing to keep their HIV a secret, and 23%-38% reported never or rarely having someone to discuss problems with.

Conclusions: Asian AYHIV in our cohort were concerned about the negative social impact of having and disclosing HIV, and one-third lacked people they could trust with their personal problems, which could have negative implications for their ability to navigate adult life.


## IMPLICATIONS AND CONTRIBUTION

As global survival rates for children with perinatally acquired HIV improve, these young people are increasingly responsible for their own care as they transition to adult care. Asian youth in this study report concerns about the negative social impact of having HIV and isolation because of their status.

## INTRODUCTION

Global survival among children with perinatally acquired HIV infection has greatly improved with the scale-up of antiretroviral therapy (ART) (1,2). As they age into adolescence, they shift from dependence on their caregivers to being responsible for managing their own infection as a chronic disease. This will eventually include needing to transition from pediatric-focused care to adult HIV care and may involve a physical transfer to another provider or clinic or other changes in care management if within an all-ages clinic. When adolescent transition is unsuccessful, serious medical problems can arise, including poor ART adherence leading to increased HIV viral load and declines in immune function, resulting in treatment failure, potential emergence of drug resistance, and death, as well as onward transmission to partners (3-5).

Adolescents and young adults with HIV (AYHIV) are at high risk for poor medication adherence because of factors such as not appreciating the need to take medications when one feels well, inconsistent daily routines, depression, substance abuse, and fear of disclosure (6-8). Although pediatric HIV providers are more likely to have adolescent-focused support systems to address poor medication adherence, adult providers may be better equipped to provide AYHIV with comprehensive care that extends to sexual, reproductive, and mental health (9).

Experiences in some Western countries have raised concerns about the ability of health care systems to adequately support transitioning youth, which are compounded by issues of poverty and limited public health infrastructure in low- and middle-income settings (10,11). Within Asia, although some adolescents are referred out to adult clinics at the age of 15 years, others may remain in pediatric clinics into their early 20s. A study in Thailand showed that treatment and retention outcomes can be good when intensive support and counseling are provided through a formal transition planning process that involved adult HIV clinicians and nursing staff (12). However, posttransition data on Asian youth who are transferred from pediatrician-staffed clinics into adult HIV care remain limited (13,14). We conducted a study to gather evidence on posttransition clinical outcomes and social aspects of transition among Asian AYHIV who had completed a transfer from pediatric to adult HIV care to guide future interventions to promote posttransition adherence and retention in care.

## METHODS

We implemented a prospective observational cohort study among AYHIV who have already transitioned to adult-based HIV care involving a physical transfer from a pediatric to an adult clinic within participating sites in the TREAT Asia network of IeDEA Asia-Pacific (International epidemiology Databases to Evaluate AIDS) (15). The baseline peritransition data at study enrollment are presented in this analysis.

### Study sites and participants

Study participants were recruited and enrolled at five participating sites in Malaysia (Sungai Buloh Hospital, Selangor), Thailand (Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok; Faculty of Medicine Srinagarind Hospital, Khon Kaen University, Khon Kaen; Chiangrai Prachanukroh Regional Hospital, Chiang Rai), and Vietnam (National Hospital of Pedi- atrics, Hanoi). The four study sites besides Sungai Buloh Hospital in Malaysia were pediatric specialty clinics within larger health care facilities that referred out to adult receiving clinics. The three Thai and one Vietnamese pediatric sites had local and national transition preparation protocols in place to facilitate preparation of adolescents and caregivers for transfer to adult HIV care that included active communication with the receiving adult HIV clinic. Besides the Malaysia site, adult HIV receiving clinics were not included in the study. HIV treatment for children, adolescents, and adults was and remains freely provided in these countries.

Female and male AYHIV aged 16-24 years were eligible to participate if they had confirmed HIV infection, were able to provide assent or consent, were aware of their HIV infection status, and had transitioned from a participating pediatric clinical care site to an adult HIV clinic within 1 year before enrollment. Eligibility was initially determined by clinic staff at the participating sites who approached potential study participants. Interested AYHIV were referred to designated onsite study staff who conducted study enrollment procedures.

### Ethics review

Institutional review board approval was obtained at the participating sites and the coordinating center (TREAT Asia/ amfAR, Bangkok, Thailand). Participants provided informed consent if they were legally old enough to consent independently to participate in all study procedures. Otherwise, parent or legal guardian consent was obtained (i.e., Vietnam) with formal participant assent if required by local institutional review boards (i.e., Malaysia and Thailand). During the enrollment period, the age of consent to participate in research was 18 years in all three countries. On reaching age 18 years, participants were formally consented as individuals. Consent and

assent processes were conducted in a private area to ensure confidentiality and in local languages (e.g., Malay, Thai, and Vietnamese).

## Study procedures

Study procedures took place at their "sending" pediatric clinic (Thailand and Vietnam) or their "receiving" adult clinic (Malaysia). At enrollment, participants had (1) clinical assessments (including demographic data and ART histories); (2) laboratory evaluations (e.g., HIV-related tests and metabolic profiles); and (3) completed questionnaires about their health and medical history, self-reported ART adherence (16), socio-economic factors (e.g., education, employment, and income), behavioral risks (e.g., sex and substance use), and transition experiences. Data were collected using standardized clinical research forms and online self-questionnaires. Social impact questions were selected from the Strategies to Optimize Antiretroviral Therapy Services for Maternal & Child Health (MCH-ART) study's Social Impact Scale (17), and social relationship and problem-solving questions were from the NIH Toolbox Emotion Battery, 2012 (Emotional Support Short/Fixed Form Age 18+ and the Self-Efficacy Computer Adaptive Tests Form Age 18+) (18).

## Data management and analysis

The study sample size was based on a convenience sample of AYHIV who had transitioned to adult HIV care at participating sites within 1 year before enrollment, estimated to be between 80 and 100 participants overall. Sites were limited to up to 25 enrollments each. Study data were entered by site study staff into paper-based research forms and by individual participants through an online portal. Data were submitted to a centralized data management center for processing. Data cleaning and analyses were then conducted with Stata version 15 (StataCorp, College Station, TX). Survey data and medical history-related variables were examined using descriptive statistics. The primary objective of this analysis was to describe peritransition, health-related outcomes of AYHIV. Multiple logistic regression was used to assess associations between demographic, socio-economic, behavioral, and clinical factors and failure to maintain viral suppression. Linearity of continuous covariates against the logit function was assessed, and in the case of nonlinearity, the covariate was modeled as quartiles. Adjacent categories were collapsed together if the odds ratio and size of the confidence intervals were similar. Covariates with $p < .1$ in univariate models were adjusted for in multivariate models.

## RESULTS

A total of 93 AYHIV were enrolled between June 2016 and April 2017, 56% were female, and 81% were Thai, with 87% acquiring HIV through perinatal exposure (Table 1). The median age at enrollment was 20 years (interquartile range [IQR] 18.5-21). This varied by country: Thailand, n=75 (25 at each site), median 20 years (IQR 19-22); Vietnam, n=10, median 17.5 years (IQR 17-18) years; Malaysia, n=8, median 17 years (IQR 17-17.5). Median time since transition was 3.4 months (IQR 2.5-8.8) from the last pediatric clinic visit for 28% of the cohort and 4.7 months (IQR 1.8-8.8) from the first adult HIV clinic visit for the remainder of the cohort; neither variable was available for all participants. Two-thirds were currently in a formal education or training program, of which 48% were in college or university. At the same time, 43% were employed, with 45% of these in full-time jobs; 40% reported having a monthly income. Half (54%) were currently single, and 40% reported having sex in the past. Of 24 (43%) sexually active females, 20 (83%) reported female-male relationships, and 4 (17%) reported female-female relationships. Of the 13 (35%) sexually active males, 10 (77%) reported male-female relationships, and 4 (31%) reported male-male relationships.

Almost all (99%) were currently on ART, for a median duration of 6.2 years (IQR 3.3-10.7), with 45% having been on second-line therapy, in 93% of cases because of treatment failure on first-line regimens (Table 2). Of the 19% who missed at least one ART dose in the previous 3 months, the median missed doses were 3 (IQR 2-4). Overall median CD4 count was 601 cells/mm3 (IQR 477-800), and 82% had HIV-RNA at $\leq$40 copies/mL. Of those with detectable virus, the median log HIV-RNA was 3.69 (IQR 3.54-4.41). The median fasting cholesterol was 169 mg/dL (IQR 152-196). In a multivariate model, being in a relationship, shorter duration from transition, self-reported adherence of $\geq$95%, and higher CD4 counts were inversely associated with detectable viral load (Table 3).

With regards to transition experiences, 90% recalled having preparatory discussions about clinic transfer and the transition process, at a median age of 19 years (IQR 18-20) (Supplemental Table 1). Their first medical visit in their adult HIV clinic was at a median age of 20 years (IQR 18-21). Of the 45 (48%) who felt very prepared for the transfer to adult HIV care, 20 (44%) reported that moving to the adult HIV clinic was a very easy process, six (13%) reported that it was not easy and not difficult, and one (2.2%) reported that it was difficult. Overall, of the three (3.2%) youth who reported that moving to adult HIV care was difficult, one each said they felt very prepared, somewhat prepared, and not prepared for the transition.

**TABLE 1.** Cohort characteristics of patients at enrollment (N=93).

| Characteristic | Value |
|---|---|
| Female, N (%) | 56 (60) |
| Ethnicity, N (%) | |
| Thai | 75 (81) |
| Vietnamese | 10 (11) |
| Malay | 6 (6.5) |
| Chinese | 2 (2.2) |
| HIV exposure category, N (%) | |
| Perinatal | 87 (94) |
| Unknown | 6 (6.5) |
| Age, median (IQR) years | |
| Female | 20 (18.5, 21) |
| Male | 20 (18, 21) |
| Overall | 20 (18, 21) |
| Time since transition, median (IQR) months | |
| If transition from first adult HIV clinic visit (N=67) | 4.7 (1, 8.8) |
| If transition from last pediatric HIV clinic visit (N=26) | 3.4 (2.5, 8.8) |
| Living situation, N (%)* | |
| Relatives | 40 (43) |
| Biological parents | 36 (39) |
| Partner or friend | 16 (17) |
| Orphanage/care home/shelter | 12 (13) |
| Alone | 5 (5.4) |
| No answer | 1 (1.1) |
| Housing situation | |
| House | 63 (68) |
| Orphanage/care home/shelter | 10 (11) |
| Dormitory | 7 (7.5) |
| Rented/temporary room | 6 (6.5) |
| Apartment/condominium | 2 (2.2) |
| No answer | 5 (5.4) |
| Currently in school or training program, N (%) | 60 (65) |
| Type of school or training program | |
| - Grade 4-6 | 2 (2.2) |
| - Grade 7-9 | 6 (6.5) |
| - Grade 10-12 | 15 (16) |
| - Vocational | 5 (5.4) |
| - College/university | 29 (31) |
| - Other | 2 (2.2) |
| - No answer | 1 (1.1) |

**TABLE 1.** Continued.

| Characteristic | Value |
|---|---|
| If not in school or training, highest level of education, N (%) | 33 (35) |
| - Grade 1-3 | 3 (3.2) |
| - Grade 4-6 | 2 (2.2) |
| - Grade 7-9 | 4 (4.3) |
| - Grade 10-12 | 11 (12) |
| - Vocational | 3 (3.2) |
| - College/university | 10 (11) |
| Currently employed, N (%) | 40 (43) |
| Type of employment | |
| - Full-time | 18 (19) |
| - Part-time | 12 (13) |
| - Temporary | 6 (6.5) |
| - No answer | 4 (4.3) |
| Monthly income, N (%)** | |
| <5,000 Baht (<161 USD) | 14 (15) |
| 5,001-10,000 Baht (161-323 USD) | 17 (18) |
| 10,001-15,000 Baht (323-484 USD) | 2 (2.2) |
| 15,001-20,000 Baht (484-645 USD) | 1 (1.1) |
| 20,001-25,000 Baht (645-806 USD) | 2 (2.2) |
| >25,000 Baht (>806 USD) | 1 (1.1) |
| Not working or no answer | 56 (60) |
| Relationship status, N (%) | |
| Single | 50 (54) |
| ≥1 partner, not married | 31 (33) |
| Married | 6 (6.5) |
| No answer | 6 (6.5) |
| Previous sexual intercourse, overall, N (%) | 37 (40) |
| - Female (among all females, N=56) | 24 (43) |
| - Male (among all males, N=37) | 13 (35) |
| Age at first intercourse, overall, median (IQR) years (N=26 responding) | 16 (16, 18) |
| Alcohol use in the past 3 months, N (%) | 27 (29) |
| Cigarette smoking in the past 3 months, N (%) | 9 (9.7) |

*Answer options are not mutually exclusive.
**US Dollar (USD) equivalent calculated at 31 Thai Baht to 1 USD; 3 participants with no answer. Monthly minimum wage ranges based on 2017 ASEAN data: Malaysia 233.83 to 254.16 USD, Thailand 285.39 to 294.90 USD, Vietnam 114.29 to 166.13 USD (source: https://www.vietnam-briefing.com/news/vietnam-minimum-wages-on-the-rise-in-2018.html/)
IQR-interquartile range

**TABLE 2.** Cohort HIV and treatment characteristics at enrollment (N=93).

| Characteristic | Value |
|---|---|
| BMI, all, median (IQR) kg<br>- Female (N=56)<br>- Male (N=37) | 19.3 (18.0, 21.8)<br>19.4 (17.9, 21.8)<br>19.0 (18.0, 21.6) |
| ART history*<br>- Prior or current first-line regimen<br>- Prior or current second-line regimen<br>- Prior or current holding regimen** | <br>89 (96)<br>42 (45)<br>3 (3.2) |
| Duration on ART, median (IQR) years | 6.2 (3.3-10.7) |
| Reasons for second-line switch, N (%) (N=42)<br>- Treatment failure<br>- Toxicity<br>- Patient preference | <br>39 (93)<br>2 (2.2)<br>1 (1.1) |
| Current ART regimen<br>- PI-based<br>- NVP-based<br>- EFV-based<br>- Others<br>- Missing | <br>39 (42)<br>23 (25)<br>24 (26)<br>5 (5)<br>2 (2) |
| Daily ART pill burden, median (IQR) | 3 ( 2, 5) |
| Median (IQR) VAS, % | 97 (90,100) |
| Missed ≥1 ART dose in the past 3 months, N (%)***<br>- Median (IQR) doses missed | 18 (19)<br>3 (2, 4) |
| Primary financial responsibility for ART<br>- National health insurance<br>- Private, employer or other health insurance<br>- Social security<br>- Self-pay<br>- Do not remember or no answer | <br>32 (34)<br>14 (15)<br>13 (14)<br>9 (10)<br>25 (27) |
| Hepatitis B virus vaccine (known), N (%) | 84 (90) |
| Hepatitis B surface antigen<br>- Negative<br>- Positive<br>- Not done | <br>87 (94)<br>5 (5.4)<br>1 (1.1) |
| Hepatitis C virus antibody, N (%)<br>- Negative<br>- Not tested, unknown | <br>45 (48)<br>48 (52) |
| CD4, median (IQR) cells/mm$^3$ | 601 (477, 800) |
| HIV-RNA ≤40 copies/mL, N (%)<br>- Log HIV-RNA in those with >40 copies/mL (N=17), median (IQR) | 76 (82)<br>3.69 (3.54, 4.41) |
| ALT, median (IQR) U/L | 17 (13, 26) |

**TABLE 2.** Continued.

| Characteristic | Value |
|---|---|
| Creatinine, median (IQR) mg/dL | 0.75 (0.60, 0.86) |
| Fasting cholesterol, median (IQR) mg/dL | 169 (152, 196) |
| Fasting high-density lipoprotein, median (IQR) mg/dL | 51 (39, 64) |
| Fasting low-density lipoprotein, median (IQR) mg/dL | 98 (80, 117) |
| Fasting triglycerides, median (IQR) mg/dL | 104 (79, 140) |

*Responses are not mutually exclusive
**This represents treatment with a non-suppressive regimen during a period of poor adherence (e.g., lamivudine monotherapy)
***Adherence by self-report

BMI-body mass index; ART-antiretroviral therapy; IQR-interquartile range; PI-protease inhibitor; NVP-nevirapine; EFV-efavirenz; VAS-visual analogue scale. The visual analogue scale is a tool to collect self-reported adherence information on a 0-100 scale (see reference 16, Finitsis DJ, et al, 2016).

Although 41% overall felt very comfortable receiving care at the adult clinic, 20% frequently and 43% sometimes still met with pediatric care providers at their clinic (not for HIV care). In general, 47% reported their health was “very good,” and 18% reported that it was “excellent,” with 6% reporting “fair” or “poor” health. Half (51%) knew their most recent CD4 count, and 39% answered that it was ≥350 cells/mm3. Of the 63% who knew their HIV-RNA level, 56% answered it was “very good” (very low or suppressed), and 7% reported that it was “not good” (not low but not high) or “bad” (high). Although 41% reported that taking their daily ART was “very easy” and 31% reported that it was “easy,” 22% reported it was “not easy, not difficult,” and 6% reported that it was “difficult” or “very difficult.” The most commonly reported methods to remind them to take their ART (not mutually exclusive) was an alarm on a mobile phone (55%), an alarm on a wristwatch or clock (45%), or having someone to remind them directly (23%).

Their responses on the social impact questions showed that although the majority disagreed that their HIV status impacted routine social interactions and relationships, 67% felt they needed to keep their HIV status a secret (Figure 1). With regards to the social relationships questions around whether they had people they could talk with about their problems, daily challenges, and feelings, 23%-38% reported never or rarely having anyone in their lives they could turn to, and 35%-42% reported usually or always having this type of support (Figure 2). With regards to their own problem-solving abilities (Supplemental Figure 1), 15%-30% reported never or rarely being able to manage difficult problems and find solutions to accomplish their goals, 34%-48% reported they felt they could do this sometimes, and 22%-44% that they usually or were always able to overcome these challenges.

**TABLE 3.** Factors associated with HIV-RNA >40 copies/mL (N=93).

| | Univariate | p value | Multivariate | p value |
|---|---|---|---|---|
| | OR (95%CI) | | aOR (95%CI) | |
| **Female** | 1.26 (0.42-3.77) | 0.67 | | |
| **Ethnicity** | | 0.89 | | |
| Thai | 0.92 (0.18-4.8) | | | |
| Vietnamese | 0.57 (0.04-7.74) | | | |
| Malay or Chinese | ref | | | |
| **Age, years** | | 0.50 | | |
| <17 | ref | | | |
| 17-21 | 0.52 (0.04-6.25) | | | |
| ≥21 | 0.29 (0.02-3.92) | | | |
| **Time since transition, months** | | 0.08 | | 0.02 |
| <8 months | 0.38 (0.13-1.11) | | 0.098 (0.011-0.849) | |
| ≥8 months | ref | | ref | |
| **Living situation** | | 0.30 | | |
| Relatives | ref | | | |
| Biological parents | 3.18 (0.86-11.83) | | | |
| Partner or friend | 4.38 (0.78-24.66) | | | |
| Orphanage/care home/shelter | 0.97 (0.10-9.80) | | | |
| Alone | 2.19 (0.19-24.68) | | | |
| **Monthly income** | | 0.43 | | |
| <5,000 Thai Baht (<161 US Dollars) | 1.44 (0.31-6.62) | | | |
| >5,000 Thai Baht (>161 US Dollars) | ref | | | |
| Not working or no answer | 0.60 (0.17-2.08) | | | |
| **Relationship status** | | 0.09 | | 0.01 |
| Single | ref | | ref | |
| ≥1 partner or married | 0.28 (0.07-1.08) | | 0.037 (0.003-0.543) | |
| No answer | 1.58 (0.26-9.75) | | 0.263 (0.011-6.455) | |
| **Alcohol use, yes** | 2.05 (0.66-6.38) | 0.20 | | |
| **Cigarette smoking, yes** | 1.04 (0.26-4.14) | 0.96 | | |
| **VAS** | | 0.01 | | 0.049 |
| <95% | ref | | ref | |
| ≥95% | 0.24 (0.08-0.76) | | 0.147 (0.018-1.174) | |

**TABLE 3.** Continued.

| | Univariate | p value | Multivariate | p value |
|---|---|---|---|---|
| | OR (95%CI) | | aOR (95%CI) | |
| **CD4 cell count/mm$^3$** | | 0.002 | | <0.001 |
| <600 | ref | | ref | |
| ≥600 | 0.16 (0.04-0.59) | | 0.02 (0.001-0.296) | |
| **I have someone I trust to talk with about my problems*** | | 0.01 | | 0.29 |
| Never (n=11) | ref | | ref | |
| Rarely/sometimes (n=42) | 0.17 (0.04-0.70) | | 0.95 (0.07-12.35) | |
| Usually/always (n=39) | 0.10 (0.02-0.46) | | 0.26 (0.01-5.82) | |
| **I can handle whatever comes my way*** | | 0.09 | | 0.81 |
| Never (n=3) | ref | | Ref | |
| Rarely/sometimes (n=52) | 0.20 (0.03-1.15) | | 0.17 (0.01-5.61) | |
| Usually/always (n=35) | 0.11 (0.01-0.79) | | 0.06 (0.001-3.87) | |
| **I can solve most problems if I try hard enough*** | | 0.06 | | 0.11 |
| Never (n=4) | ref | | Ref | |
| Rarely/sometimes (n=48) | 0.30 (0.04-2.36) | | 0.46 (0.003-64.88) | |
| Usually/always (n=39) | 0.08 (0.01-0.82) | | 0.12 (0.001-19.54) | |

VAS-visual analogue scale

*Responses included in the analysis excluded the remainder of the individuals who chose “rather not answer.”

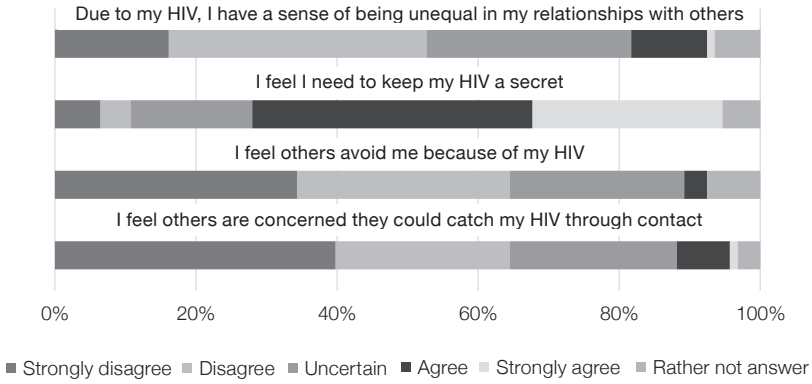


**FIGURE 1.** Social impact questionnaire responses at enrollment (N=93)

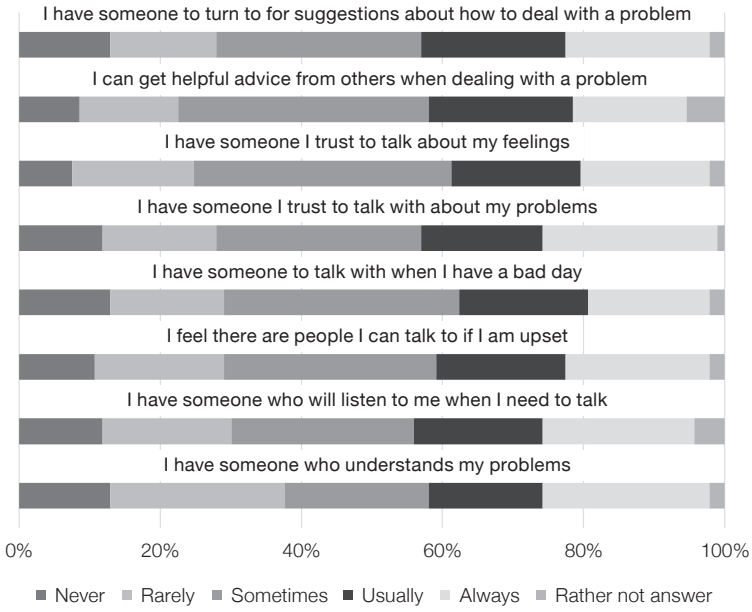


**FIGURE 2.** Social relationships questionnaire responses at enrollment (N=93)

## DISCUSSION

Across geographic and cultural settings, life-long HIV is associated with complex social, economic, mental, and developmental consequences for those who have perinatally acquired infection. These challenges become increasingly apparent during adolescence and continue into young adult life. The study represents the first regional effort to characterize the immediate peritransition period in AYHIV in Southeast Asia. In this cohort with primarily perinatally acquired HIV, all were transferred from specialist pediatric to adult care at a median age of 20 years, and half reported feeling well-prepared for the change. Overall health within 6 months of transition was good, with a median CD4 count of 601 cells/mm$^3$, and 82% having HIV viral suppression. This is higher than the 73% viral suppression we have reported before transfer to adult HIV care in our routine cohort data, which includes a mix of targeted and standard interval viral load testing (19). This compares to only half or fewer of AYHIV with undetectable HIV-RNA entering adult HIV care in some U.S. and United Kingdom cohorts and may be related to the differing social and demographic factors associated with pediatric and maternal HIV infection in these contexts or our convenience sampling methods (10,20-22).

Stable immune status by CD4 count, self-reported good adherence around the time of transfer, and a shorter time from transition were associated with undetectable HIV-RNA. With the majority having a regular ongoing connection to their pediatric providers, longer follow-up would be needed to study the resilience of AYHIV to successfully remain in adult care and on treatment as they perceive needing less support from their pediatric HIV clinics.

More than half still visited their “former” pediatric clinics and met with their “old” providers. From discussions with the study teams, this was for reasons other than routine HIV medical care and included the youth asking help with emotional support or advice around family and personal relationships. For those who require a physical transfer from specialist pediatric to adult HIV care, the transition may involve losing key health support systems, leading to increased vulnerability and risk of treatment failure and death (4,23-25). Because of the often close relationships that AYHIV establish with their pediatric providers, transfers in care can be emotionally difficult and associated with a deep sense of personal loss (8,24,26). AYHIV and their pediatric providers may be concerned about discrimination from new adult providers or other patients in the adult health care system associated with HIV-related stigma or worry about the potential loss of confidentiality (27-29). Such concerns can delay the transition process.

Two-thirds of our cohort reported needing to avoid disclosure of their HIV status, which may have been a factor in the lack of people in their lives they felt they could rely on for advice and encouragement. They would consequently have a greater need to maintain the contacts they had, such as their pediatric providers, who knew about their family and personal histories of living with HIV. Notably, in addition to being retained in HIV care and on treatment, most of the youth in our cohort were in active formal education or training programs, and about half were employed, reflecting a high level of structure in their lives. However, other studies have raised the concern that this type of general social engagement through education and work may be insufficient to build the types of relationships needed to sustain AYHIV through adult life, particularly in the absence of disclosure of their HIV status to family and friends and while living with the fear of stigma (4,23,24).

In Southeast Asia, although HIV treatment and care are often freely provided through government- and external donor-funded programs to both children and adults, HIV awareness is less integrated into everyday life than in high-prevalence settings, and stigma is often associated with the key affected populations at greatest risk of incident infection (e.g., males who have sex with males, sex workers, people who use drugs, transgender individuals) (1,29). This may place an added burden on AYHIV to educate their peers about living with perinatally acquired HIV or could lead them to feel pressured to hide their status (30,31), with the majority of our cohort choosing the latter. Fear of discrimination is especially high around disclosing to employers. Our study sites have reported that some multinational companies in the region can obtain HIV testing information through employment or health insurance-related medical testing, which discourages individuals from seeking formal employment situations.

Because of ART scale-up in the mid-2000s, there are growing populations of older youth with perinatally acquired HIV in the region – many who will need to be transferred to adult care. In Thailand and Malaysia, they are more often transferred as young adults than older adolescents, whereas the Vietnamese health care system requires transfer between 16 and 18 years of age (12). Despite differences in how transition is practiced, regional providers share a common priority to expand youth-specific HIV care interventions around adherence and retention (14). As more AYHIV reach transition ages, the need for health systems-level coordination of the adult care transfer process will increase. This may require joint training for pediatric and adult providers to consider how to optimize both the process of “letting go” of adolescents with perinatally acquired HIV as well as how to receive them in a way that engenders trust.

Our results are limited by the scope of our sample, which reflects a cohort that largely transitioned at older ages and successfully engaged in adult HIV care, with high rates of viral suppression and advanced educational attainment. As a result, our results may not be generalizable to settings where transfers occur at younger ages or AYHIV remain in the same clinics in a family-centered care model. The cohort also was predominantly Thai, although most eligible youth at the Malaysian site (8 of 9) and the Vietnamese site (10 of 15) were enrolled. Those in Thailand and Vietnam completed study procedures at their pediatric ("sending") clinic, and their responses to the participants surveys (especially with regards to social impact, problem solving, and risk behaviors) may have been different if they had been obtained at their adult clinics, as was done in Malaysia. Moreover, the preparation for transition that each individual patient received would have varied, as study sites offered differing combinations of standardized counseling, patient navigation support, adult HIV clinic engagement, and transitional adolescent clinics. Although this was a peritransition cohort, the high levels of ongoing contact reported with their former pediatric clinics implies that some youth had not completely moved on to rely on their adult HIV providers for their health and support needs. We also did not enroll control patients, which prevented us from evaluating sociodemographic factors or social relationships in comparison to HIV-uninfected peers (32,33).

In summary, in this Southeast Asian cohort of AYHIV who were transferred from pediatric to adult HIV care, most reported feeling prepared for the shift in care, found the transfer process smooth, and were comfortable at their adult HIV clinic. However, during this early posttransition period, the majority were having ongoing contact with their "sending" pediatric clinics and providers. Many were concerned about the negative social impact of having HIV, and most felt they needed to keep their HIV status an ongoing secret. One-third did not have people in their lives they could trust with their personal problems, which could have negative implications for their ability to navigate adult life. Posttransition data over more extended periods of time can help guide future interventions to ensure successful transfers and promote ongoing retention in adult-based HIV care of this vulnerable population.

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## Conflicts of interest

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### Author contributions

AHS, KC, PL, RH, YMG, LVN, TJM, CS, TS, and SJK conceptualized and designed the study. KC, PL, RH, YMG, LVN, and TJM conducted clinical study visits; together with ST and TS, they performed data curation and contributed to data collection. CS and TS coordinated the study. AHS and SJK designed the methodology of the study, and ST and SJK conducted the formal analysis. AHS obtained funding and supervised the conduct of the study. AHS wrote the original draft of the manuscript. All authors critically reviewed, revised, and approved the final version for publication.

## SUPPLEMENTAL INFORMATION

- Supplemental Figure 1. Problem-solving questionnaire responses at enrollment (N=93)
  - o Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6928413/bin/NIHMS1539700-supplement-1.docx
  - · Supplemental Table 1. Self-reported transition experiences at enrollment (N=93)
  - o Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6928413/bin/NIHMS1539700-supplement-2.docx

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CHAPTER 11

# General Discussion

# 1. BACKGROUND

The health and treatment challenges faced today by adolescents with perinatally acquired HIV are the legacies of the early decades of the HIV pandemic, and of our collective failures to invest human, technical, and financial resources into preventing, diagnosing, and treating their HIV infections. Whether these adolescents live in high-income or LMIC settings, those who have survived long enough to be under our care today are survivors of a "plague" with multi-generational consequences – where parents living with HIV transmitted infection vertically to children, who survived to grow up into adolescents, and then had the opportunity to have children of their own. Between 1990 and 2020, UNAIDS estimates that 7.26 million children with HIV died before they could reach adolescence (1). While this situation will change as more children aging into adolescence will have had greater access to PCR diagnostics and combination antiretroviral therapy (ART), many of those born in previous decades never had the chance to start treatment, while others were treated too late or with insufficiently potent medicines.

The preceding chapters characterize different aspects of the epidemiology of perinatally acquired HIV in Asian contexts. They help us better understand how adolescents have navigated their health challenges, and inform the development of future research and policy directions.

## The consequences of growing up taking HIV treatment

The slower scale-up of diagnostic capacity and access to ART for children meant that most adolescents with perinatal HIV today were born before early infant diagnosis through DNA PCR testing became locally available. Even if a diagnosis could be made clinically or based on blood tests, access to antiretroviral drugs for these children was restricted due to the lack of child-friendly formulations and, in some contexts, high medicine costs. Early in the global pediatric HIV epidemic, children with HIV in the US, UK, and Europe were initially started on mono- and then dual-nucleoside reverse transcriptase inhibitor regimens, which were combined with nelfinavir after that drug was approved in 1997 (2-5). In LMICs, nelfinavir was rarely available due to high costs and lack of pediatric formulations. This meant that providers often would use dual-nucleoside reverse transcriptase inhibitor regimens rather than no treatment at all, which involved combining drugs like stavudine or didanosine that were cheaper and available. This was the case in Thailand – the first Asian country to use and study these dual-drug regimens and their outcomes (6). Unfortunately, this class of drugs caused serious side effects that could be worse in children than in adults, like lipodystrophy, which resulted in visible "stigmata" of having HIV, and gastrointestinal distress, both of which had negative impacts on growth and made it

harder to adhere to (7, 8). Without other options, pediatricians had to push families to administer them. When children could not tolerate the medicines and developed treatment failure, they were blamed for their poor adherence, causing additional stress within families.

It was subsequently learned that to be effective over time, ART needed to be delivered in combinations of at least 3 drugs, usually a combination of a nucleoside reverse transcriptase inhibitor backbone (2 drugs) with a more potent "anchor" drug, which would have been a non-nucleoside reverse transcriptase inhibitor or protease inhibitor. This was especially complicated to do in children, who had fewer antiretrovirals and formulations to choose from, and whose medicine dosing had to be changed at appropriate intervals due to growth over time (weight, height). As a result of using sub-optimal regimens and adherence challenges across childhood, those who lived to adolescence were at increased risk of treatment failure and accumulation of drug resistance mutations (9, 10). In some Asian countries, like Thailand and Vietnam, early dual-drug use in younger children made it harder to find suppressive regimens for these children when they became older adolescents (11). There was consequently greater pressure from providers and caregivers on adolescents to adhere to their ART, to avoid running out of treatment options (*Chapter 1*) (12). However, the developmental challenges of adolescence and the stigma associated with HIV makes sustained adherence especially challenging during this vulnerable period (*Chapter 5*) (13, 14).

Pediatric researchers studied structured treatment interruptions as a way to try and give adolescents a break for two days over the weekend and encourage better adherence during the week, but were criticized for risking HIV viremia and resistance. The BREATHER trial (PENTA 16) conducted in Europe, North and South America, Thailand, and Uganda did not show this approach to be non-inferior, and as a result the approach was abandoned as far as future trials or clinical practice guidelines were concerned (15). However, there was some suggestion of lower drug-related side effects, and qualitative research from the study reinforced why efforts to improve treatment and delivery for adolescents remains a critical priority (16). Anecdotally, this practice has continued in special circumstances for those struggling to maintain daily adherence, with close monitoring, for reasons highlighted by the two participants who shared their perspectives (included in the study publication) on what it meant to have a short break below:

- *I don't know what it is about those two days, but it's the best days ever (…) I can go somewhere and not have to worry about taking that pill. Sometimes when I take the pill, my stomach hurts sometimes (…) but I don't have to worry about that, and*

*I don't have to worry about taking this big pill, and I don't got to worry about coming home at a certain time and taking it, I don't got to worry about getting up and taking it. I'm just free for those two days. (USA)*

- *It gave me freedom inside my heart and I saw that, eeh, at least here I have started to be like a normal person. (Uganda)*

Current adolescent HIV treatment programs have evolved to try to compensate for these historic challenges, and to cope with emerging co-morbidities and co-infections as adolescents live longer with HIV and prepare to transition to adult HIV care. Subsequent sections of this chapter will highlight data on these aspects of long-term care for adolescents with perinatally acquired HIV.

## 2. ADOLESCENT HIV TREATMENT PRIORITIES

### ART

The most commonly prescribed first-line ART regimens in children in LMICs have included NNRTIs as the anchor drug (i.e., nevirapine or efavirenz) (17). Because these medicines have low genetic barriers to resistance, the risk of even moderate levels of imperfect adherence is rebound viremia, which can rapidly progress to viral failure and eventually to treatment failure (10, 18). If early rebound viremia is not managed with improvements in adherence with or without switches to more potent regimens, adolescents develop immune failure that puts them at risk for opportunistic infections and death (*Chapters 5, 7*) (19-21).

The development of the INSTI dolutegravir (DTG) led to the first durable regimen that could be harmonized across almost all age groups, using an anchor drug that was "forgiving" enough to reduce the risk of early treatment failure. The WHO revised global treatment guidelines to prioritize DTG for children, adolescents, and adults in 2018 (22). Subsequent data from the ODYSSEY trial, conducted in Europe, South America, Thailand, Uganda, and Zimbabwe, demonstrated its superiority in both first- and second-line regimens in children, cementing its importance for all age groups except infants (23). Pharmacokinetic data from the IMPAACT P1093 trial, conducted in the US and Thailand, supported the use of once-daily dolutegravir in infants from four weeks to children under six years of age (24). However, the experience with P1093 exemplifies the delays usually experienced with developing and implementing delivery of formulations for infants. The study started enrolling in April 2011 before being published in May 2022, and investigators switched formulations from granules to a 5mg dispersible tablet due to stakeholder feedback (25). There are as yet no global data on DTG uptake by age group, but it is likely that it will take longer

for DTG to be scaled up in children and adolescents than for adults because of the slow speed at which pediatric formulations are being procured (26). So while dolutegravir is still looked on as true game-changer for global HIV programs, it has not served that purpose yet for children and adolescents.

## Novel formulations and delivery methods

Beyond optimizing ART regimens, there are ongoing efforts to develop drug formulations and delivery methods that will help adolescents to manage daily adherence (27). These include long-acting injectable and implantable antiretrovirals, which have been studied more for prevention than treatment in young adults (28-30). There are two sub-studies of the HIV Prevention Trials Network (HPTN) using cabotegravir for long-acting prevention that are enrolling adolescent females (084; NCT04824131) and males (083; NCT04692077). HPTN 084 is being conducted in South Africa, Uganda, and Zimbabwe, and HPTN 083 is being done in the US. To date, most of the focus has been on demonstrating efficacy at varying dosing (e.g., every one or two months) and pre-implementation assessments of feasibility and acceptability. Cabotegravir in combination with rilpivirine is currently the only treatment combination being evaluated for treatment of children and adolescents 12-17 years of age. The *More Options for Children and Adolescents* or MOCHA study (NCT03497676) is being conducted in the US (including Puerto Rico), Botswana, South Africa, Thailand, and Uganda. Completion of primary study data collection is projected to be by the end of 2022 and will include both quantitative and qualitative outcomes.

Recent data on the use of broadly neutralizing antibodies (bNAbs) for infant prophylaxis have been promising (31), but their utlity in routine treatment of children and adolescents with perinatal HIV is unclear. Studies of bNAbs for treatment of acute and chronic HIV in adults have had mixed results (32, 33), but have provided a foundation on which to consider further research in children and adolescents.

## Adherence and viral suppression

Ensuring HIV control is essentially dependent on whether adolecents take their ART. While improving the potency and tolerability of antiretrovirals is central to supporting adherence as is the development of long-acting therapies mentioned earlier, there are other interventions of varying complexity to support them with what remains a daily commitment. The most common approaches used to promote daily adherence among adolescents in Asia have included individual and family counseling, highlighting negative consequences of poor adherence (e.g., treatment failure), and strategies to remind them to take their medicines (e.g., reminders, pill boxes) (*Chapter 6*) (13). All are focused on the individual and their immediate social circle who already know

about their HIV status. It is not surprising then that the community-based support and adherence groups that have successfully been used in African youth are not a common option in Asia (34, 35). The very low HIV prevalence across the region (<0.1% in 15-24-year-olds and 0.2% in all adults) means that people with HIV are often isolated due to fear of stigma and discrimination, and engage less frequently with others with HIV (1). However, increasing regional awareness of the undetectable=un-transmissible or "U=U" findings offer communities and providers a way to focus on the positive aspects of adherence (i.e., those with undetectable HIV viral load cannot transmit HIV sexually to their partners) (36). Positive framing to promote adherence in this way remains relatively new for the adolescent population.

By adolescence, many with perinatally acquired HIV have failed their first-line regimens, which is associated with acquisition of resistance-associated mutations to nucleoside reverse transcriptase inhibitors (10). These mutations can compromise the effectiveness of second-line regimens that use drugs from this class. However, the potency of boosted protease inhibitors and integrase inhibitors have been sufficient to suppress viral loads of most children and adolescents when ART is taken daily (10, 23, 37, 38). Conversely, the primary consequence of low levels of adherence is its impact on rising HIV viral load and the subsequent risk of treatment failure. Data on viral suppression among adolescents have consistently been worse for adolescents than adults. A global analysis of IeDEA cohort data from 2010-2019 showed that suppression among adults was 89% at one year after starting ART, 89% at two years, and 90% at three years (39). The same analysis of children and adolescents up to 18 years of age in LMICs showed that suppression was 74% at one year, 75% at two years, and 76% at three years of ART. In the Population-based HIV Impact Assessment (PHIA) cross-sectional surveys implemented by PEPFAR in seven African countries, the suppression rate was 89% among all adolescents and adults over age 15 (40), and 82% for adolescent girls and young women 15-24 years of age (41). When limited to cohorts of adolescents with perinatally acquired HIV in LMICs, rates of viral suppression have ranged from 53-86%, with outcomes generally being worse as they age (18, 42).

Adolescents with perinatally acquired HIV in Asia have been reported to have suppression rates of ~80% with viral failure rates of 2.0 per 100 person-years (43). Even low-level viremia can be associated with future risk of viral failure, emphasizing the importance of adherence interventions to prevent longer term immune decline and risk of opportunistic infections and death (44).

## Mortality

Mortality analyses of adolescents with HIV have characterized varying comparative outcomes by HIV exposure category. Two studies of pediatric and youth mortality in LMICs in IeDEA (*Chapter 5*) showed that mortality rates were either similar for those with perinatally acquired HIV compared to those with non-perinatally acquired HIV (4.0% vs. 3.8%) (45), or even lower (1.4 vs. 2.5 per 100 person-years) (46). In contrast, the US PHACS study showed that mortality among adolescents and young adults with perinatally acquired HIV was 5.6-fold higher among those 15-19 years of age and 12.3-fold higher among those 20-29 years compared to youth in the general population (19). The difference between these two geographical contexts is that older children and adolescents in LMICs often reflect a more pronounced "survivor effect," whereby those with more rapidly progressing HIV have died at younger ages, potentially creating a bias towards reducing longer-term mortality. However, as these adolescents age into young adults, there is some indication from both higher- and lower-income contexts that mortality rates may increase due to the consequences of chronic illness and co-morbidities that emerge over time (47, 48).

There are limited data on underlying causes of death among adolescents with perinatally acquired HIV in Asia to help guide clinical management. A study done in the TREAT Asia pediatric cohort showed that infections have continued to be the leading causes, with the most common individual diagnoses including pneumonia (17%), TB (16%), and sepsis (8.0%) (*Chapter 7*, Figure 4) (20).

Although most of the infections captured in this study were considered "non AIDS-related" according to WHO criteria for stage 4 diagnoses, it is likely that they were the result of immune decline, as they were associated with lower CD4 counts and microbiologic diagnostics were limited in the study context to detect opportunistic pathogens. In addition, the increase in non-infectious deaths, including from trauma and cancers, is similar to trends seen in high-income contexts (49), and highlights the emergence of non-communicable disease (NCD) risks associated with aging youth with perinatally acquired HIV. Additional research is needed to determine how much of these risks are associated with the direct effects of HIV on organ systems, relative to social determinants of health and mental health.

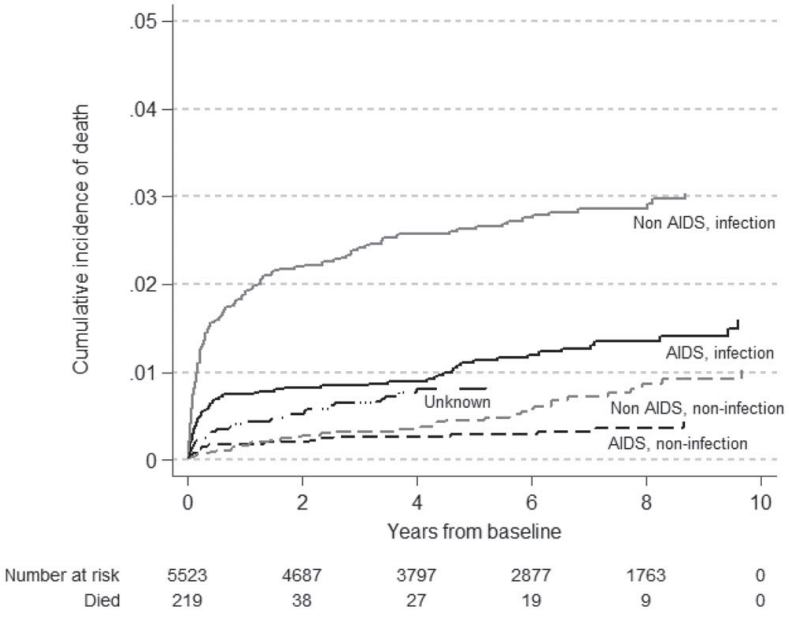


**FIGURE 4.** Cumulative incidence of death by AIDS and infection categories among children and adolescents in the TREAT Asia Pediatric HIV Observational Database of IeDEA Asia-Pacific, 2008-2017 (20).

## 3. CO-MORBIDITIES AND CO-INFECTIONS DURING ADOLESCENCE

Comprehensive care for adolescents with perinatally acquired HIV requires building on primary HIV treatment priorities to address the secondary risks of living with HIV. These broader health concerns are shaped by the side effects of life-long ART, development stage, and social context.

### NCD risks

In the case of NCDs, adolescents are already experiencing risk factors associated with future cardiovascular and metabolic diseases. Sub-clinical cardiovascular disease and arterial stiffness have been observed in cohorts of youth with perinatally acquired HIV in Europe and the US, who have been on ART for longer periods (50-52). In a South African study of neurocognitive, cardiac, respiratory, and renal function, 43.5% of adolescents with perinatally acquired HIV had impairment of at least one system and 10% had impairment of at least three systems (53). In Asia, initial signs of

dyslipidemia and abnormal glucose metabolism are being reported, such as in Thai youth in association with PI use (54-56). In a study of Thai young adults with perinatally acquired HIV who had been transitioned to adult HIV care, 60% had at least one NCD-related risk or condition, which was largely due to the 58% with dyslipidemia, but 2.6% met criteria for metabolic syndrome and 6.4% had central obesity (57). In contrast, an earlier echocardiography study of Thai adolescents with perinatally acquired HIV showed comparable carotid intima media thickness as HIV-negative controls (55).

As monitoring for metabolic diseases is becoming added to routine HIV clinical care in Asia (e.g., fasting glucose, lipids), it is likely that patterns of these clinical and laboratory biomarkers in adolescents with perinatally acquired HIV will be shown to be similar to those in other regional cohorts. In addition, although the anticipated shift away from PIs to INSTIs could be beneficial to cardiovascular health, DTG has been associated with weight gain and body fat changes in small cohorts of adolescents in Africa, Australia, and Europe (58-60). This raises potential concerns for these adolescents to be at greater risk of NCDs in adult life and for weight-associated stigma. Short- and long-term risks should encourage further research, including for when and how public health programs could consider introducing preventive interventions (51). However, to date, local and global guidelines have focused solely on monitoring, without clear recommendations for when to initiate weight-reduction efforts, cholesterol-lowering medicines, or switch regimens on the basis of these metabolic side effects.

## Adolescent co-infections

Underappreciated co-infections specific to this developmental period, when sexual activity increases, are sexually transmitted infections (STI). The US Adolescent Trials Network reported that the incidence of any STI was 17 per 100 person-years among youth with perinatally acquired HIV compared to 55 per 100 person-years among youth with non-perinatally acquired HIV, which correlated with higher levels of sexual activity in the latter group (61). This contrasted with lower rates of STIs in the US national population of those 15-24 years of age for chlamydia (3.7 per 100 person-years for females, 1.4 per 100 person-years for males) and gonorrhea (0.6 per 100 person-years for females, 0.5 per 100 person-years for males) in 2018. Notably, among female adolescents with perinatally acquired HIV, the most common STIs were viral (12 per 100 person-years), of which the majority were due to human papillomavirus (HPV).

There are few studies of STIs in adolescents with perinatally acquired HIV in Asia, where sexual activity before marriage often remains highly stigmatized (62). However, monitoring HPV infections is of critical importance for women with HIV, as they are at higher risk of cervical cancer compared to HIV-negative women (63), and because it is one of few vaccine-preventable co-morbidities they experience. Adolescence is an optimal time to study HPV; infections are more prevalent soon after initiation of sexual activity during this age period, which is related to the immaturity of the cervical epithelium that makes the cervix more susceptible to HPV (64). Available data from a TREAT Asia study of Thai and Vietnamese adolescents (median age 19 years) have shown that having perinatally acquired HIV is a risk factor for high-risk HPV infection (*Chapter 8*) (65), persistence of HPV in the anogenital tract (66), and sequential cervicovaginal to anal infection (*Chapter 9*) (67). While the duration of follow-up is too short to see cervical cancer cases in the oldest females with perinatally acquired HIV in the region, trends in abnormal cervical cytology raise concerns about future outcomes and emphasize the critical importance of expanding access to HPV vaccination regardless of prior sexual activity (Figure 5) (66).

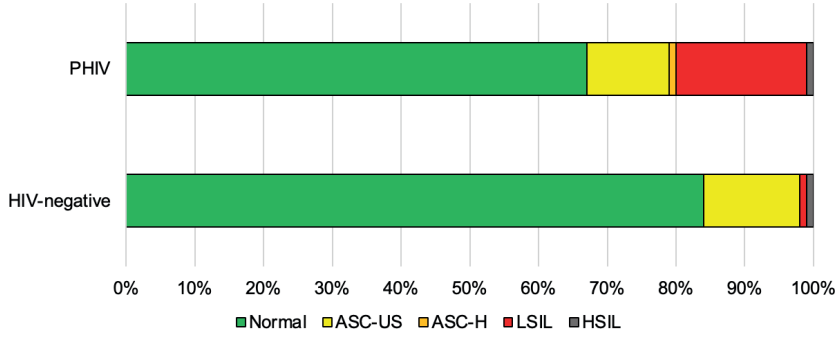


**FIGURE 5.** Cervical cytology data from Thai and Vietnamese adolescents with perinatally acquired HIV (65)

ASC-H, atypical squamous cells, cannot exclude HSIL; ASC-US, atypical squamous cells of unknown significance; HIV, human immunodeficiency virus; HIV-neg, HIV uninfected; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; PHIV, perinatally acquired HIV.

## Mental health

Mental health disorders generate intersecting risks for poor adherence and HIV treatment outcomes (68, 69). For adolescents with perinatally acquired HIV , there are multiple psychosocial and biological factors that can contribute to poor mental health and behavioral problems (70). HIV can have direct effects to worsen cognition

and neuropsychological functioning (71-73). Loss of parents, which is common among adolescents with perinatally acquired HIV, leads to emotional trauma, caregiver disruptions and financial challenges, which directly impact adherence and retention in care (74-76). In addition, the pressures of daily adherence often become more difficult to manage during this developmental stage. This can be related to a fear of inadvertent disclosure (e.g., through others seeing them store or take pills) and of side effects that can impact their physical appearance (e.g., lipodystrophy, weight gain) and social lives (e.g., when ART dosing schedules conflict with other activities) (77-79).

Stigma and discrimination are key factors compromising quality of life and mental health. Self-stigma can differ among those who have grown up with HIV compared to those who acquired HIV non-perinatally in terms of the age at which it starts, but remains a barrier to disclosure, relationships, and engagement within their community (80). HIV-related stigma and discrimination can lead to social isolation from a young age. Data from a study of Southeast Asian youth soon after transfer from pediatric to adult HIV care reflect the ongoing social impact of living with HIV (*Chapter 10;* Figure 6) (81). Notably, the majority of youth did not perceive HIV-related avoidance or inequality in their relationships, but this was in the context of hiding their HIV status. Persistent fear of disclosure escalates as children and adolescents become more socially exposed in their communities and online, and shapes their daily interactions.

In particular, as Asian adolescents with and without HIV age, there are indications that they are increasingly struggling with depression and anxiety (82-84). Studies of resilience in Thai and Cambodian adolescents with perinatally acquired HIV have shown that there can be both stability in the overall management of their HIV treatment, as well as problems with cognition and mental health, which could make it more difficult to identify those in need of mental health screening and treatment (70, 85).

These mental health challenges ultimately threaten the potential for adolescents with HIV to thrive as adults. While adolescents with perinatally acquired HIV in some cohorts have comparable quality of life and social functioning to those without HIV (86), globally, adolescents and young adults have the highest rates of loss to follow-up and treatment default of any age group (41, 47, 87).

## Substance use

Substance use, particularly of alcohol, following by tobacco and cannabis, and other risk behaviors increase during adolescence (88, 89). Onset of use has been shown to be earlier and prevalence higher among youth of minority gender identities (e.g., non-cisgender) (90). While there is strong evidence for the linkage between sexualized

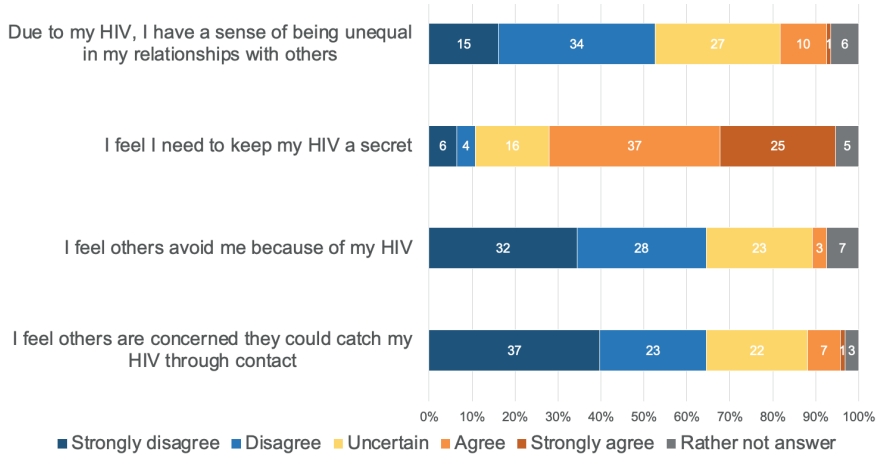


**FIGURE 6.** Social impact questionnaire responses among Asian adolescents with HIV (81)

drug use ("chemsex") and HIV acquision risk for youth (91, 92), substance use has been less excessive among those living with perinatally acquired HIV. A study from South Africa found that adolescents with non-perinatally acquired HIV had an over 9 times greater odds of excessive substance use in the previous year compared to those with perinatally acquired HIV (93). Data from the US have not shown increased substance use among youth with perinatally acquired HIV relative to the national population (94). In a cohort study in Asia, there were comparable proportions of adolescents with perinatally acquired HIV who drank alcohol compared to HIV-negative controls who were matched by sex and age (58% vs. 65%) (75). However, there are likely to be differences to those in young key populations (e.g., MSM, transgender individuals) who are at highest risk of incident HIV infection in the Asia-Pacific region (95). Nevertheless, excess alcohol and other substance use can increase risky sexual behavior and STIs in youth with and without HIV. Notably, alcohol use has been shown to be associated with higher incidence and persistence of HPV infection in Thai and Vietnamese female youth with perinatally acquired HIV (66).

These co-morbidities and co-infections that occur during adolescence contribute to the list of medical and social priorities that need to be addressed before and after transition to adult HIV care.

## 4. TRANSITION FROM PEDIATRIC TO ADULT HIV CARE

Children who grow up with chronic diseases face transitions in their healthcare after they age into young adults and become responsible for their own medical care management (96). This usually includes structural changes in their individual providers and clinics, as well as shifting social expectations for their behavior around coordinating appointments and treatment adherence. Those with perinatally acquired HIV are a unique population who experience the social, emotional, and mental consequences of growing up with HIV that go far beyond the physical impact of chronic infection. They live with a multi-generational disease, acquired from parents who have frequently died as a result. Unlike hereditary conditions passed on through genetic mutations, perinatal HIV transmission is preventable – a fact that makes every case of pediatric HIV reflective of a failure of the public health system and subject to familial guilt and blame. Adolescents with perinatally acquired HIV learn about this legacy of parental HIV when their HIV infection is disclosed to them. The pressures of living with HIV are simply enormous and set these adolescents apart from those with non-perinally acquired HIV and youth with other chronic diseases.

One key consequence on care management for adolescents, is that they often become intensely and personally connected to their pediatric providers, in contexts where HIV care is not provided to the family as a whole through the same provider. The relationships of trust that are built over their lives are emotionally difficult to set aside when they are expected to transfer care to adult HIV clinics. This necessitates careful preparation and implemention of the pediatric transition process in order to be successful.

### The history of pediatric HIV transition

The field of "transition medicine" was initially built on the management of chronic conditions like diabetes and developmental disabilities. The first US consensus statement on transition for youth with "special health care needs" was issued in 2002 by the American Academy of Pediatrics (97). As medical advances improved the lifespans of those with cystic fibrosis, congenital heart defects, kidney failure, and other diseases, the field expanded, leading to broader initiatives among physicians' societies (e.g., American College of Physicians) (98), and programs like "Got Transition," of the US National Health Care Transition Center (https://www.gottransition.org). However, these types of programs have seldom been a key resource for adolescent HIV programs.

A major reason for this may have been that during the first few decades of the HIV pandemic, pediatric HIV providers around the world often retained control of the management of their patients with perinatally acquired HIV well into their 20s (99, 100). These relationships were arrangements that the adolescents themselves often wanted to continue, as they benefited from having additional social and emotional support for their daily activities and self-care (101). The stigma and discrimination associated with vertical transmission of HIV also meant that an adolescent's HIV status was not only about them as individuals, but about their families. Keeping their HIV a secret from all but the most trusted few was a priority. A study in South Africa demonstrated how critical such support could be. In their cohort, only half of adolescents who were transitioned to adult HIV care at age 12 remained in care two years later, which compared to 92% of those who stayed in the pediatric clinic (102).

Other data have shown that older youth also can be lost to care after transition, such as in one US Adolescent Trials Network multicenter study where only 37% of those in their early 20s were successfully transitioned 9 months after the change had been made (103). In a national study in the Netherlands where these youth are in small numbers that are carefully tracked, 14% of their adolescents were lost to care after transition (104). While better than the US rates, there clearly remains room for improvement through careful preparation and engagement of adult providers.

Negative attitudes around healthcare transition for adolescents with perinatally acquired HIV are changing, as there is increasing evidence of the benefits of multi-disciplinary approaches and formal transition processes, with subsequent uptake of sexual and reproductive health interventions, and improvements in ART adherence (105, 106).

## Transition management in Asia

In many LMIC contexts, delaying transition until after adolescence is not feasible. For example, family-centered HIV care, where all ages are cared for together, is the predominant public health practice in most global contexts, such as in sub-Saharan Africa (107). While there are growing efforts to create better support specific for adolescents through setting aside certain days or providers for adolescent-focused care, this is not consistently offered (108). In Asia, there is a mix of stand-alone pediatric centers and general hospitals where pediatric HIV clinics have been established. In some countries, like Vietnam and Cambodia, transition to an adult HIV clinic must occur by age 16-18, while Thailand has greater flexibility to delay until age 18 or the early 20s (*Chapter 6*) (13).

There is substantial inconsistency in how patients and providers prepare for the physical hand-over of care. Surveys of clinics in the region have shown varying use of standard operating procedures, such as written transition guidance, communications between pediatric and adult providers, formal coordination of the handover, or orientation of the adolescent to adult HIV clinic requirements for managing appointments and medication refills (13, 109). Although there have been efforts to develop transition tools that are nationally focused or adapted to the multicultural and multilingual contexts, they tend to be used within networks or countries, rather than as a regional standard (e.g., TREAT Asia regional flip chart on transferring care (110)). Pediatric HIV providers working with the US Centers for Disease Control and Prevention developed the Happy Teen program as a way to prepare adolescents for living more independently and transitioning to adult care, which included a focus on HIV status disclosure (111)). This was promoted within the country, but has not been adapted for use elsewhere. Without clear and authoritative policy guidance at the national or regional level, it continues to be a challenge to elevate pediatric transition to adult HIV care as an implementation priority.

Whether or not they remained in pediatric care, youth with HIV often have had complicated ART histories, with persistent or intermittent viremia and multi-class antiretroviral drug resistance, putting them at high risk of treatment failure and mortality (104, 112, 113). There are limited data on transition outcomes in the region. Youth with perinatally acquired HIV who transitioned from pediatric sites in the TREAT Asia regional cohort had been a median 5.5 years of age when they were diagnosed and 18 years at transition (114). Although 85% were virally suppressed, 40% were on at least their second combination ART regimen. A regional follow-up study of a cohort within 5 months after transition showed that 82% were virally suppressed, and 63% were still meeting with their pediatric HIV providers (*Chapter 10*) (81). Notably, 32% were in college or university, 43% were employed, and 40% were sexually active – all reflective of age-appropriate personal growth into adult life.

Even if Asia's health systems are not ready to care for them, adolescents with perinatally acquired HIV are growing up. Because the most common model of care starts in pediatric clinics, transition preparedness must start there. Although pediatricians are rightly concerned that these types of care burdens fall on them to manage and advocate for, the reality is that they are in the optimal position to prepare adolescents. This process should start early and be normalized over years rather than months of time.

An approach that has worked in Chiang Rai, Thailand, has been to set up weekend workshops where adolescents can meet together with peer counselors and clinic staff to review practical steps in the transition process (115). When deemed ready to move to the adult clinic, they are accompanied by a care navigator who helps them make appointments, ensures medical records are shared, and a "warm hand-off" is arranged with the adult provider whereby they are introduced through physician-to-physician communication about the patient to be transferred. When this does not succeed, they welcome back the adolescent and work towards scheduling a second attempt at transition in the future. Another example comes from Malawi, where the Lighthouse Trust has established the Tiwale Adolescent Service, which prepares their adolescents to transition to adult care through their teen clubs. The program ends in a formal graduation ceremony that celebrates the resilience of the adolescents, and reminds them of the broad community support they enjoy (116).

While the models used at individual clinics in Asia should be based on the needs of the adolescents and available resources at individual clinics, there is ample local and global evidence for basic common processes that can be followed. What remains missing is clear policy guidance from an international advisory body like the WHO or UNICEF that countries can more easily adapt to local needs, and the accountability that comes with establishing such recommendations for care standards. To build the rationale for such guidance, it may be useful to routinely track the proportions of youth who have transitioned to adult care over time and those aging into transition.

## 5. POLICY IMPLICATIONS AND RECOMMENDATIONS FOR THE FUTURE

The data presented and reviewed in this thesis represent only some of the multiple dimensions of clinical care, program implementation, and research that touch on the complex lives of adolescents with perinatally acquired HIV. Nevertheless, they have direct and indirect implications for policy and practice, and point to how we can improve monitoring and care for this vulnerable population in Asia and more broadly.

### Surveillance

A concern for those studying health and treatment outcomes of adolescents with perinatally acquired HIV around the world is that they will be lost among the much larger numbers of young adults with non-perinatally acquired HIV. Current UNAIDS estimates are that the global ratio of adolescents 15-19 years of age living with HIV is approximately 60% with non-perinatally acquired HIV to 40% with perinatally acquired HIV (presentation by Mary Mahy, International Workshop on HIV and Pediatrics, 27

July 2022). By sex, those with perinatally acquired HIV make up about one-third of females and half of males in this age group (117). With more time, those with perinatally acquired HIV will represent an even smaller proportion of all adults living with HIV. Fortunately, we are still within a "window" to ***adjust local and global surveillance and data modeling platforms to track young adults and, eventually, older adults with perinatally acquired HIV.***

The UNAIDS Global AIDS Monitoring (GAM) program utilizes the Spectrum model to generate a range of metrics on the HIV epidemic each year (aidsinfo.unaids.org) (118). These estimates are used by implementers and donors for HIV program planning, funding allocations, and advocacy (119). In collaboration with IeDEA, UNAIDS began producing model inputs to support estimates of adolescents with perinatally acquired and non-perinatally acquired HIV in 2017, which were first published in *Chapter 4* (117, 120). While data on the mode of HIV transmission are seldom collected, UNAIDS used other methods to estimate the proportions of those with perinatally acquired HIV and applied them to the aggregated country data. Similar approaches also have been taken by the IeDEA global cohort consortium and the US PEPFAR program's Population-based HIV Impact Assessments (PHIA; conducted across Africa and Haiti) to disaggregate their data by perinatal infection, including in *Chapter 5* (45, 121), showing that model inputs and algorithms can be developed, validated, and used to ensure we do not "lose track" of those with perinatally acquired HIV (122). These methods also should be adopted by the Global Burden of Disease program at the Institute for Health Metrics and Evaluation, which is the world's leading data source for cause of death data (healthdata.org/gbd/2019) (123, 124). As presented in *Chapters 5 and 7*, expanding our limited understanding of what is causing adolescents to die would help us to intervene sooner to prevent it.

## Recommendations

- As the primary implementer and authority on the capture, reporting, and analysis of regional and global HIV surveillance data, UNAIDS should routinely disaggregate adolescent and young adult data by perinatal HIV status.
  - o This includes establishing standard Spectrum data specifications for country reporting (see below), and projecting forward those who will and have been transitioned to adult HIV care.
  - o These modeled estimates would be made available annually on the aidsinfo.unaids.org website, and their production remain a priority for the UNAIDS Reference Group on Estimates, Modelling and Projections (epidem.org).
- National HIV programs in the Asia region that submit surveillance data to UNAIDS should disaggregate their pediatric and adolescent data by perinatal infection status.

  - o UNAIDS should develop data tools and job aids to help countries harmonize their approach to categorizing perinatal infection, in order to reduce the barriers to reporting.
- The Global Burden of Disease program should integrate these disggregated data from the Global AIDS Monitoring program into their models for children, adolescent, and young adult health outcomes for mortality and disease burden (e.g., through disability-adjusted life year analyses).

## Prevention

There are a range of acute and long-term complications of ART and chronic HIV that adolescents with perinatally acquired HIV are at risk for. In particular, data emerging from sub-Saharan Africa and Asia show that higher rates of dyslipidemia and vascular inflammation are being found among adolescents on ART, which add to data from high-income contexts (48, 53, 54, 56). This is particularly concerning as questions grow around weight gain in adults associated with dolutegravir and tenofovir alafenamide (125), both WHO-preferred antiretrovirals that will increasingly become part of global regimens. Data to date have not shown substantial weight gain in children, but this is also thought to be mitigated by growth and development trends (23). As Asian adolescents are experiencing these metabolic abnormalities at younger ages, their future adult HIV providers may need to be more aggressive in managing them, which is likely to require greater medical intervention and could compromise their adherence to ART.

Sexual activity increases as adolescents transition to adults, and adds new risks of STIs. Previous discussions around sexual health were largely focused on "prevention for positives," to stop sexual transmission of HIV to their partners (126). However, with evidence to support U=U, this risk can be controlled through adherence, and prevention should be refocused to their own sexual and reproductive health. This must become a routine aspect of comprehensive care for adolescents in ways that emphasize prevention for their own health, which has secondary benefits for the health of their partners. While some STIs can be easily treated, others can not be, and can lead to serious outcomes – examples include *Neisseria gonorrhoeae*, which is highly drug-resistant in Asia. The greater risk of HPV infection and early cervical dysplasia data among Asian adolescents with perinatally acquired HIV should lead to stronger advocacy for HPV vaccination for both females and males (*Chapters 8 and 9*) (65, 67). However, even routine preventive healthcare maintenance, such as ensuring immunity against hepatitis B, has been sub-optimal or poor. Data from TREAT Asia showed that 76% of children with perinatally acquired HIV in the region did not have protective antibody – despite all represented countries offering free access to hepatitis B vaccine (127). This may have been caused by incomplete

primary vaccination or HIV-associated immunosuppression after infant vaccination, but there are already standard re-vaccination protocols for children with HIV that could be more consistently applied to protect these children and adolescents (128).

The mindset of Asia's policymakers and providers needs to move away from the acute response to HIV to consider how to support adolescents with perinatally acquired HIV to achieve the full life expectancies that are touted to adults who acquire HIV later in life (129). Instead of focusing solely on ART management and monitoring CD4 and HIV viral load, ***the scope of care for Asian adolescents with perinatally acquired HIV should match their changing risk profiles***. This requires a paradigm shift to view these adolescents not as children, but as emerging adults with a complex chronic disease. This must include provisions for integrated mental health care to prevent or limit the impact of common conditions like anxiety and depression. While UNAIDS and WHO have recently recommended the integration of mental health and HIV interventions, including designating adolescents as a special population to receive such care, there are few plans for how to fund or capacitate national HIV programs to make this happen (130).

In Asia, the field of adolescent health is still nascent, with few sub-specialists (131), and we cannot rely on them to support our adolescent HIV provider workforce. It is consequently up to their pediatric and adult providers to diversify the care they deliver to adolescents with perinatally acquired HIV to encompass fields not traditionally within the scope of pediatric HIV, and make prevention an equivalent priority to HIV-specific treatment and care.

## Recommendations

- Regional adolescent HIV care should include routine monitoring for NCD risks that are guided by their previous ART exposures, clinical history, and research data.
  - This can include low-cost anthropometric and blood pressure measurements, lipid and glucose monitoring, biomarkers of chronic kidney and liver disease, and referral systems for specialized care.
  - Integrated mental health care should be a standard part of NCD prevention packages.
  - Medical assessments should include questions about sexual health and behavior in order to guide STI screening, including referral for HPV testing or Pap smears for those who meet evaluation criteria.
    - Support for HIV testing, pre- and post-exposure HIV prophylaxis, and STI screening and treatment for sexual partners can be used to encourage adolescents and youth with perinatally acquired HIV to seek care for their own sexual health and promote disclosure.

- HPV vaccination should be provided for all adolescents with HIV in childhood or through catch-up programs, regardless of sex or gender.
- National HIV treatment guideline development processes can review data on prevention and clinical management of early co-morbidity and co-infection risks of adolescents to guide recommendations to providers. Engagement of regional United Nations partners as technical advisors would be a valuable component of those efforts (e.g., WHO's Western Pacific and South East Asia Regional Offices, UNAIDS Asia-Pacific, UNICEF East Asia and Pacific).

## Research

***Future research directions should be guided by adolescents with perinatally acquired HIV – both by what their HIV treatment outcomes show us they need to maintain their health, and by what they tell us they need to thrive and ensure good quality of life***. While the thesis research provides evidence for the former, additional qualitative and mixed methods study designs are needed to address the latter.

Research questions should focus on understanding what is needed to secure life-long treatment success, and how to prevent and manage associated co-morbidities and co-infections. Although most Asian adolescents with perinatally acquired HIV are adhering to their ART and have suppressed viral loads, there is a sub-group of 15-25% that is struggling to take their medicines or access regimens that are potent enough to overcome prior drug resistance, as seen in *Chapters 5, 7, and 10*. These youth are falling through the cracks of public health systems, being lost to follow-up, and some are dying of opportunistic infections. An emerging concern is suicide. To date, very little data are available around the prevalence of suicidal ideation or frequency of attempts in Asian youth with perinatally acquired HIV. The stigma around mental health disorders and suicide layer on top of stigmas around HIV to make this especially challenging to both study and address in the region (132).

Other neglected research areas in Asia are on sexual health and how social relationships (sexual and non-sexual) impact longer term quality of life. Part of the reason for this is cultural, as discussion of sexual lives outside of marriage in some regional contexts remains stigmatized. In addition, the fear of disclosure in relationships means that HIV status can be hidden and a source of ongoing anxiety. These relationships are increasingly important to individual well-being during the transition into adulthood, but are not well understood.

Unfortunately, research to understand what interventions we can offer to achieve better physical and mental health are seldom conducted in the region. Programs

offering economic empowerment (133) and combinations of social protections (134) have been promising approaches to keep youth in school and on HIV treatment in African contexts, but are rarely studied in Asia. The lower amounts of domestic funding and external donor support that go to adolescent HIV-related programs and research in the region limit what can be done to study more innovative approaches and conduct implementation science research on evidence-based interventions (135). To some degree, the field is a "victim" of its own success. As more countries in Asia improve their vertical prevention programs and there are fewer children with perinatally acquired HIV, there is less awareness of the needs of those who survived (136). And as adolescents are transitioned into adult HIV care, the more unique needs of those with perinatally acquired HIV can be lost amidst broader HIV program priorities.

Researchers in Asia must consequently be more strategic and leverage regional and global opportunities. This includes maximizing the use of routinely collected data, as discussed in *Chapter 3*. The TREAT Asia network links pediatric and adolescent HIV researchers from six South and Southeast Asian countries to focus on epidemiology research using these observational data (amfar.org/treat-asia-network-sites/). Utilizing data informatics tools can help to harmonize data within and between countries, which was how TREAT Asia data were combined with other global data to study loss to follow-up and mortality in the IeDEA cohort consortium in *Chapter 5* (iedea.org). Thai data also are included in the EPPICC cohort collaboration of the European PENTA clinical trials group (penta-id.org/hiv/eppicc/). The most sophisticated HIV clinical trials in children and adolescents happening in the region are in Thailand and India. This is largely due to having clinical research sites within the US National Institutes of Health-funded clinical trials networks IMPAACT (impaactnetwork.org/about/sites) and HPTN (hptn.org/research/sites), and PENTA (penta-id.org/who-we-are/the-penta-id-network/). Intra- and inter-regional collaboration will help ensure that future research questions impacting Asian adolescents with perinatally acquired HIV can be addressed.

## Recommendations

- Research on treatment outcomes of Asian adolescents with perinatally acquired HIV should include studying co-morbidities and co-infections to better understand how related risks and behaviors intersect to impact HIV viral load suppression vs. viremia, retention vs. loss to follow-up, and survival vs. death.
- Expansion of regional capacity to implement and funding to support qualitative and mixed methods research would provide critical insights to complement quantitative data and guide future interventions. Initial priorities of this research could be on the barriers to and facilitators of treatment success and resilience of Asian adolescents

with perinatally acquired HIV, stigma and the impact on social relationships, and mental health and quality of life in relation to HIV treatment outcomes.
- Opportunities to add additional Asian countries to research and clinical trials networks should be explored by the dominant global networks. In addition, sites already involved in these research collaborations could be viewed as local "champions" to build research capacity and advocate for clinical and program priorities of adolescents with perinatally acquired HIV.

## 6. CONCLUSIONS

This thesis offers historical perspectives on the clinical epidemiology and long-term outcomes of the "second-generation" of those who acquired HIV perinatally and have grown up living with HIV. As HIV is a relatively newer chronic infection, we are able to fully trace back the experiences of those we have lost and others who have survived. There are providers across Asia who cared for the very first cohorts of infants and children with HIV, and are now helping to prevent HIV in the "third-generation" to be affected, as those with perinatally acquired HIV become pregnant and seek to have families of their own.

Pediatric HIV-related priorities for clinicians, programs, and policy makers have shifted as our patients have aged, but they are no less complex. We may have antiretrovirals that can suppress the virus, but they alone are not enough to ensure that a child with HIV can grow up to thrive as an adult.

The research presented in Chapters 2-10 built on emerging knowledge around the outcomes of adolescents and young adults who grew up with HIV, and offered additional evidence for how to understand what was happening in their physical, emotional, and social lives. It is clear that Asian adolescents with perinatally acquired HIV each reach a crossroads where they will choose how they will live their lives with the virus. In Figure 3 (which also is the cover of this thesis), the painting by an 18-year-old Thai youth living with HIV showed them facing a river of "pain and suffering" that they needed to cross. They are standing alone as they look across to a green pasture or to a fork in the river. Adolescents with perinatally acquired HIV need us to work together to help them to cross that river into a hopeful future.

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CHAPTER 12

# Summary and Nederlandse Samenvatting

# THE POST-PEDIATRIC HIV GENERATION IN ASIA: ADOLESCENT HIV CARE, TREATMENT, AND TRANSITIONS INTO ADULT LIFE

## Part 1: Global challenges and solutions for the adolescent HIV epidemic

Children have for too long been at the bottom of the priority list when it comes to HIV prevention and care. As they have grown up into adolescents, we are continuing to react to their problems rather than preventing poor outcomes that could have been predicted. Because their numbers are small, those with perinatally acquired HIV are especially vulnerable to being lost amidst the larger groups of adolescents and young adults with non-perinatally acquired HIV.

***Chapter 2*** reflects the early stages of the thinking process that led to the development of this thesis. Written as an invited editorial commentary prior to the initiation of this doctoral work, it characterized aging children and adolescents with perinatally acquired HIV as being of the "post-pediatric HIV generation." Following care transition, their new adult HIV providers would be responsible to take on the clinical management of patients who had already lived with HIV for ~20 years. While some were stable on their ART, there was a sub-group of youth who had struggled during adolescence with adherence, and who had extensive, multi-class antiretroviral drug resistance, opportunistic infections, and long-term and often debilitating side effects due to sub-optimal ART management during childhood. The importance of the peri- and post-transition period for these adolescents and young adults was obvious, but there had been few studies on this topic in Asia to compare to high-income countries in the global North.

Because of the relatively limited funding available to study pediatric and adolescent HIV outcomes in the region, the best available source of data to begin studying these outcomes and associated risk factors was routinely collected observational data. ***Chapter 3*** was a narrative review and commentary from a global perspective that considered how these data could be used to guide improvements in HIV-related policy and practice. It highlighted the potential value of national surveillance databases and prospective cohorts, while acknowledging the weaknesses in accuracy, completeness, and granularity. These limitations stemmed from the data sources relying on data collection infrastructure that could be donor-driven rather than guided by local implementers to directly feedback into quality improvement. Nevertheless, improving the scope and depth of local-to-national data management would be more sustainable and provide greater benefit to national HIV programs into the future.

To dig down into how these data were being used at the global level, we examined prevalence and mortality estimates generated through the UNAIDS Spectrum model, which uses annually reported country-level data. For the first time in print, ***Chapter 4*** included UNAIDS global estimates of the distribution of adolescent HIV infections due to perinatally acquired HIV. Prior to this work, adolescent deaths had been widely reported to have been continually rising. Working with the Strategic Information team at UNAIDS, we disaggregated the data to show that deaths among younger adolescents (10-14 years) were in fact falling. The numbers of deaths among older adolescents (15-19 years) were stagnant, among a group predominantly made up of females with non-perinatally acquired HIV (e.g., through sex). However, relying solely on these combined, high-level data risked losing the granularity needed to understand the complex causes of adolescent deaths and geographic inequalities in program quality. In our review, we highlighted data from research cohorts that used routinely collected observational data (e.g., EPPICC, IeDEA) as a way to complement the country reporting systems with more detailed data. We raised the need for differentiated care services to tailor treatment programs by age, sex, and mode of HIV acquisition to better meet the needs of youth and help them overcome adherence and retention challenges. The UNAIDS pediatric reference group that oversees the annual global pediatric and adolescent modeling process has now integrated the estimates around perinatal HIV acquisition and data from IeDEA (e.g., CD4, mortality) into their model.

To explore more granular data to study adolescent loss to follow-up as well as mortality, ***Chapter 5*** was an analysis across six global regions of IeDEA – Asia, Central, East, Southern, and West Africa, and the Caribbean and Central and South America. With data from 61,242 adolescents from 270 sites in 34 countries, this was IeDEA's most complex adolescent data analysis to date and the largest ever global cohort study comparing adolescents with perinatally and non-perinatally acquired HIV. We made the case for setting the age threshold for likely perinatal HIV at 15 years – which was higher than proxies used in previous research cohort papers, but was consistent with methods used in the UNAIDS Spectrum model. With 69% of those entering care before age 15 and 31% after age 15, we were able to make comparisons by likely HIV exposure status for critical HIV treatment cascade outcomes. Notably, only 84% of those with likely perinatal infection and 51% of those with non-perinatally acquired infection were on combination ART during the period of follow-up, which extended between before 2006 up to 2016. Among those with likely perinatal infection who had survived to age 15, 4% went on to die while still in pediatric care, 27% were lost to follow-up, and 9.7% were transferred to other care facilities; among those with non-perinatally acquired infection, 3.8% died, 38% were lost to follow-up, and 4.6% were transferred. Factors associated with increased hazards of death included

starting ART above the age of 5 years and being female, and factors associated with lower hazards were higher current CD4 counts and weights, and more recent ART start year. Increased hazards of being lost to follow-up similarly included older age at ART start and being female, while higher CD4 was protective. This analysis serves as a valuable reminder of the serious risks of late diagnosis, care entry, and ART initiation – which continue to be challenges for adolescents, regardless of how they acquired HIV infection.

## Part 2: Adolescents living with HIV in Asia: How life-long HIV infection impacts clinical and program outcomes

Those who have survived into adolescence are now facing what it means to have life-long HIV as they transition into adult life. This includes developmental changes common to all youth that impact sexual and reproductive health, as well as emerging social and emotional needs. There have been relatively fewer opportunities to study outcomes among Asian youth with perinatally acquired HIV, which risks our missing opportunities to intervene to support them.

Awareness of the importance of adolescent HIV care emerged later in the Asia region compared to sub-Saharan Africa, where the focus on the burden of HIV and associated social and sexual risks among adolescent girls and young women was a priority for donors and programs (e.g., PEPFAR, Global Fund). The organization Paediatric AIDS Treatment for Africa (PATA) was commissioned by the WHO to conduct a survey of treatment and care services for adolescents in preparation for their 2015 HIV guidelines development process. We collaborated with them to adapt their survey tool for the Asia region, and conducted an online survey of care providers from 2015-2016. Translations were developed in six regional languages. The results were presented and compared to the Africa data in ***Chapter 6***. There was a total of 82 respondents from 7 countries (Cambodia, China, India, Indonesia, Malaysia, Thailand, Vietnam). The results provided a highly detailed breakdown of the scope of adolescent-specific services, including ways that clinics supported adherence and retention in care, and preparation for transition to adult HIV care. Both surveys reflected clear limitations in services focused on young key populations. Notable differences with the Africa survey were the infrequency of adolescent-specific clinics and family planning and contraception services – as care was largely provided in pediatric clinics rather than all-age clinics. Of concern was that half of the respondents lacked formal guidelines for managing the transition process. These data reinforced the importance of studying adolescent HIV care experiences and outcomes in Asia during this period when more younger adolescents were aging into older adolescence and young adulthood.

One of the emerging concerns among Asian pediatric HIV providers was how poor adherence was leading to treatment failure, opportunistic infections, and in some cases death among older adolescents. These patterns had previously been documented in UK and US adolescents and youth with perinatally acquired HIV. However, deaths among children and adolescents with HIV are largely considered to be from "HIV" by the Global Burden of Disease study, without further breakdowns in individual causes that could inform clinical and program interventions to prevent them. The TREAT Asia Pediatric HIV Observational Database had adapted the Cause of Death reporting tool of the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, and established a detailed process by which deaths were reported on standardized forms, externally reviewed, and adjudicated by an expert panel. In order to maintain consistency across the process, I participated in all of the adjudication panels of deaths that occurred through September 2017 and we analyzed the causes in ***Chapter 7***. Among the 6567 children and adolescents in the cohort through that period, 91% had acquired HIV perinatally. There were a total of 371 (6.3%) deaths. We were able to break down the deaths to show that 27% were AIDS-related infections or non-infectious complications (e.g., severe malnutrition) associated with severe disease progression. However, another 47% were due to non-AIDS-related infections, including pneumonia and less severe or disseminated forms of tuberculosis, which also implied underlying immunosuppression – despite the patients in our cohort having access to second-line and in some cases third-line therapy. We lacked data to explore why some adolescents were developing progressive clinical disease and immunosuppression after having achieved control of their HIV at younger ages. However, we hypothesized that mental health issues could have played a role in negatively impacting adherence to their ART regimens. This work established a key reference on pediatric HIV mortality for the region, and evidence to show that opportunistic infections remained a concern or were reemerging despite access to potent ART.

***Chapters 8 and 9*** report on research to compare adolescents and young women with perinatally acquired HIV to those without HIV. An important and preventable cause of death among women living with HIV is cervical cancer. A systematic review and meta-analysis reported that HIV infection was associated with a 6-fold higher risk of cervical cancer, which was even higher in African contexts. This is due in large part to the higher risk of acquiring HPV and of having persistent infection among women with HIV, which also has been shown among young women with perinatally acquired HIV. As they have life-long HIV infection, they are at potentially even higher risk of poorer outcomes from HPV, something which could be prevented by HPV vaccination. Unfortunately, HPV vaccination programs have been slow to scale up in the Asia region, and have prioritized younger school-age children without catch-up vaccination options for adolescents.

We conducted a prospective cohort study to assess how perinatally acquired HIV impacted HPV infection acquisition and persistence, and cervical cytology and histology, in comparison to matched HIV-negative peers. The HPV in Adolescents Study was conducted in Thailand and Vietnam, with participants followed for up to three years. The baseline analysis and study of concordant and sequential HPV infection are included in this thesis. ***Chapter 8*** included the initial infection, cytology, and histology data among the 93 adolescents and young women with perinatal HIV and 99 without HIV (median age 19 [IQR 18-20] years). Both groups had a median of two lifetime sexual partners. Cervical HPV infection was higher among those with HIV (62% vs. 40%; high-risk HPV 43% vs. 29%), as were abnormal Pap smears (e.g., low-grade squamous intraepithelial lesions 19% vs. 1%). These data were the first to show this degree of risk associated with perinatally acquired HIV, and emphasized the importance of securing HPV vaccinations for adolescents with HIV – even if they had already initiated sexual activity.

Having 6-12-monthly anogenital HPV infection data in this cohort allowed us to further assess when infections were in multiple compartments (e.g., vaginal and anal), and the sequence of infections with the same HPV genotypes). In ***Chapter 9***, we found that more youth with HIV had simultaneous and concordant HPV infection detected over time than those who were HIV-negative (66% vs. 34%). They also had slower declines or clearance of their infections. In addition, the incidence of sequential cervicovaginal to anal high-risk HPV infections was substantially higher in those with HIV (9.76 vs. 2.24 per 100 person-years), and anal to cervicovaginal infection only occurred in those with HIV (1.78 per 100 person-years vs. 0). Both of these studies consistently showed that life-long, perinatally acquired HIV was an independent risk factor for HPV infections and persistence. Although pediatric HIV programs are largely focused on delivery of ART, this research emphasized that adolescents will need increasingly comprehensive approaches to care as they age.

The final chapter sought to understand what was happening at the end of the pediatric HIV care process, when adolescents and young adults were transitioned to adult HIV care. Previous studies of our regional cohort were only able to look at the “pre-transfer” period. With the Study of Transitioning Asian Youth (STAY), we were able to assess them in the immediate post-transfer period. ***Chapter 10*** reflects the baseline data for this cohort, which included 93 adolescents and young adults in Malaysia, Thailand, and Vietnam. Almost all acquired HIV perinatally (87%), their median age was 20 years, and their median time on ART was 6.2 years. While 82% had undetectable viral loads, 45% were on second- or third-line regimens. The approach to this study was substantially different to our previous cohort research in that there were more detailed assessments of participants’ living and housing

situations, education and employment, monthly income, sexual behavior and substance use, social impact of living with HIV, and transition experiences. Participants reported varying limitations in their social support networks and an ongoing fear of HIV disclosure. Notably, 23-38% reported never or rarely having someone in their lives that they could talk with about their daily challenges and problems, and 67% felt they needed to keep their HIV status a secret from others.

# DE POST-PEDIATRISCHE GENERATIE MET HIV IN AZIË: HIV ZORG EN BEHANDELING VOOR ADOLESCENTEN EN TRANSITIE NAAR VOLWASSENHEID

## Deel 1: Wereldwijde uitdagingen en oplossingen voor de hiv-epidemie bij adolescenten

Kinderen hebben te lang onderaan de prioriteitenlijst gestaan daar waar het om de preventie en zorg van hiv gaat. Terwijl ze opgroeien tot adolescenten, blijven wij reactief ten aanzien van het omgaan met hun problemen in plaats van slechte uitkomsten die voorspeld hadden kunnen worden te voorkómen. Omdat zij relatief in de minderheid zijn, zijn vooral degenen met perinataal opgelopen hiv kwetsbaar om verloren te gaan tussen de grotere groepen adolescenten en jongvolwassenen met niet-perinataal opgelopen hiv.

***Hoofdstuk 2*** geeft het begin weer van het denkproces dat leidde tot de ontwikkeling van dit proefschrift. Geschreven naar aanleiding van een uitnodiging tot een redactioneel commentaar voorafgaand aan de start van dit doctoraat, typeerde dit commentaar ouder wordende kinderen en adolescenten met perinataal opgelopen hiv als behorend tot de “postpediatrische hiv-generatie”. Volgend op hun transitie naar zorg voor volwassenen, zouden hun nieuwe zorgverleners verantwoordelijk worden voor de zorg van patiënten die al ~20 jaar met hiv hadden geleefd. Terwijl sommigen stabiel waren op hun ART, was er een subgroep van jongeren die tijdens de adolescentie moeite hadden gehad met therapietrouw met uitgebreide anti-retrovirale geneesmiddelenresistentie voor meerdere klassen, die opportunistische infecties kregen en vaak ernstige lange termijn bijwerkingen hadden als gevolg van suboptimaal ART-beleid tijdens hun kindertijd. Het belang van de peri- en post-transitieperiode voor deze adolescenten en jongvolwassenen was duidelijk, maar er waren weinig studies over dit onderwerp in Azië die vergelijkbaar waren met studies in hoge inkomenslanden op het Noordelijk halfrond.

Vanwege de relatief beperkt beschikbare financiering om uitkomsten van hiv bij kinderen en adolescenten in de Aziatische regio te bestuderen, waren routinematig verzamelde observationele gegevens de best beschikbare gegevensbron om mee te beginnen dergelijke uitkomsten en de eraan gerelateerde risicofactoren te bestuderen. ***Hoofdstuk 3*** is een beschouwend overzicht en commentaar vanuit een mondiaal perspectief hoe dergelijke gegevens gebruikt zouden kunnen worden om verbetering van beleid en praktijk inzake hiv aan te sturen. Het benadrukte de potentiële waarde van nationale surveillancedatabases en prospectieve cohortstudies, met erkenning

van de beperkingen daarvan aangaande nauwkeurigheid, volledigheid en gedetailleerdheid van de verzamelde gegevens. Deze beperkingen vloeiden voort uit het feit dat de gegevensbronnen afhankelijk waren van een infrastructuur voor gegevensverzameling die donor-gestuurd was in plaats van gestuurd door lokale uitvoerders met als doel tot directe kwaliteitsverbetering te leiden. Niettemin zou het verbeteren van de reikwijdte en diepgang van lokaal-naar-nationaal gegevensbeheer naar verwachting duurzamer zijn en naar de toekomst meer voordeel kunnen opleveren voor nationale hiv programma's.

Om nader te onderzoeken hoe gegevens op mondiaal niveau werden gebruikt, hebben we prevalentie- en mortaliteitsschattingen zoals gegenereerd door het UNAIDS Spectrum-model nader onderzocht. Dit model maakt gebruik van jaarlijks gerapporteerde landelijke gegevens. ***Hoofdstuk 4*** bevatte, voor het eerst in druk verschenen, schattingen door UNAIDS van de wereldwijde verspreiding van perinataal opgelopen hiv-infecties bij adolescenten. Daarvóór was gerapporteerd dat sterfgevallen onder adolescenten voortdurend waren gestegen. In samenwerking met het Strategische Informatieteam van UNAIDS hebben wij de gegevens kunnen uitsplitsen en kunnen aantonen dat sterfgevallen onder jongere adolescenten (10-14 jaar) in feite aan het afnemen waren. Het aantal sterfgevallen onder oudere adolescenten (15-19 jaar) stagneerde, in een groep voornamelijk bestaande uit meisjes en jonge vrouwen met niet-perinataal opgelopen hiv (bijvoorbeeld via seks). Het uitsluitend vertrouwen op de gecombineerde niet uitgesplitste gegevens bracht het risico met zich mee de gedetailleerdheid te verliezen die nodig is om de complexe oorzaken van sterfte onder adolescenten en geografische ongelijkheden in programmatische kwaliteit te kunnen duiden. In onze review hebben we door research cohorten ((bijv. EPPICC, IeDEA) routinematig verzamelde observationele gegevens uitgelicht als een manier om de rapportagesystemen van landen aan te vullen met meer gedetailleerde gegevens. We hebben de behoefte aangekaart voor meer gedifferentieerde vormen van zorg teneinde hiv behandelprogramma's beter af te kunnen stemmen op leeftijd, geslacht en wijze van hiv acquisitie om daarmee beter te kunnen voldoen aan de behoeften van jongeren en hen te helpen uitdagingen betreffende therapietrouw en retentie in zorg te overwinnen. De pediatrische referentiegroep van UNAIDS die toezicht houdt op het jaarlijkse proces om wereldwijde gegevens over kinderen en adolescenten te modelleren heeft de schattingen wat betreft perinatale acquisitie van hiv en de gegevens van IeDEA (bijv. CD4, mortaliteit) nu in hun model geïntegreerd.

Teneinde meer gedetailleerde gegevens over zowel "loss to follow-up" als mortaliteit van adolescenten te bestuderen, beschrijft ***Hoofdstuk 5*** een analyse van data verzameld in al de zes door IeDEA bestreken wereldwijde regio's : Azië, Centraal-, Oost-,Zuidelijk- en West-Afrika, en het Caribisch gebied met Midden- en Zuid-Amerika.

Met gegevens over 61.242 adolescenten uit 270 sites in 34 landen, was dit IeDEA's meest complexe analyse van data over adolescenten tot nu toe en de grootste wereldwijde cohortstudie ooit die adolescenten met perinataal en niet-perinataal opgelopen hiv heeft vergeleken. Wij hebben aan de hand van de resultaten bepleit om de leeftijdsdrempel dat er sprake is van een waarschijnlijke perinatale hiv-infectie bij 15 jaar te leggen, hetgeen hoger was dan proxies die werden gebruikt in eerdere publikaties van cohortonderzoeken, maar overeenkwam met de gebruikte methoden in het UNAIDS Spectrum-model. Gezien 69% van de adolescenten in zorg gekomen waren voor de leeftijd van 15 jaar en 31% na de leeftijd van 15 jaar, konden wij belangrijke onderdelen van de hiv-zorgcascade vergelijken op basis van de waarschijnlijke wijze van acquisitie van hiv. Opvallend was dat tijdens de periode van follow-up, die reikte van vóór 2006 tot 2016, slechts 84% van degenen met een waarschijnlijk perinataal opgelopen infectie en 51% van degenen met een niet-perinataal opgelopen infectie combinatie-ART gebruikte. Van de kinderen met een waarschijnlijke perinataal opgelopen hiv infectie die de leeftijd van 15 hadden bereikt, stierf 4% alsnog terwijl zij nog kindergeneeskundige zorg kregen, 27% raakte uit follow-up en 9,7% waren overgedragen naar andere zorginstellingen; van de kinderen met een niet-perinataal opgelopen hiv infectie stierf 3,8%, raakte 38% uit follow-up, en waren 4,6% overgedragen. Meisjes die met ART gestart waren bij een leeftijd boven de 5 jaar hadden een verhoogd risico op overlijden, terwijl een hoger huidig CD4-getal, hoger huidig gewicht en recenter met ART gestart zijn geassocieerd waren met een lager risico op overlijden. Ook voor de kans om uit follow-up te raken gold dat deze hoger was bij meisjes die op oudere leeftijd met ART waren gestart en lager bij degenen met een hoger huidig CD4-getal. De resultaten van deze analyse benadrukken eens te meer de ernstige risico's van het laat stellen van een hiv diagnose, laat toegang krijgen tot zorg en laat met ART beginnen – uitdagingen die allen heden nog steeds bestaan voor adolescenten, ongeacht hoe ze een hiv-infectie hebben opgelopen.

## Deel 2: Adolescenten die leven met hiv in Azië: hoe een levenslange hiv-infectie de uitkomsten op zowel klinisch als programma niveau beinvloedt

Degenen die hebben overleefd tot aan hun adolescentie, worden nu geconfronteerd met wat het betekent om levenslang hiv te hebben bij hun overgang naar het volwassen leven. Dit omvat de ontwikkelingsveranderingen die alle jongeren gemeen hebben en invloed hebben op hun seksuele en reproductieve gezondheid, maar daarnaast ook de nu zichtbaar wordende behoeften op sociaal en emotioneel gebied. Er zijn relatief minder mogelijkheden om lange termijn uitkomsten te bestuderen onder Aziatische

jongeren met perinataal opgelopen hiv, waardoor we mogelijk kansen missen om in te grijpen en deze jongeren te kunnen ondersteunen.

Bewustwording van het belang van hiv-zorg voor adolescenten ontstond in de Aziatische regio later dan in Afrika bezuiden de Sahara, waar meer nadruk ligt op de last van hiv en aanverwante sociale en seksuele risico's bij adolescente meisjes en jonge vrouwen en dit een prioriteit vormt voor donoren en programma's (bijv. PEPFAR, Global Fund). De organisatie Pediatric AIDS Treatment for Africa (PATA) heeft in opdracht van de WHO de beschikbare behandeling en zorgmogelijkheden voor adolescenten in kaart gebracht ter voorbereiding op het proces van het ontwikkelen van hun hiv-richtlijn uit 2015.

Wij hebben met hen samengewerkt om de door hun gebruikte vragenlijsten aan te passen voor de regio Azië en daarmee vervolgens in 2015-2016 een online enquête onder zorgverleners uitgezet. Vertalingen werden daarvoor ontwikkeld in zes regionale talen. De resultaten zijn weergegeven en vergeleken met de Afrikaanse gegevens in ***Hoofdstuk 6***.

Er waren in totaal 82 respondenten uit 7 landen (Cambodja, China, India, Indonesië, Maleisië, Thailand, Vietnam). De resultaten gaven een zeer gedetailleerde uitsplitsing van de reikwijdte van adolescent-specifieke diensten, inclusief manieren waarop klinieken therapietrouw en in zorg blijven ondersteunden en adolescenten voorbereidden op de overgang naar hiv-zorg voor volwassenen. De enquête weerspiegelde duidelijke beperkingen in diensten gericht op deze jonge sleutelpopulaties. Opmerkelijke verschillen met de Afrika-enquête waren de beperkte aanwezigheid van adolescent-specifieke klinieken en diensten gericht op gezinsplanning en anticonceptie - aangezien de zorg grotendeels werd verleend in pediatrische klinieken in plaats van klinieken voor alle leeftijden. Zorgwekkend was dat de helft van de respondenten aangaf geen formele richtlijnen te hebben voor het begeleiden van het transitieproces naar de volwassen hiv-zorg. Deze gegevens versterkten het belang van het bestuderen van de ervaringen met en de uitkomsten van zorg voor adolescenten in Azië gedurende deze periode waarin vele jongere adolescenten ouder en vervolgens jong volwassenen werden.

Eén van de opkomende punten van zorg onder pediatrische hiv-behandelaren in Azië was hoe slechte therapietrouw onder oudere adolescenten begon te leiden tot falen van de hiv-behandeling, het optreden van opportunistische infecties en in sommige gevallen zelfs tot sterfte. Vergelijkbare observaties waren eerder gedocumenteerd onder adolescenten en jongeren met perinataal opgelopen hiv in het Verenigd Koninkrijk en de Verenigde Staten. Echter, sterfgevallen onder kinderen en adolescenten

met hiv worden door de Global Burden of Disease studie grotendeels beschouwd als ten gevolge van “hiv”, zonder verdere uitsplitsing naar individuele doodsoorzaken. Dat laatste zou informatie kunnen verschaffen hoe zowel in de kliniek als binnen programma’s bepaalde doodsoorzaken te voorkomen zouden zijn. De TREAT Asia Pediatric HIV Observational Database had de tool voor het rapporteren van doodsoorzaken, zoals ontworpen door de Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) studie, aangepast en een gedetailleerde procedure opgesteld waarbij sterfgevallen werden gemeld op gestandaardiseerde formulieren, extern werden beoordeeld en uiteindelijk vastgesteld door een expertpanel. Om de consistentie in het proces te behouden, heb ik deelgenomen aan alle beoordelingspanels van sterfgevallen die plaatsvonden tot en met september 2017. In ***hoofdstuk 7*** hebben we een analyse van deze doodsoorzaken gerapporteerd. Onder de 6567 kinderen en adolescenten in het cohort gedurende deze periode had 91% hiv perinataal opgelopen. Er waren in totaal 371 (6,3%) sterfgevallen. We konden de sterfgevallen uitsplitsen en aantonen dat 27% van de sterfte te wijten was aan aids-gerelateerde infecties of niet-infectieuze complicaties (bijv. ernstige ondervoeding) bij ernstige ziekteprogressie. Nog eens 47% was echter te wijten aan niet-aids-gerelateerde infecties, waaronder longontsteking en minder ernstige of gedissemineerde vormen van tuberculose, wat ook een onderliggende immunosuppressie impliceerde – ondanks dat de patiënten in ons cohort toegang hadden tot tweedelijns- en in sommige gevallen derdelijns antiretrovirale therapie. We hadden onvoldoende gegevens om te kunnen onderzoeken waarom sommige adolescenten klinische ziekteprogressie ontwikkelden en immunosuppressie terwijl hun hiv eerder op jongere leeftijd onder controle was geweest. Onze hypothese was dat psychische problemen een rol konden hebben gespeeld bij het negatief beïnvloeden van therapietrouw ten aanzien van ART.

Deze studie heeft gezorgd voor een belangrijke referentie wat betreft sterfte onder kinderen met hiv in de regio, en voor aanwijzingen dat opportunistische infecties een blijvend punt van zorg zijn of mogelijk opnieuw de kop hebben opgestoken ondanks toegang tot effectieve ART.

***Hoofdstukken 8 en 9*** doen verslag van onderzoek waarin adolescenten en jonge vrouwen met en zonder perinataal opgelopen hiv met elkaar vergeleken worden. Een belangrijke en vermijdbare doodsoorzaak bij vrouwen met hiv is baarmoederhalskanker. Een systematische review en meta-analyse heeft aangegeven dat het hebben van een hiv-infectie geassocieerd is met een 6 keer hoger risico op baarmoederhalskanker, wat zelfs nog hoger was in Afrikaanse settings. Dit komt voor een groot deel door een hoger risico op het oplopen van HPV en het hebben van een persisterende infectie daarmee bij vrouwen met hiv, hetgeen ook is aangetoond voor jonge vrouwen

met perinataal opgelopen hiv. Omdat deze vrouwen een levenslange hiv-infectie hebben, lopen ze mogelijk ook een hoger risico op HPV-gerelateerde ziekteverschijnselen, iets wat kan worden voorkomen door HPV-vaccinatie. Helaas verloopt de opschaling van HPV-vaccinatieprogramma's in de Aziatische regio traag en is vaccinatie geprioriteerd voor jonge schoolgaande kinderen zonder de mogelijkheid voor inhaalvaccinatie voor adolescenten.

Wij hebben een prospectieve cohortstudie uitgevoerd om te beoordelen hoe een perinataal opgelopen hiv-infectie van invloed was op de acquisitie en persistentie van HPV, op cervix cytologie en histologie, in vergelijking met gematchte hiv-negatieve leeftijdsgenoten. De HPV in Adolescents Study werd uitgevoerd in Thailand en Vietnam, waarbij deelnemers maximaal drie jaar werden gevolgd. De analyse van gegevens ten tijde van inclusie in de studie en van concordante en sequentiële HPV-infectie zijn opgenomen in dit proefschrift.

***Hoofdstuk 8*** bevat de gegevens over de initiële infectie, cytologie en histologie van de 93 adolescenten en jonge vrouwen met perinataal opgelopen hiv en de 99 zonder hiv (mediane leeftijd 19 [IQR 18-20] jaar). Beide groepen hadden gemiddeld twee seksuele partners gedurende hun leven. Een cervicale HPV infectie was frequenter bij degenen met hiv (62% vs. 40%; hoog-risico HPV 43% vs. 29%), evenals een abnormale Pap-uitstrijkje (bijv. laaggradige squameuze intra-epitheliale laesies bij 19% vs. 1%).

Deze gegevens toonden als eerste de mate van risico geassocieerd met het hebben van een perinataal opgelopen hiv, en benadrukten nog eens het belang van het veiligstellen van HPV-vaccinatie voor adolescenten met hiv – ook indien ze al seksueel actief waren.

Het beschikken over 6-12-maandelijkse anogenitale HPV-infectiegegevens in dit cohort gaf ons de mogelijkheid vast te stellen in hoeverre er sprake was van HPV-infectie in verschillende compartimenten (bijv. vaginaal en anaal), en van sequentiele infectie met hetzelfde HPV genotype. In ***hoofdstuk 9*** vonden we dat meer jongeren met hiv in de loop van de tijd een gelijktijdige en concordante HPV-infectie in verschillende compartimenten had dan degenen zonder hiv (66% vs. 34%). De jongeren met hiv toonden ook een langzamer afname of verdwijnen van hun HPV infectie. Daarnaast was de incidentie van het sequentiëel optreden van een cervicovaginale gevolgd door een anale hoog-risico HPV-infectie aanzienlijk hoger bij mensen met hiv (9,76 vs. 2,24 per 100 persoonsjaren), en kwam een anale gevolgd door een cervicovaginale infectie alleen voor bij mensen met hiv (1,78 per 100 persoonsjaren versus 0). Beide onderzoeken toonden consistent aan dat een

levenslange perinataal opgelopen hiv infectie een onafhankelijke risicofactor is voor HPV en het persisteren daarvan. Hoewel pediatrische hiv-programma's grotendeels gericht zijn op het geven van ART, benadrukt dit onderzoek dat adolescenten met hiv een toenemend uitgebreidere benadering van zorg nodig zullen hebben naarmate ze ouder worden.

Het laatste hoofdstuk tracht beter te begrijpen wat er gebeurt aan het eind van de pediatrische zorg voor hiv wanneer de transitie plaatsvindt van adolescenten en jong-volwassenen naar de hiv-zorg voor volwassenen. Eerdere studies van ons regionale cohort hadden alleen kunnen kijken naar de periode vóór de transitie.

Met de Study of Transitioning Asian Youth (STAY) konden we jongeren beoordelen in de periode onmiddellijk na de transitie. ***Hoofdstuk 10*** beschrijft de gegevens op moment van inclusie in STAY voor 93 adolescenten en jong volwassenen in Maleisië, Thailand en Vietnam. Een grote meerderheid had hiv perinataal opgelopen (87%), hun mediane leeftijd was 20 jaar en de mediane tijd dat zij ART gebruikten was 6,2 jaar. Ook al had 82% een ondetecteerbare virale lading, gebruikte 45% reeds een tweede of derde lijnsbehandeling. De aanpak van dit onderzoek was wezenlijk anders dan bij ons eerdere cohort onderzoek in die zin dat er een meer gedetailleerde verzameling van gegevens plaatsvond over leef- en woon-situatie, opleiding en werk, maandelijks inkomen, seksueel gedrag en middelengebruik, de sociale impact van het leven met hiv, en ervaringen met de transitie naar hiv-zorg voor volwassenen. Deelnemers meldden verschillende beperkingen in sociale ondersteuning binnen hun netwerk en een voortdurende angst voor het onthullen van hun hiv-status. Opmerkelijk was dat 23-38% aangaf nooit of zelden iemand in hun leven te hebben om mee te praten over hun dagelijkse uitdagingen en problemen, en 67% vond dat ze hun hiv-status geheim moesten houden voor anderen.

ADDENDUM

Abbreviations

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PhD Portfolio

List of Publications

Dankwoord (Acknowledgements)

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## ABBREVIATIONS

| | |
|---|---|
| AIDS | Acquired immunodeficiency syndrome |
| ART | Antiretroviral therapy |
| CDC | US Centers for Disease Control and Prevention |
| EPPICC | European Pregnancy and Paediatric HIV Cohort Collaboration |
| GAM | Global AIDS Monitoring System |
| HIV | Human immunodeficiency virus |
| HPV | Human papillomavirus |
| IeDEA | International Epidemiology Databases to Evaluate AIDS |
| INSTI | Integrase strand transfer inhibitor |
| LMIC | Low- and middle-income countries |
| NCD | Non-communicable disease |
| PEPFAR | US President's Emergency Plan for AIDS Relief |
| PI | Protease inhibitor |
| PLHIV | People living with HIV |
| STI | Sexually transmitted infection |
| UNAIDS | Joint United Nations Programme on HIV/AIDS |
| WHO | World Health Organization |

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Name of student: Annette H. Sohn
PhD period: February 2018 – December 2021
PhD supervisors: Prof. Dr. Jintanat Ananworanich, Prof. Dr. Peter Reiss

1 ECT = 28 hours

**Overall portfolio total: 33.18 ECT**

| | **PhD-related training** | **ECTs Total: 13.79** |
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| **Year** | **Online courses** | |
| 2019 | American Board of Pediatrics, Adolescent Medicine Self-Assessment, USA (10 points) | 0.36 |
| 2019 | American Board of Pediatrics, Pediatric Infectious Diseases Self-Assessment (2018 version), USA (10 points) | 0.36 |
| 2019 | American Board of Pediatrics, Pediatric Infectious Diseases Self-Assessment (2019 version), USA (10 points) | 0.36 |
| 2019 | American Board of Pediatrics, Child Abuse Pediatrics Self-Assessment, USA (10 points) | 0.36 |
| 2019 | American Board of Pediatrics, Refugee and Immigrant Health Care, USA (15 points) | 0.54 |
| 2020 | American Board of Pediatrics, COVID-19 (Part 2), USA (25 points) | 0.89 |
| 2020 | American Board of Pediatrics, COVID-19 (Part 4), USA (25 points) | 0.89 |
| **Year** | **Seminars** | |
| 2020-2021 | Monthly-quarterly online seminars for the CHIMERA D43 HIV research program on HIV, mental health, implementation science, Thailand (2020: March, May, October, November; 2021: January, February x 2, March, July, October, November) 1.5 hours/webinar | 0.59 |

| Year | Workshops | |
|---|---|---|
| 2019 | 21st Bangkok International Symposium on HIV Medicine, January 2019, Thailand (6h/d x 3 d) | 0.64 |
| 2019 | CHIMERA D43 HIV research workshop on HIV, mental health, and implementation science – TREAT Asia and Columbia University, September 2019, Thailand (9 d) | 2.57 |
| 2020 | 22nd Bangkok International Symposium on HIV Medicine, January 2020, Thailand (6h/d x 3 d) | 0.64 |
| 2020 | CHIMERA D43 HIV research workshop on HIV, mental health, and implementation science – TREAT Asia and Columbia University, February 2020, Thailand (5 d) | 1.43 |
| 2020 | CHIMERA D43 HIV research workshop on qualitative research methods – TREAT Asia and Columbia University, Thailand, July-August 2020, virtual (4h/day x 5d) | 0.71 |
| 2020 | CHIMERA D43 HIV research workshop on HIV, mental health, and implementation science – TREAT Asia and Columbia University, Thailand, December 2020, virtual (4h/d x 4d) | 0.57 |
| 2021 | 23rd Bangkok International Symposium on HIV Medicine, January 2021, Thailand, virtual (5h/d x 2 d) | 0.36 |
| 2021 | CHIMERA D43 HIV research workshop on HIV, mental health, and implementation science – TREAT Asia and Columbia University, Thailand, April 2021, virtual (asynchronous and live; 7 h total) | 0.25 |
| 2021 | CHIMERA D43 HIV research workshop on HIV, mental health, and implementation science – TREAT Asia and Columbia University, Thailand, May-June 2021, virtual (4h/day x 5d) | 0.71 |
| 2021 | CHIMERA D43 HIV research workshop on qualitative research methods – TREAT Asia and Columbia University, Thailand, August 2021, virtual (4h/day x 5d) | 0.71 |
| 2021 | MIST D43 Summer Boot Camp – Real-life Implementation Science, University of Malaya and Yale University, Malaysia, August 2021, virtual (4 h total) | 0.14 |
| 2021 | CHIMERA D43 HIV research workshop on HIV, mental health, and implementation science – TREAT Asia and Columbia University, Thailand, October 2021, virtual (4h/d x 5 days) | 0.71 |

| | **Presentations** | **ECTs Total: 2.00** |
|---|---|---|
| 2018 | Oral presentation at a scientific conference<br>· Characterizing the double-sided cascade of care for HIV-infected adolescents transitioning to adult-centered care in the IeDEA Southern Africa Collaboration. *22nd International Workshop on HIV and Hepatitis Observational Databases (IWHOD),* Fuengirola, Spain. | 0.50 |
| 2018<br><br><br><br>2019 | Poster presentations at scientific conferences<br>· An algorithm to determine likely mode of infection in adolescents living with HIV enrolling in care at age 10-15 years. *22nd International Workshop on HIV and Hepatitis Observational Databases (IWHOD),* Fuengirola, Spain.<br>· Increased burden of concordant and sequential anogenital high-risk human papillomavirus infections among Asian young adult females with perinatally acquired HIV compared to uninfected peers. *23rd International Workshop on HIV and Hepatitis Observational Databases (IWHOD),* Athens, Greece. | 0.50<br><br><br><br>0.50 |
| 2019 | Other oral presentation<br>· Invited debate: The development of an HIV vaccine is the best way to eliminate the HIV epidemic, *12th World Congress of the World Society for Pediatric Infectious Diseases (WSPID),* Manila, Philippines. | 0.50 |

| | **International conference attendance** | **ECTs Total: 10.64** |
|---|---|---|
| 2018 | 25th Conference on Retroviruses and Opportunistic Infections (CROI), Boston, USA | 1.00 |
| 2018 | 22nd International Workshop on HIV and Hepatitis Observational Databases (IWHOD), Fuengirola, Spain | 0.75 |
| 2018 | 3rd Asia Pacific AIDS & Co-infections Conference (APACC), Hong Kong SAR, China | 0.75 |
| 2018 | 10th International Workshop on HIV Pediatrics, Amsterdam, The Netherlands | 0.57 |
| 2018 | 22nd International AIDS Conference (AIDS 2018), Amsterdam, The Netherlands | 1.00 |
| 2019 | 26th Conference on Retroviruses and Opportunistic Infections (CROI), Seattle, USA | 1.00 |
| 2019 | 23rd International Workshop on HIV and Hepatitis Observational Databases (IWHOD), Athens, Greece | 0.75 |

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| 2019 | 4th Asia Pacific AIDS & Co-infections Conference (APACC), Hong Kong SAR, China | 0.75 |
| 2019 | 11th International Workshop on HIV Pediatrics, Mexico City, Mexico | 0.57 |
| 2019 | 10th IAS Conference on HIV Science (IAS 2019), Mexico City, Mexico | 0.86 |
| 2019 | 12th World Congress of the World Society for Pediatric Infectious Diseases (WSPID), Manila, Philippines (4h) | 0.14 |
| 2020 | 27th Conference on Retroviruses and Opportunistic Infections (CROI), Boston, USA (5h/d x3) | 0.54 |
| 2020 | 23rd International AIDS Conference (AIDS 2020), Virtual (3h/d x3) | 0.32 |
| 2020 | 5th Asia Pacific AIDS & Co-infections Conference (APACC), Virtual (4h/d x3) | 0.43 |
| 2021 | 28th Conference on Retroviruses and Opportunistic Infections (CROI), Virtual (4h/day x 4) | 0.57 |
| 2021 | 6th Asia Pacific AIDS & Co-infections Conference (APACC), Virtual (4h/d x 3) | 0.43 |
| 2021 | 11th IAS Conference on HIV Science (IAS 2021), Virtual (6h total) | 0.21 |

| | **Teaching** | **ECTs Total: 6.75** |
|---|---|---|
| 2018-2019 | Primary capstone research project mentor: Rhea Matthew, Masters of Global Health, University of California, San Francisco, USA<br>· Title: *Stigma and Discrimination Against HIV-Positive Adolescents and Young Adults in Bangkok, Thailand*<br>· Publication: Mathew RS, Boonsuk P, Dandu M, Sohn AH. Experiences with stigma and discrimination among adolescents and young adults living with HIV in Bangkok, Thailand. AIDS Care 2020 Apr;32(4):530-535. doi: 10.1080/09540121.2019.1679707. Epub 2019 Oct 18. | 2.50 |
| 2018, 2019, 2020, 2021 | Invited lectures (annual, N=4) on careers in global health, University of California, San Francisco, USA (4 hours each) | 0.57 |
| 2019 | Invited lecture on designing clinical research, CHIMERA D43 research training program, Thailand, virtual (4 h) | 0.14 |
| 2019 | Invited lecture on the path to global elimination of vertical transmission of HIV, congenital syphilis, and hepatitis B, University of California, San Francisco, USA, virtual (4 hours) | 0.14 |

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|---|---|---|
| | Invited lectures on scientific writing, responding to editorial feedback, and publishing (3 hours each) | |
| 2019, 2020, 2021 | International AIDS Society: Conference on HIV Science (IAS 2019), Mexico City, Mexico; International AIDS Conference (AIDS 2020), virtual; Conference on HIV Science (IAS 2021), Berlin, virtual; | 0.32 |
| 2020 | Bangkok Symposium, Thailand | 0.11 |
| 2020 | HIV and Adolescence workshop, virtual | 0.11 |
| 2020, 2021 | CHIMERA NIH D43 HIV research training program, Thailand, virtual | 0.21 |
| 2021 | Fogarty-IeDEA Mentorship Program, global, virtual | 0.11 |
| 2021 | International AIDS Society Educational Fund, Asia-Pacific, virtual | 0.11 |
| 2020 | Invited lecture on public speaking, CHIMERA D43 HIV research training program, Thailand, virtual (4 hours) | 0.14 |
| 2020-2021 | Primary capstone research project mentor: Sophie Ahmad, Masters of Global Health, University of California, San Francisco, USA<br>· Title: *The Impact of COVID-19 on HIV treatment and care delivery for adults in South and Southeast Asia* | 2.00 |
| 2021 | Invited lecture on academic publishing to PhD students of the Amsterdam Institute for Global Health and Development, The Netherlands, virtual | 0.11 |
| 2021 | Invited lecture on HIV research and program implementation through local partnerships to undergraduate students of the Mahidol University of International College, Thailand, virtual (5 h) | 0.18 |

# LIST OF PUBLICATIONS

From February 2018 through December 2021
PhD papers in bold


1. Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Global Cohort Collaboration, Slogrove AL, Schomaker M, Davies MA, Williams P, Balkan S, Ben-Farhat J, Calles N, Chokephaibulkit K, Duff C, Eboua TF, Kekitiinwa-Rukyalekere A, Maxwell N, Pinto J, Seage G 3rd, Teasdale CA, Wanless S, Warszawski J, Wools-Kaloustian K, Yotebieng M, Timmerman V, Collins IJ, Goodall R, Smith C, Patel K, Paul M, Gibb D, Vreeman R, Abrams EJ, Hazra R, Van Dyke R, Bekker LG, Mofenson L, Vicari M, Essajee S, Penazzato M, Anabwani G, Q Mohapi E, N Kazembe P, Hlatshwayo M, Lumumba M, Goetghebuer T, Thorne C, Galli L, van Rossum A, Giaquinto C, Marczynska M, Marques L, Prata F, Ene L, Okhonskaia L, Rojo P, Fortuny C, Naver L, Rudin C, Le Coeur S, Volokha A, Rouzier V, Succi R, **Sohn A**, Kariminia A, Edmonds A, Lelo P, Ayaya S, Ongwen P, Jefferys LF, Phiri S, Mubiana-Mbewe M, Sawry S, Renner L, Sylla M, Abzug MJ, Levin M, Oleske J, Chernoff M, Traite S, Purswani M, Chadwick EG, Judd A, Leroy V. The epidemiology of adolescents living with perinatally acquired HIV: A cross-region global cohort analysis. PLoS Med. 2018 Mar 1;15(3):e1002514.
2. **Slogrove AL, Sohn AH. The global epidemiology of adolescents living with HIV: time for more granular data to improve adolescent health outcomes. Curr Opin HIV AIDS. 2018 May;13(3):170-178.**
3. Wools-Kaloustian K, Marete I, Ayaya S, **Sohn AH**, Van Nguyen L, Li S, Leroy V, Musick BS, Newman JE, Edmonds A, Davies MA, Eboua FT, Obama MT, Yotebieng M, Sawry S, Mofenson LM, Yiannoutsos CT. Time to First-Line ART Failure and Time to Second-Line ART Switch in the IeDEA Pediatric Cohort. J Acquir Immune Defic Syndr. 2018 Jun 1;78(2):221-230.
4. Bartlett AW, Khanh TH, Songtaweesin WN, Chokephaibulkit K, Hansudewechakul R, Ly PS, Lumbiganon P, Sudjaritruk T, Van Lam N, Viet DC, Kumarasamy N, Yusoff NKN, Kurniati N, Fong MS, Wati DK, Nallusamy R, **Sohn AH**, Law MG, Mohamed TJ. Characteristics, mortality and outcomes at transition for adolescents with perinatal HIV infection in Asia. AIDS. 2018 Jul 31;32(12):1689-1697.
5. Mehta N, Ho J, Boonsuk P, Fuller S, **Sohn AH**. Investigating the role of stigma on fertility desire among HIV-positive women in Bangkok, Thailand: a qualitative study. J Virus Erad. 2018 Jul 1;4(3):165-169.
6. **Sohn AH, Judd A, Mofenson L, Vicari M, Jerene D, Leroy V, Bekker LG, Davies MA. Using Observational Data to Inform HIV Policy Change for Children and Youth. J Acquir Immune Defic Syndr. 2018 Aug 15;78 Suppl 1:S22-S26.**
7. Armstrong A, Nagata JM, Vicari M, Irvine C, Cluver L, **Sohn AH**, Ferguson J, Caswell G, Njenga LW, Oliveras C, Ross D, Puthanakit T, Baggaley R, Penazzato M. Global Research Agenda for Adolescents Living With HIV. J Acquir Immune Defic Syndr. 2018 Aug 15;78 Suppl 1:S16-S21.
8. Ciaranello A, **Sohn AH**, Collins IJ, Rothery C, Abrams EJ, Woods B, Pei P, Penazzato M, Mahy M. Simulation Modeling and Metamodeling to Inform National and International HIV Policies for Children and Adolescents. J Acquir Immune Defic Syndr. 2018 Aug 15;78 Suppl 1:S49-S57.
9. Aurpibul L, Kariminia A, Vibol U, Fong MS, Le ON, Hansudewechakul R, Bunupuradah T, Kurniati N, Chokephaibulkit K, Kumarasamy N, Wati DK, Yusoff NKN, Razali KAM, Nallusamy RA, **Sohn AH**, Lumbiganon P; TREAT Asia Pediatric HIV Observational Database (TApHOD) of IeDEA Asia-Pacific. Seroprevalence of Hepatitis B among HIV-infected Children and Adolescents Receiving Antiretroviral Therapy in the TREAT Asia Pediatric HIV Observational Database. Pediatr Infect Dis J. 2018 Aug;37(8):788-793.
10. **Sohn AH, Kerr SJ, Hansudewechakul R, Gatechompol S, Chokephaibulkit K, Dang HLD, Tran DNH, Achalapong J, Teeratakulpisarn N, Chalermchockcharoenkit A, Thamkhantho M, Pankam T, Singtoroj T, Termrungruanglert W, Chaithongwongwatthana S, Phanuphak N; HPV in Adolescents Study. Risk Factors for Human Papillomavirus Infection and Abnormal Cervical Cytology Among Perinatally Human Immunodeficiency Virus-Infected and Uninfected Asian Youth. Clin Infect Dis. 2018 Aug 1;67(4):606-613. doi: 10.1093/cid/ciy144.**

**11.** **Sohn AH**, Ross J, Wainberg ML. Barriers to mental healthcare and treatment for people living with HIV in the Asia-Pacific. J Int AIDS Soc. 2018 Oct;21(10):e25189.

12. Zaniewski E, Tymejczyk O, Kariminia A, Desmonde S, Leroy V, Ford N, **Sohn AH**, Nash D, Yotebieng M, Cornell M, Althoff KN, Rebeiro PF, Egger M. IeDEA-WHO Research-Policy Collaboration: contributing real-world evidence to HIV progress reporting and guideline development. J Virus Erad. 2018 Nov 15;4(Suppl 2):9-15.

13. Nash D, Yotebieng M, **Sohn AH**. Treating all people living with HIV in sub-Saharan Africa: a new era calling for new approaches. J Virus Erad. 2018 Nov 15;4(Suppl 2):1-4.

**14. Kariminia A, Law M, Davies MA, Vinikoor M, Wools-Kaloustian K, Leroy V, Edmonds A, McGowan C, Vreeman R, Fairlie L, Ayaya S, Yotebieng M, Takassi E, Pinto J, Adedimeji A, Malateste K, Machado DM, Penazzato M, Hazra R, Sohn AH; IeDEA. Mortality and losses to follow-up among adolescents living with HIV in the IeDEA global cohort collaboration. J Int AIDS Soc. 2018 Dec;21(12):e25215**

15. Yotebieng M, Brazier E, Addison D, Kimmel AD, Cornell M, Keiser O, Parcesepe AM, Onovo A, Lancaster KE, Castelnuovo B, Murnane PM, Cohen CR, Vreeman RC, Davies MA, Duda SN, Yiannoutsos CT, Bono RS, Agler R, Bernard C, Syvertsen JL, Sinayobye JD, Wikramanayake R, **Sohn AH**, von Groote PM, Wandeler G, Leroy V, Williams CF, Wools-Kaloustian K, Nash D; IeDEA Treat All in sub-Saharan Africa Consensus Statement Working Group. Research priorities to inform "Treat All" policy implementation for people living with HIV in sub-Saharan Africa: a consensus statement from the International epidemiology Databases to Evaluate AIDS (IeDEA). J Int AIDS Soc. 2019 Jan;22(1):e25218.

16. Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Global Cohort Collaboration. Incidence of switching to second-line antiretroviral therapy and associated factors in children with HIV: an international cohort collaboration. (group authors) Lancet HIV. 2019 Feb;6(2):e105-e115.

17. Bartlett AW, Mohamed TJ, Sudjaritruk T, Kurniati N, Nallusamy R, Hansudewechakul R, Ly PS, Truong KH, Lumbiganon P, Puthanakit T, Chokephaibulkit K, Nguyen LV, Do VC, Kumarasamy N, Nik Yusoff KN, Fong MS, Wati DK, **Sohn AH**, Kariminia A; TREAT Asia Pediatric HIV Observational Database of IeDEA Asia-Pacific. Disease- and Treatment-Related Morbidity in Adolescents with Perinatal HIV Infection in Asia. Pediatr Infect Dis J. 2019 Mar;38(3):287-292. doi: 10.1097/INF.0000000000002208.

18. Mu W, Bartlett AW, Bunupuradah T, Chokephaibulkit K, Kumarasamy N, Ly PS, Hansudewechakul R, Van Lam N, Lumbiganon P, Sudjaritruk T, Jamal Mohamed TA, Nik Yusoff NK, Khanh TH, Viet DC, Fong MS, Nallusamy R, Kurniati N, Wati DK, **Sohn AH**, Kariminia A, Zhang F; TREAT Asia Pediatric HIV Observational Database of IeDEA Asia-Pacific. Early and late virologic failure following virologic suppression in HIV-infected Asian children and adolescents. J Acquir Immune Defic Syndr. 2019 Mar 1;80(3):308-315. doi: 10.1097/QAI.0000000000001921.

19. Ross JL, Teeraananchai S, Lumbiganon P, Hansudewechakul R, Chokephaibulkit K, Khanh TH, Van Nguyen L, Mohamed TAJ, Yusoff NKN, Fong MS, Prasitsuebsai W, **Sohn AH**, Kerr SJ. A Longitudinal Study of Behavioral Risk, Adherence, and Virologic Control in Adolescents Living With HIV in Asia. J Acquir Immune Defic Syndr. 2019 Jun 1;81(2):e28-e38.

**20. Sohn AH, Boonsuk P, Andrade C, Ananworanich J, Mark D. Identifying gaps in adolescent HIV care and treatment delivery in Asia: results of a regional health provider survey. Vulnerable Children and Youth Studies. 2019;14:2,166-180, DOI: 10.1080/17450128.2019.1576958.**

21. Sudjaritruk T, Boettiger DC, Nguyen LV, Mohamed TJ, Wati DK, Bunupuradah T, Hansudewechakul R, Ly PS, Lumbiganon P, Nallusamy RA, Fong MS, Chokephaibulkit K, Nik Yusoff NK, Truong KH, Do VC, **Sohn AH**, Sirisanthana V; TREAT Asia Pediatric HIV Observational Database of IeDEA Asia-Pacific. Impact of the frequency of plasma viral load monitoring on treatment outcomes among children with perinatally acquired HIV. J Int AIDS Soc. 2019 Jun;22(6):e25312.

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infection and high-grade anal lesions in women: a collaborative pooled analysis. Lancet Infect Dis. 2019 Aug;19(8):880-891.

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24. Schröeder SE, Pedrana A, Scott N, Wilson D, Kuschel C, Aufegger L, Atun R, Baptista-Leite R, Butsashvili M, El-Sayed M, Getahun A, Hamid S, Hammad R, 't Hoen E, Hutchinson SJ, Lazarus JV, Lesi O, Li W, Binti Mohamed R, Olafsson S, Peck R, **Sohn AH**, Sonderup M, Spearman CW, Swan T, Thursz M, Walker T, Hellard M, Howell J. Innovative strategies for the elimination of viral hepatitis at a national level: A country case series. Liver Int. 2019 Aug 21. doi: 10.1111/liv.14222.
25. Mathew RS, Boonsuk P, Dandu M, **Sohn AH**. Experiences with stigma and discrimination among adolescents and young adults living with HIV in Bangkok, Thailand. AIDS Care. 2019 Oct 18:1-6.
26. Boettiger DC, Law MG, **Sohn AH**, Davies MA, Wools-Kaloustian K, Leroy V, Yotebieng M, Vinikoor M, Vreeman R, Amorissani-Folquet M, Edmonds A, Fatti G, Batte J, Renner L, Adedimeji A, Kariminia A; International Epidemiology Databases to Evaluate AIDS. Temporal Trends in Co-trimoxazole Use Among Children on Antiretroviral Therapy and the Impact of Co-trimoxazole on Mortality Rates in Children Without Severe Immunodeficiency. J Pediatric Infect Dis Soc. 2019 Nov 6;8(5):450-460. doi: 10.1093/jpids/piy087.
27. Bartlett AW, Lumbiganon P, Kurniati N, Sudjaritruk T, Mohamed TJ, Hansudewechakul R, Ly PS, Truong KH, Puthanakit T, Nguyen LV, Chokephaibulkit K, Do VC, Kumarasamy N, Nik Yusoff NK, Fong MS, Watu DK, Nallusamy R, **Sohn AH**, Law MG; TREAT Asia Pediatric HIV Observational Database of IeDEA Asia-Pacific. Use and Outcomes of Antiretroviral Monotherapy and Treatment Interruption in Adolescents With Perinatal HIV Infection in Asia. J Adolesc Health. 2019 Nov;65(5):651-659. doi: 10.1016/j.jadohealth.2019.05.025.
28. Bartlett AW, Lumbiganon P, Jamal Mohamed TA, Lapphra K, Muktiarti D, Du QT, Hansudewechakul R, Ly PS, Truong KH, Van Nguyen L, Puthanakit T, Sudjaritruk T, Chokephaibulkit K, Do VC, Kumarasamy N, Nik Yusoff NK, Kurniati N, Fong MS, Wati DK, Nallusamy R, **Sohn AH**, Kariminia A; TREAT Asia Pediatric HIV Observational Database of IeDEA Asia-Pacific. Dual Analysis of Loss to Follow-up for Perinatally HIV-Infected Adolescents Receiving Combination Antiretroviral Therapy in Asia. J Acquir Immune Defic Syndr. 2019 Dec 15;82(5):431-438.
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32. Tsondai PR, **Sohn AH**, Phiri S, Sikombe K, Sawry S, Chimbetete C, Fatti G, Hobbins MA, Technau KG, Rabie H, Bernheimer J, Fox MP, Judd A, Collins IJ, Davies MA; International epidemiology to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration. Characterizing the double-sided cascade of care for adolescents living with HIV transitioning to adulthood across Southern Africa. J Int AIDS Soc. 2020 Jan;23(1):e25447.

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## ABOUT THE AUTHOR

Annette Haeran Sohn was born in the US to parents from South Korea. She attended Wellesley College for her undergraduate studies in history, and the University of California, Los Angeles, for medical school. She completed her residency in Pediatrics at the University of California, San Francisco (UCSF). She then joined the Epidemic Intelligence Service of the US Centers for Disease Control and Prevention in Atlanta, serving in the Commissioned Corps of the US Public Health Service. Her training continued with a clinical fellowship in Pediatric Infectious Diseases at UCSF.

After joining the faculty of the Division of Pediatric Infectious Diseases at UCSF, she moved to Ho Chi Minh City, Vietnam, where she conducted research on pediatric HIV in collaboration with Children's Hospital 1. In 2008, she became Vice President of Global Initiatives for amfAR – The Foundation for AIDS Research, to direct their TREAT Asia program, based in Bangkok, Thailand. In that role, she oversees the implementation of TREAT Asia's research, education and training, and community advocacy and policy activities that address the regional impact of HIV and related co-infections and co-morbidities through a network of over 50 program partners across 13 Asia-Pacific countries. She retains a faculty appointment as an Associate Clinical Professor in the Department of Pediatrics at UCSF.

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