Characteristics and outcomes of adolescents living with HIV transitioning to adulthood in different health care models across Southern Africa

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February 2025

Declaration

This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) in the School of Public Health, Faculty of Health Sciences, University of Cape Town. The work on which this thesis is based is original research and has not, in whole or in part, been submitted for another degree at this or any other university. The contents of this thesis are entirely the work of the candidate, or in the case of multi-authored published papers, constitutes work for which the candidate was the lead author. The contribution of the candidate to included multi-authored papers is further delineated in the preface to the thesis and in the introduction to each included paper as appropriate.

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February 2025

Declaration on the Inclusion of Publications in a PhD Thesis

This thesis includes published manuscripts, as per general provision 6.7 in the General Rules for the Degree of Doctor of Philosophy (PhD) of the University of Cape Town. I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publications in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include these publications. The following three published papers are included in the thesis, and are presented as self-contained chapters in the following order:

1. **Tsondai PR**, Davies MA, Singtoroj T, Maxwell N, McGowan CC, Songtaweesin WN, et al.; IeDEA Consortium. Improving Methods to Classify Perinatal versus Nonperinatal HIV Acquisition in Young Adolescents 10-14 Years of Age. *Pediatric Infectious Disease Journal*. 2021; 40(5): 453-456
2. **Tsondai PR**, Braithwaite K, Fatti G, Bolton Moore C, Chimbetete C, Rabie H, et al. Characteristics and outcomes of adolescents living with perinatally acquired HIV within Southern Africa. *AIDS* 2020; 34(15): 2275-2284
3. **Tsondai PR**, Sohn AH, Phiri S, Sikombe K, Sawry S, Chimbetete C, et al.; 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. *Journal of the International AIDS Society* 2020; 23(1): e25447

I further confirm that l have included the following manuscript which was published after the University of Cape Town's Doctoral Degrees Board had granted me permission to include publications in my PhD thesis. All the co-authors gave permission to include this manuscript in my PhD thesis.

4. **Tsondai PR**, Davies M-A, Singtoroj T, Maxwell N, Technau K-G, Chokephaibulkit K, et al. Creating a data collection and management platform to support measurement of adolescent HIV care transition processes within low- and middle-income countries: The GRADUATE project. *PLOS Glob Public Health* 2024; 4(8): e0002705

The contribution of the candidate to each manuscript is outlined at the start of each chapter. The candidate was the lead and corresponding author on all manuscripts, prepared the datasets for analysis, conducted all analyses, and drafted all versions of the manuscripts. All coauthors reviewed and approved the submitted manuscripts, and the candidate reviewed co-author comments and integrated them into the manuscripts prior to submission.

Acknowledgement

I wish to express my deepest gratitude to everyone who supported me throughout the journey of completing this dissertation.

First and foremost, I extend my heartfelt thanks to my supervisor, Professor Mary-Ann Davies, for her unwavering guidance, constant support, insightful feedback, and most importantly, for her patience. I am deeply grateful for the opportunity to engage in HIV cohort research through IeDEA and GRADUATE. Your expertise and mentorship have been invaluable, and l appreciate the time and effort you dedicated to helping me succeed.

I also wish to thank Dr. Annette Sohn for inspiring me to strive for excellence in all that I do. Your scientific leadership, encouragement, and support have been instrumental in my growth. Thank you for entrusting me with the project management of the GRADUATE project and for always expecting the best from me.

To the IeDEA investigators, and the staff at the IeDEA Southern Africa Data Centres, notably Dr. Morna Cornell and Ms. Nicola Maxwell, l am truly grateful for the knowledge and experience I have gained from working with you. Thank you to the staff at each of the IeDEA collaborating sites for co-ordinating data collection and for your valuable input. I am deeply appreciative of the children, adolescents, youth, and caregivers who contributed data for these analyses; this work would not have been possible without you

My heartfelt appreciation goes to my family and friends, whose love, patience, and unwavering support have sustained me through the challenges of this journey. To my siblings, Tapiwa, Carol, Dennis, Munashe, and Stompy thank you for always believing in me and being my source of strength. To my friends, Tsungai, Lindani, Thoko, Agnes, Mark, Anna, Katie, Kathleen, Alexis and Christa, your encouragement kept me going, even when the road seemed insurmountable.

To my parents, Webster and Naume Tsondayi, you believed in me long before I believed in myself. Your sacrifices have brought me to where I am today, and I am truly blessed to have you as my parents.

Finally, to my husband, Velaphi, and my children, Anthony and Anashe – we did it! You have been my source of inspiration, teaching me to believe in myself and to persevere. I love you dearly.

Thank you all for being a part of this journey.

List of abbreviations

AALPHI	Adolescents & Adults Living with Perinatal HIV
AHOD	Australian HIV Observational database
aHR	adjusted hazard ratio
AIDS	Acquired immunodeficiency syndrome
aOR	adjusted odds ratio
aRR	adjusted risk ratio
ART	antiretroviral therapy
AYLH	adolescents and young adults living with HIV
amfAR	The Foundation for AIDS Research
AUROC	area under the receiver operating characteristic curve
BAZ	body mass index-for-age z-score
BD2K	Big Data to Knowledge
BMI	body mass index
CCASAnet	Caribbean, Central and South America network for HIV epidemiology
CHC	community health centre
CI	confidence interval
CIDER	Centre for Integrated Data and Epidemiological Research
CIPHER	Collaborative Initiative for Paediatric HIV Education and Research
CMIS	Centre Maternel et Infantile sur le SIDA
CTAAC	Cape Town Adolescent Antiretroviral Cohort
DAG	directed acyclic graphs
DES	data exchange standard
DSD	differentiated service delivery
DTP	data transfer protocol
EMS	electronic monitoring system
GRADUATE	Global fRAmework of Data collection Used for Adolescent HIV Transition Evaluation
HAZ	height-for-age z-score
HR	hazards ratio
HIV	Human immunodeficiency virus
HIVRN	HIV Research Network
HICDEP	HIV Cohorts Data Exchange Protocol
IAS	International AIDS Society
IeDEA	International epidemiology Database to Evaluate AIDS
IQR	inter-quartile range

IRB	Institutional Review Board
LMICs	low- and middle-income countries
LTFU	loss to follow-up
N/A	not applicable
NHLS	National Health Laboratory Service
MSF	Médecins Sans Frontières
NNRTI	non-nucleoside reverse transcriptase inhibitor
NR	not recorded
PATA	Paediatric-Adolescent Treatment Africa
PEPFAR	President's Emergency Plan for AIDS Relief
PHACS	Pediatric HIV/AIDS Cohort Study
PHDC	Provincial Health Data Centre
PI	protease inhibitor
REDCap	Research Electronic Data Capture
SD	standard deviation
STAY	Study of Transitioning Asian Youth
STI	sexually transmitted infection
TAHOD	TREAT Asia HIV Observational Database
TFO	transfer out
TREAT Asia	Therapeutics Research, Education, and AIDS Training in Asia
UCT-HREC	University of Cape Town Faculty of Health Sciences Human Research Ethics Committee
UNAIDS	United Nations Joint Programme on HIV/AIDS
WHO	World Health Organization

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Chapter 1: Introduction

1.1 Overview

Adolescents and young people constitute an increasing proportion of the global population living with HIV, relative to younger children, reflecting the shift in the burden of paediatric HIV towards older age groups. In 2023, out of the estimated 39.9 million people living with HIV worldwide, approximately 1.5 million are adolescents aged between 10 to 19 years (1). Notably, a substantial majority of these individuals, around 1.28 million (85%), reside in sub-Saharan Africa. The emergence of this cohort of young people living with HIV can be attributed to various factors. Firstly, the increased availability and accessibility of antiretroviral therapy (ART) has resulted in a growing number of children with perinatally acquired HIV surviving into adolescence and beyond. Concurrently, new HIV infections continue to occur among young people, with over one-third of all new cases in 2023 occurring among adolescents and young people (1). Over the course of that year alone, 500,000 young people between the ages of 10 to 24 had newly acquired HIV, with 140,000 of them falling within the 10 to 19-year range (2). Sub-Saharan Africa bears the brunt of this HIV incidence among adolescents and young people, accounting for nearly 70% of the new infections in this age group (3). Lastly, a number of children with perinatally acquired HIV with slow-progressing disease that survived without treatment present for the first-time during adolescence (4,5).

HIV in adolescence

Adolescence is a transformative phase characterized by significant physical, mental, physiological, and social development. During this period, the body undergoes puberty, a complex biological process involving hormonal and physical changes that lead to physical growth and sexual maturity. Simultaneously, the brain goes through substantial structural maturation, starting with sensory areas and progressing to regions responsible for coordination, decision-making, problem-solving, and critical thinking, which fully develop in the mid-twenties (6,7). As a result, complex cognitive processes including judgment, behavioural control, planning, and risk assessment mature later, making adolescence a phase of experimentation and risk-taking while progressively becoming more independent (6,7).

Adolescents living with chronic diseases navigate this intricate and transformative stage with the added responsibilities of managing their health conditions. They must adhere to medical appointments and medications and may engage in risky behaviours that are typical of adolescent development, but that carries additional health risks for them (8). The World Health Organization (WHO) has recognized that individuals with chronic diseases associated with stigma or discrimination are at a higher risk of mental health issues (9). Adolescents living with chronic conditions, such as HIV, encounter similar challenges

to their peers during this period. However, the changes and complexities that characterize adolescence are further compounded as they also navigate the management of a chronic, often stigmatized disease (10,11).

In addition to the physical, emotional, and psychosocial challenges faced by all adolescents, adolescents and young adults living with HIV (AYLH) face unique obstacles. These include initiating or continuing lifelong ART, managing drug side-effects, disclosing their HIV status, and coping with mental health challenges associated with living with a stigmatized chronic illness (12–14). These challenges impact the quality of life and social relationships of adolescents, making them more susceptible to disease complications and mortality (12).

The current population of AYLH is comprised of two distinct sub-groups: those who acquired HIV perinatally (in utero, during birth or postnatally through breastfeeding) and those who acquired it non-perinatally (e.g. through consensual or non-consensual sexual contact, intravenous drug use, blood transfusion). While there are similarities, these groups often differ in terms of disease characteristics, socio-demographic factors, vulnerabilities, and risk behaviours, potentially leading to different outcomes (15–17). Adolescents with perinatally acquired HIV possess unique characteristics compared to those with more recent infection. Firstly, they were exposed to HIV at a very early stage of life before their immune systems were fully developed. During their childhood, they were managed during the earlier phases of ART treatment programs when treatment initiation criteria were more restrictive, paediatric antiretroviral options limited, and suboptimal mono- and dual-therapy regimens were sometimes used in certain countries (18,19). Consequently, some were exposed to untreated or sub-optimally treated HIV for extended periods, leading to prolonged viral replication, chronic inflammation, and resulting complications from HIV infection itself or the effects of antiretroviral drugs.

Research has shown that adolescents with perinatally acquired HIV, particularly those who initiated HIV care with advanced disease, experience decreased growth and delays in pubertal onset. These effects can be attributed to the overall impact of chronic illness, recurrent infections, chronic immune activation, and the influence of HIV on the hormones that regulate and control pubertal initiation (20). Additionally, metabolic, and cardiovascular abnormalities, chronic lung diseases, altered bone metabolism, renal complications, skin diseases, abnormal fat distribution, and cognitive impairment have been reported among this group (4,21–26).

Outcomes among adolescents living with HIV

In 2014, the United Nations Joint Programme on HIV/AIDS (UNAIDS) launched the 90-90-90 targets as part of their global HIV treatment scale-up strategy These targets aimed for 90% of people living with HIV to know their status, 90% of those who know their status to receive sustained ART, and 90%

of those on treatment to achieve viral suppression by 2020 (27). To further accelerate progress towards ending AIDS by 2030, UNAIDS introduced the Fast-Track agenda in 2020, which raised the targets to 95-95-95 (28). However, the current trends suggest that achieving these Fast-Track targets for AYLH is unlikely.

Evidence indicates that the HIV response has generally overlooked AYLH, focusing primarily on adults, infants, and young children. Research studies and programs often exclude or inadequately address the unique needs of adolescents, frequently grouping them with either children or adults (e.g., reporting in the age bands of 0–15 years, 15+ years). Compared to young children and adults living with HIV, AYLH tend to experience poorer outcomes. They face significant challenges in accessing ART, achieving viral suppression, and retaining engagement in care (29–40). Rates of treatment failure and the need for switching to second-line regimens are three times higher for adolescents than adults (41) 2023, it was estimated that nearly 70 adolescents were dying from AIDS-related causes every day, with over 90% of these deaths occurring in sub-Saharan Africa (1). AYLH exhibit significant drop-offs throughout the HIV care cascade, both prior to and following ART initiation (33,34,37,42). This is concerning, as delayed initiation leads to declining immune function that may go unrecognised. Additionally, poor retention prior to or following ART initiation allows uncontrolled HIV viral replication, leading to advanced HIV disease and an increased risk of onward transmission. Suboptimal adherence to ART results in the emergence of drug-resistant strains and an elevated risk of HIV-related morbidity and mortality (43). Interventions targeting factors that hinder AYLH from achieving viral suppression and maintaining engagement in care are crucial to ensure positive outcomes in this growing population.

One strategy to address these challenges has been the implementation of differentiated models of care throughout the continuum of HIV care, encompassing the period before, during, and after ART initiation. Differentiated service delivery (DSD) models are client-centred approaches that simplify HIV services to align with the preferences and expectations of different groups of people with HIV, while also reducing the burden on healthcare systems (44). DSD models that enhance ART management efficiency by reducing visit frequency, streamlining drug collection mechanisms, minimizing unnecessary clinical follow-up visits, and incorporating peer support have shown improved retention and viral suppression outcomes (45–47). However, most of the research on DSD models has focused on the outcomes of stable adult patients who are already virally suppressed, tolerant to their medication regimens, and fully adherent (46). It is crucial to expand the research on models of care within developing countries that specifically target AYLH at various stages of the HIV care continuum. It is widely acknowledged that healthcare systems should provide youth-friendly services, peer support, flexible opening hours, integrated care, and support for HIV status disclosure to both caregivers and AYLH (48). Nonetheless, there is a significant lack of data on patient outcomes related to models of care tailored for AYLH in developing countries.

Transition of adolescents and young adults living with HIV to adulthood

As AYLH mature into adulthood, their healthcare needs undergo significant changes. They are expected to take on increasing responsibility for their own healthcare and transition from child-centred to adult-centred healthcare. They are expected to increasingly become self-reliant, making decisions about their health, scheduling and attending clinic appointments independently, managing their medications, and directly communicating with healthcare providers about any challenges or side effects they may experience. Healthcare providers in these settings must recognize the need for greater autonomy among these young individuals and provide services that are appropriate for their age and developmental stage. For those who have relied on adult caregivers throughout their paediatric care, this period entails assuming self-reliance in managing their HIV care (15,49).

Healthcare transition is defined as the purposeful and planned movement of adolescents and young people with chronic medical conditions from child-centred to adult-oriented healthcare systems (50). The goal is to empower adolescents to self-manage their disease while ensuring uninterrupted, coordinated, developmentally appropriate, and psychosocially sound healthcare services (11). Transitioning healthcare from paediatric to adult settings is not exclusive to HIV but has been occurring for adolescents living with other chronic illnesses including juvenile-onset diabetes mellitus, congenital heart disease, sickle cell disease and cystic fibrosis (51,52).

In developed countries, children living with HIV are managed within dedicated paediatric/adolescent clinics throughout adolescence and sometimes into young adulthood. The transition from adolescent HIV care often involves transferring from specialist paediatric HIV care to an adult clinic, typically between the ages of 18 and 24 years, coinciding with the developmental shift toward adulthood. This transition is often conducted through a systematic and structured process (53–56). This transition phase, therefore, involves a change in the physical environment as well as a change in healthcare providers, together with the shift in balance of responsibility and reliance. Guidelines for transitioning youth with chronic diseases to adult health care have been published by organizations like the Society for Adolescent Health and Medicine and the American Academy of Paediatrics, with resources developed by centres such as the US-based Got transition (57). These guidelines serve as widely accepted benchmarks and provide a framework for the transition of youth living with HIV, including the following major steps:

i. Development of a formal written transition policy by the current healthcare provider in collaboration with the adult HIV care providers, outlining the goals and timeline of the transition.
ii. Introduction of the concept of transition to the youth and their family during early adolescence, considering their stage of development and neurocognitive abilities, before the

actual transfer takes place (58). It involves fully disclosing the HIV status to the adolescent and providing explanations. Readiness assessment tools may also be used.

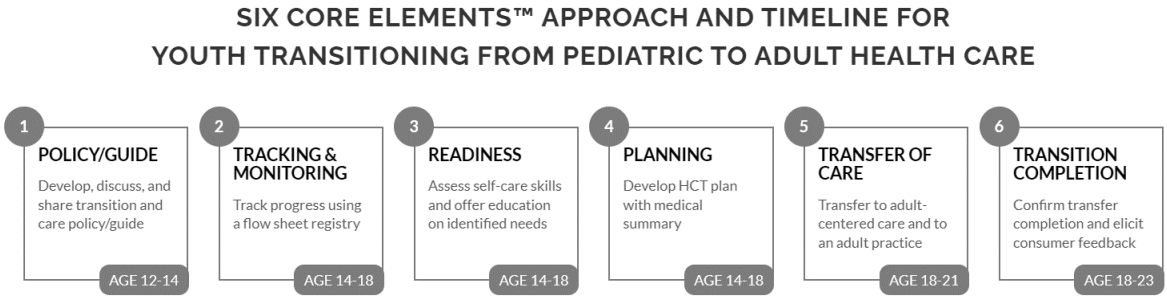
iii. Collaboration with the AYLH and their family to develop an individualized written transition plan by the referring provider, setting realistic goals to empower the youth to assume responsibility for their own healthcare.

iv. Initiation of the actual transition to adult healthcare, which may involve a pre-transfer visit to meet the adult healthcare provider. Appropriate documentation, including a transfer letter, should be shared with the adult healthcare provider.

v. Completion of the transition, with documentation of the process and outcomes, including confirmation that the young adult has established care in the adult clinic (59).

An example of these core elements is summarized in Figure 1.1.

Figure 1.1 Six core elements of healthcare transition



**Adapted from the US-based Got transition US national resource center on health care transition (www.gottransition.org/).*

The applicability and use of these guidelines within resource-limited setting where healthcare transition for AYLH does not generally involve a change in the facility or healthcare providers needs to be determined.

HIV status disclosure and its role in HIV healthcare transition

HIV status disclosure is a complex and multi-layered process that encompasses being informed of one's own HIV status as well as the process of disclosing one's own HIV status to others. It is not a one-time event, but rather a fluid, iterative, and evolving process that requires continuous adaptation to the individual's developmental maturity, readiness, social context and the evolving capacity to make decisions about their own health (60).

WHO recommends that children advance through a planned and structured disclosure process, with younger children receiving age-appropriate, incremental information to accommodate their cognitive skills and emotional maturity, in preparation for full disclosure at an older age (61). Furthermore, WHO outlines key principles for effective disclosure, including people-centred care, informed consent, respect for privacy and autonomy, the child's best interest, doing no harm, and prioritizing mental health and well-being (62). However, despite these guidelines, global rates of disclosure remain low due to a range of individual, relational, and systemic barriers (62).

Caregivers frequently experience uncertainty disclosing the HIV status to a child or adolescent, fearing negative consequences from disclosure, such as psychological problems, stigma, inability to comprehend and deal with the diagnosis, and unintended disclosure to others (63). This is especially so for those who acquired HIV perinatally. These concerns can lead to delayed or partial disclosure. In contrast, AYLH with horizontally acquired HIV may already know their HIV status and instead require tailored support to navigate disclosure to peers, family members, and partners.

Healthcare providers, too, face challenges in facilitating disclosure, including limited time, lack of training, and uncertainty about how to engage adolescents and caregivers in a sensitive and supportive manner. As a result, disclosure is often delayed, poorly supported, or approached inconsistently across settings (64).

In the context of healthcare transition, full disclosure is often considered a key milestone for initiating transition-related planning. Being aware of one's HIV status is a basic prerequisite for healthcare transition as it lays the groundwork for assuming responsibility and participating meaningfully in health-related decision-making. It is a critical first step to building health literacy and promoting autonomy among AYLH (64). It is foundational to the success of adolescent healthcare transition as it enables young people to understand their HIV status, fosters agency, and supports long-term engagement in care. Missed opportunities for disclosure can hinder adolescents' ability to adopt essential self-management practices and impedes timely transition planning.

Research highlights that early and well-supported HIV status disclosure among AYLH prior to transitioning to adult care enhances engagement in care (65). Disclosure reduces stigma and secrecy, enabling adolescents to access vital social support and fostering open communication around adherence. This process supports self-acceptance, reinforces self-worth, and strengthens personal relationships which in turn improve mental health, foster a sense of belonging and promote sustained engagement in care. In contrast, delayed or inadequate disclosure, or the inability to disclose to others, can negatively impact care engagement and psychosocial well-being (65).

A life course perspective on disclosure acknowledges that adolescents' needs and priorities evolve over time. It emphasizes the importance of linking early disclosure approaches with those that support adolescents as they navigate disclosure within broader familial, social, and sexual networks.

For AYLH, disclosure is a critical step in the care continuum with direct implications for treatment adherence, retention in care, psychosocial well-being, prevention, and successful transition to adult HIV care (66). Integrating disclosure and transition support can help adolescents build confidence, self-efficacy, and support networks. Few interventions designed for adolescents living with HIV target onwards disclosure specifically, limiting opportunities to recognize adolescents' growing autonomy and help them reflect on navigating risks and benefits.

1.2 Problem statement and rationale

The recognition of an emerging cohort of young individuals living with HIV is indisputable. Nevertheless, there exists a notable dearth of understanding concerning the identification and timing of their transition to adulthood within the sub-Saharan Africa context. Although progress has been made in research on the transition of AYLH into adult care within high income nations, the field remains in its nascent stages in low- and middle-income countries (LMICs), where most of this population resides. Particularly concerning is the lack of information regarding the outcomes experienced by AYLH as they progress into adulthood in settings where the transition to adulthood necessitates the assumption of greater responsibility for their healthcare, without the physical transfer of care from paediatric or adolescent clinics to specialized adult HIV clinics, as may be the prevalent scenario within sub-Saharan Africa.

To effectively evaluate and compare transition outcomes, it is imperative to establish optimal measurement approaches and implement comprehensive data collection practices across diverse settings. Collaborative initiatives such as the International AIDS Society's Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) and the International Epidemiologic Databases to Evaluate AIDS (IeDEA) Collaboration have played substantial roles in utilizing large data to address pivotal questions. However, these initiatives have not adequately prioritized variables that capture transition preparation, implementation, and post-transition outcomes. National programs and research cohorts in LMICs have made limited efforts to document the transition experience and associated factors. Moreover, the absence of a standardized approach to measure and compare transition-related processes and outcomes across different settings severely impedes the surveillance of outcomes specific to transitioning adolescents. Without capturing data on transitioning youth, overwhelmed healthcare systems in resource-limited settings could lose valuable information to inform transition policy and practice. Failure to adequately quantify and report on this population may reduce the urgency for policymakers to advocate for and support interventions that improve outcomes for adolescents living with HIV. It is important to establish an evaluated, dedicated, and comprehensive platform that effectively documents the clinical, social, psychological, and economic outcomes that are unique to adolescents before, during, and after the transition to adult healthcare.

Furthermore, most studies that have scrutinized transition-related outcomes have predominantly focused on post-transition outcomes, paying limited attention to the engagement in care among transitioning youth during the pre-transition period. Given that transitioning adolescents often undergo a protracted period of HIV care and ART prior to the formal transition, it is necessary to establish a comprehensive "adolescent transition cascade" that assesses outcomes both preceding and succeeding this critical phase.

There is a subset of adolescents with perinatally acquired HIV who present for care during adolescence after surviving without treatment due to slow-progressing infection. There is a paucity of data regarding the specific numbers, characteristics, and outcomes of this group in comparison to those who seek care at an earlier stage. Additionally, it would be useful to develop innovative approaches to accurately differentiate AYLH who acquired HIV perinatally from those who acquired it non-perinatally, as relying solely on age cut-offs may result in erroneous classification and information on likely mode and timing of HIV acquisition may not have been collected or may not be readily available.

Therefore, there is a need for comprehensive longitudinal studies that track AYLH. Employing quantitative research methods that combine data using linked medical records will provide a more nuanced understanding of the complex transition process. Encouraging collaboration and networking among researchers across different countries could foster development of standardized measurement tools that accurately assess transition-related processes and outcomes. This will enhance the comparability of data across various studies and settings, facilitating a more comprehensive analysis of the factors that influence successful transitions.

1.3 Aim and Objectives

The primary aim of this thesis is to provide a comprehensive description of the characteristics and outcomes of AYLH throughout the adolescent transition cascade, accessing HIV care through different healthcare models within Southern Africa. Additionally, it aims to identify the factors that contribute to these outcomes. The analyses are not causal in nature; they explore associations that are critical for understanding the transition experience and informing improvements in care.

Given the limited availability of standardized measurement tools that accurately assess transition-related processes and outcomes in resource-limited settings, this thesis also endeavours to develop and pilot a widely applicable and accessible data collection and management platform that will facilitate the measurement of transition processes and outcomes in adolescent HIV care.

The specific objectives include:

1. Developing an algorithm that determines the likely mode of HIV acquisition for adolescents living with HIV who enrol into HIV care between the ages of 10 and 15 years.
2. Evaluating the characteristics and outcomes of adolescents living with HIV in Southern Africa and the determinants that influence these outcomes through three main analyses:
    a. Describing the characteristics and outcomes of adolescents living with HIV in Southern Africa and ascertaining the determinants that influence these outcomes.
    b. Describing the characteristics and outcomes of AYLH receiving care in a differentiated model of care and those receiving routine care during transition to adulthood using linked electronic medical records data.
    c. Assessing the continuum of care for AYLH throughout the adolescent transition cascade and identifying the factors associated with gaps in care and virologic outcomes.
3. Designing a data collection and management platform that effectively captures transition-related processes and outcomes of AYLH within resource-limited countries by:
    a. Identifying key data variables and data definitions that capture the process of transition, its predictors, and the outcomes across the transition period, and creating data tables and tools to facilitate data collection.
    b. Evaluating the feasibility and utility of the data-capturing tools.

1.4 Data Sources

To address the aim and objectives of the research, analyses were conducted using a combination of:

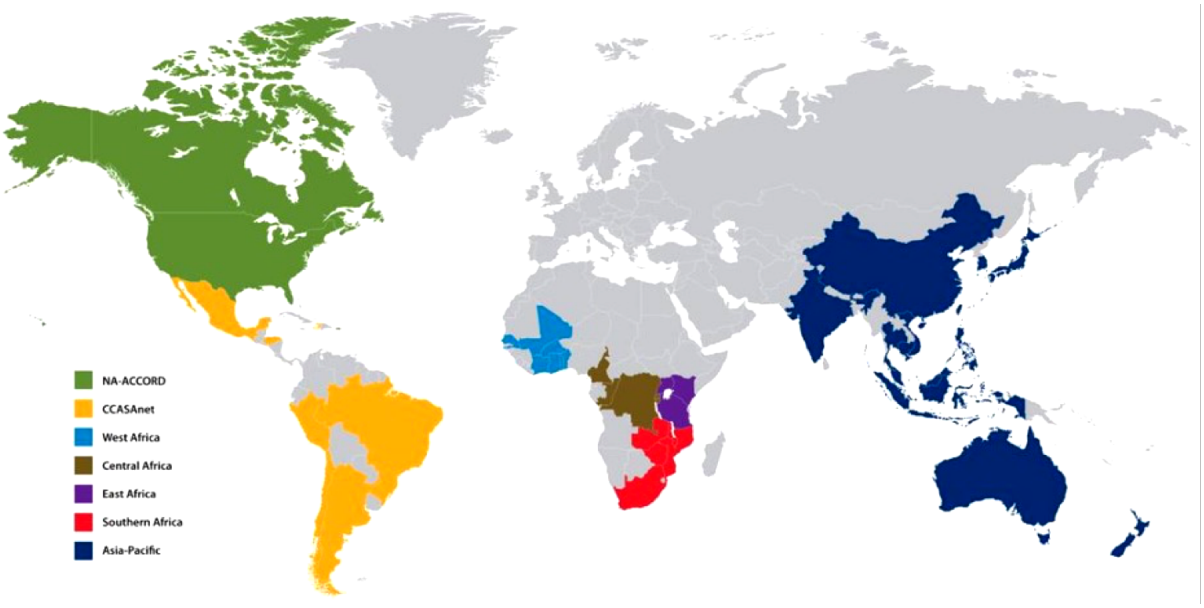
1. Routine electronic medical records data obtained from the:
    i. The IeDEA collaboration.
    ii. Provincial Health Data Centre (PHDC) of the Western Cape Department of Health and Wellness.
2. Data collected prospectively through the Global fRAmework of Data collection Used for Adolescent HIV Transition Evaluation (GRADUATE) study.

The IeDEA Collaboration

The IeDEA collaboration (iedea.org) is an international research consortium that was established by the US National Institutes of Health in 2006 to provide a resource for globally diverse HIV data that can be used to evaluate and compare the impact of HIV disease, co-infections, co-morbidities, and ART management on clinical and programmatic outcomes. It collects observational data of people living

with and at risk for HIV from 44 countries. IeDEA data are organized into seven geographic regions (Figure 1.2), each of which is coordinated by centres for the relevant region (North America, Caribbean, Central and South America, West, Central, East, and Southern Africa, and Asia-Pacific).

Figure 1.2 International Epidemiologic Databases to Evaluate AIDS (IeDEA) regional cohorts



**Map adapted from https://www.iedea.org/regions/*

This thesis utilized data from the following IeDEA regions: IeDEA Southern Africa, IeDEA Asia-Pacific, and the Caribbean, Central and South America network for HIV epidemiology (CCASAnet).

IeDEA Southern Africa (iedea-sa.org) undertakes epidemiologic, clinical, and health services research to inform and improve the delivery of HIV care and ART services in the region (67). It receives observational data from 17 large collaborating cohorts in Lesotho, Malawi, Mozambique, South Africa, Zambia, and Zimbabwe with the combined database having individual-level data on nearly 1.5 million adults and children on ART. Administrative and scientific oversight is provided at data centres at the Universities of Cape Town and Bern. The University of Cape Town has primary responsibility for managing data and relationships with South African sites, while the University of Bern liaises with sites in other Southern African countries.

The IeDEA Asia-Pacific (https://iedea-ap.org/) Research Collaboration combines data from the Australian HIV Observational Database (AHOD) as well as the TREAT Asia HIV Observational Database (TAHOD). The AHOD and TAHOD are observational clinical cohort studies of patients living with HIV in Australia and New Zealand (AHOD) and 12 countries in Asia and the Pacific region

(Cambodia, China and Hong Kong SAR, India, Indonesia, Japan, Malaysia, the Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam) (TAHOD). The regional cohort databases have data on over 107,000 children, adolescents, and adults. Therapeutics Research, Education, and AIDS Training in Asia (TREAT Asia) serves as the coordinating centre for IeDEA Asia-Pacific while the regional data and statistical analysis centre is based at the Kirby Institute, University of New South Wales, Australia.

CCASAnet (https://www.ccasanet.org/) is the observational HIV research network for Central and South America and the Caribbean. It combines clinical data from HIV and ART facilities from clinical sites in Argentina, Brazil, Chile, Haiti, Honduras, Mexico, and Peru. CCASAnet sites receive funding from various sources including government, non-governmental organizations, and various global health partners. Vanderbilt University in Nashville, USA serves as the network's Coordinating Centre.

The IeDEA Data Centres manage the organizational aspects of the collaboration including relationships with sites and management of the process that has been developed to govern analyses of shared datasets, collaborative writing committees and authorship processes. Patient data are transferred anonymously from participating sites to the data centres using each region's data transfer protocol. Based on the HIV Cohorts Data Exchange Protocol (HICDEP) used by the large European network EuroCoord, the data transfer protocol, the IeDEA Data Exchange Standard (DES) provides the structure and format for IeDEA globally and for data imports from sites to the database. After transfer, data from different sites are stored securely at each data centre, with access restricted to data managers.

The consortium is supported by the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Cancer Institute, the National Institute of Mental Health, the National Institute on Drug Abuse, the National Heart, Lung, and Blood Institute, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Fogarty International Center: Asia-Pacific, U01AI069907, CCASAnet, U01AI069923, Southern Africa, U01AI069924. Informatics resources are supported by the Harmonist project, R24AI24872.

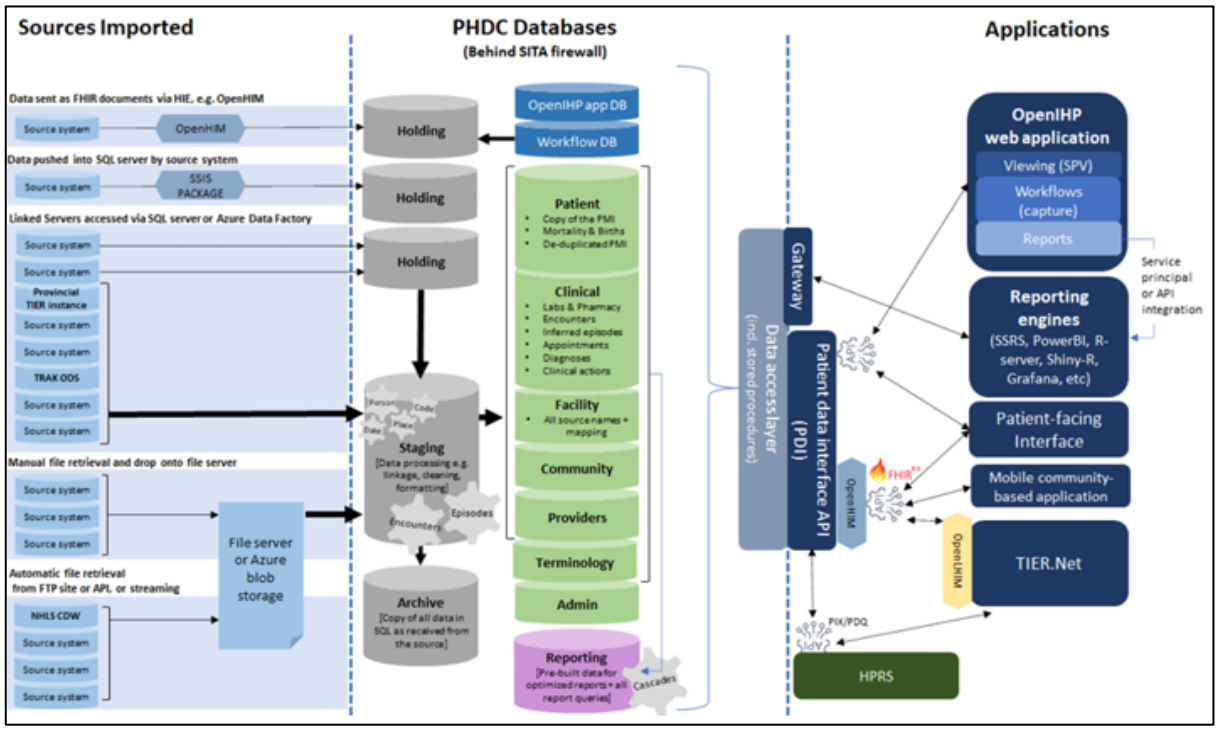
Data obtained from the IeDEA collaboration were used for Objective 1, 2, and 3.

Western Cape Provincial Health Data Centre

Within the Western Cape Province of South Africa, the Western Cape Provincial Department of Health and Wellness has implemented electronic patient administration systems in all fixed public sector services and facilities (primary care clinics, secondary and tertiary level hospitals) to manage clinic and hospital administration, pharmacy and laboratory data. The province also established a unique patient identifier which facilitates linkage of medical records between a variety of patient registration systems (disease registers, health facility patient information systems (visits and admissions), National Health

Laboratory Service, and electronic pharmacy management systems). This unique patient identifier enhances the integration of health data in the PHDC, a patient-level interlinked health information exchange, to centrally combine various routine electronic clinical, clerical, and administrative database platforms across the province to generate an individual-level population database (Figure 1.3) (68–72).

Figure 1.3 High level architecture of the Western Cape Provincial Health Data Centre



**Adapted from A cyclical dynamic HIV cascade in the Western Cape. Jonathan Euvrard on behalf of Provincial Health Data Centre Department of Health, Western Cape, South Africa. CQUIN Differentiated Service Delivery Across the HIV Cascade Workshop August 15 –19, 2022 | Kigali, Rwanda* (72)

The PHDC is thus a hub that consolidates data from the disparate administrative and clinical health data systems into an enriched dataset from which various data products and tools are then developed to support clinical care and epidemiological requirements in the department. The data from various sources are uploaded on a periodic basis from their source systems and linked to a person through the unique identifier as well as other identifiers. For individuals with multiple folder numbers, de-duplication algorithms are used to identify duplicate folder numbers that most likely represent one individual. (68–72).

Data obtained from the Western Cape PHDC were used for Objective 2.

GRADUATE study

The GRADUATE study was a prospective observational study conducted between 2017-2020 which sought to establish a data collection and management platform that can be used to guide clinical programs as to the demographic, socio-economic, clinical, and laboratory data they should be documenting to describe how adolescents are moving through the transition period within clinical care systems by:

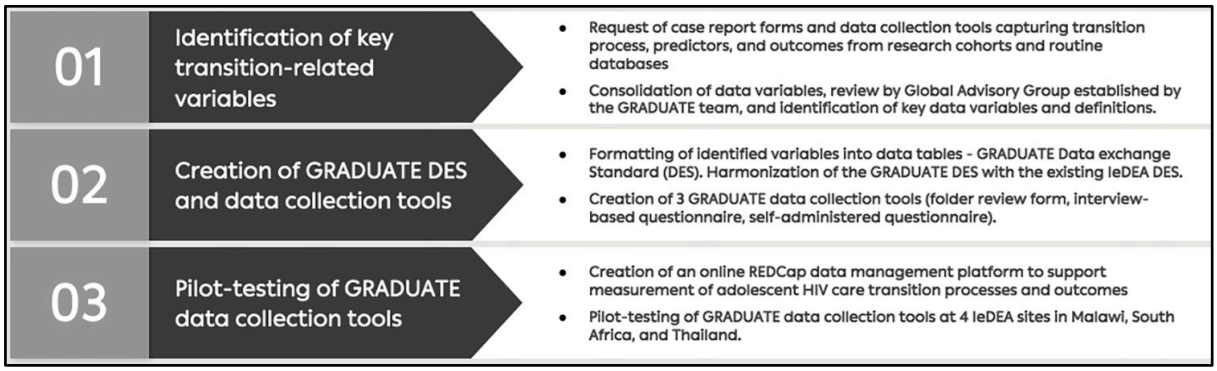
i. Identifying key data variables and data definitions that capture the process of transition and clinical and socio-economic predictors and outcomes across the transition period

ii. Creating data tables and online tools using proven and reliable open access software to facilitate data collection at the clinic level and for research purposes

iii. Pilot testing the data-capture methods in Asia and sub-Saharan Africa to evaluate data availability and the utility of the platform

The GRADUATE project was conducted in three phases as shown in Figure 1.4, with the candidate leading the research team.

Figure 1.4 Phases of the GRADUATE project in creating a data collection and management platform to support measurement of adolescent HIV care transition processes and outcomes



CRFs – case report forms; DES – Data exchange Standard; GRADUATE - Global fRAmework of Data collection Used for Adolescent HIV Transition Evaluation; IeDEA - International epidemiology Databases to Evaluate AIDS

Phase 1 identified the key demographic, socioeconomic, clinical, and laboratory aspects central to capturing characteristics of AYLH transitioning to adulthood across LMICs, as well as the processes, predictors, and outcomes across the transition period.

In phase 2, selected variables were defined, formatted, and organized into tables. These tables were added to and harmonized with the existing IeDEA DES to create the GRADUATE DES. Data collection tools were then developed to facilitate patient-level data collection of variables included in the

GRADUATE DES through abstraction of information from paper-based and electronic routine medical records and databases, as well as interviewing participants.

Phase 3 was a cross-sectional study (March-July 2019) of AYLH aged 18-24 years and in care at participating IeDEA sites to:

i. Test the utility of the GRADUATE DES and associated data collection tools within routine care
ii. Evaluate the proportion of key variables in describing the processes, predictors, and outcomes of transition available in routine medical records
iii. Examine the proportion of these variables not available that can be obtained from additional data collection efforts, such as through questionnaires, and
iv. Compare the completeness and quality of transition-related data across participating sites.

All data were captured on an online Research Electronic Data Capture (REDCap) data management platform. The study was funded by the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases for GRADUATE (R21HD089859).

Data collected through the GRADUATE study were used for Objective 3.

Data sources and their contributions are described in detail in Table 1.1

Table 1.1 Summary of thesis results chapters, objectives, manuscripts, status, and data sources

Chapter	Objective	Manuscript title and status	Data Source
3	Objective 1: Developing an algorithm that determines the likely mode of HIV acquisition for adolescents living with HIV who enrol into HIV care between the ages of 10 and 15 years	Tsondai PR, Davies MA, Singtoroj T, Maxwell N, McGowan CC, Songtaweesin WN, et al.; IeDEA Consortium. Improving Methods to Classify Perinatal versus Nonperinatal HIV Acquisition in Young Adolescents 10-14 Years of Age. *Pediatric Infectious Disease Journal*. 2021; 40(5): 453-456 *Status: Published*	IeDEA Southern Africa, Asia-Pacific, and CCASAnet
4	Objective 2a: Describing the characteristics and outcomes of adolescents living with HIV in Southern Africa and ascertaining the determinants that influence these outcomes	Tsondai PR, Braithwaite K, Fatti G, Bolton Moore C, Chimbetete C, Rabie H, et al. Characteristics and outcomes of adolescents living with perinatally acquired HIV within Southern Africa. *AIDS* 2020; 34(15): 2275-2284 *Status: Published*	IeDEA Southern Africa
5	Objective 2b: Comparing the characteristics and outcomes of AYLH receiving care in a differentiated model of care to those receiving routine care during transition to adulthood using linked electronic medical records data	Tsondai PR, Davies MA. Characteristics and outcomes among youth living with HIV receiving care in youth clubs vs. standard care at a Youth Clinic in Cape Town, South Africa *Status: Being prepared for submission*	PHDC
6	Objective 2c: Assessing the continuum of care for AYLH throughout the adolescent transition cascade and identifying the factors associated with gaps in care and virologic outcomes	Tsondai PR, Sohn AH, Phiri S, Sikombe K, Sawry S, Chimbetete C, et al.; 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. *Journal of the International AIDS Society* 2020; 23(1): e25447. *Status: Published*	IeDEA Southern Africa
7	Objective 3: Designing a data collection and management platform that effectively captures transition-related processes and outcomes of AYLH within resource-limited countries	Tsondai PR, Davies M-A, Singtoroj T, Maxwell N, Technau K-G, Chokephaibulkit K, et al. Creating a data collection and management platform to support measurement of adolescent HIV care transition processes within low- and middle-income countries: The GRADUATE project. *PLOS Glob Public Health* 2024; 4(8): e0002705 *Status: Published*	GRADUATE

AYLH – adolescents and young adults living with HIV; CCASAnet – Caribbean, Central and South America network for HIV epidemiology; GRADUATE – Global fRAmework of Data collection Used for Adolescent HIV Transition Evaluation; IeDEA – International epidemiology Database to Evaluate AIDS; PHDC – Provincial Health Data Centre

1.5 Data management and processing

Each of the results chapters gives an account of the role that the candidate played through all the stages of analysis, from the conceptualization to the dissemination of the findings. Also, the methods section of each results chapter gives an account of the data management pertaining to that analysis.

The supervisor of the candidate has separately confirmed to the University of Cape Town Doctoral Degrees Board that the included papers overwhelmingly reflect the candidate's own scientific work.

In summary, for all analyses that used data from the IeDEA collaboration and Western Cape PHDC, the candidate was responsible for coordinating and managing the process to access and analyse the data, as well as to publish the findings. This included:

i. Developing, circulating, and finalizing the concept sheet, which describes the analysis and specifies the required variables. The concept sheet is circulated to the data centres and to all site investigators, who decide whether to participate in the analysis

ii. Accessing the data, merging it, and conducting data quality checks and cleaning

iii. Conducting exploratory and advanced analyses on the received data

iv. Drafting and circulating study findings for review by co-authors, as well as incorporating any revisions and finalizing

v. Disseminating study findings through publications with peer-reviewed journals or presentations at international conferences

One analysis used data collected during the GRADUATE project. The candidate played a key role in the development and project management of the GRADUATE project including supervising the project teams, developing the study questionnaires and adapting them into data collection tools, and designing the REDCap project database with guidance from Professor Davies, Dr Sohn, and Ms Maxwell. The candidate was involved in liaising with all collaborating sites (in Thailand, Malawi, and South Africa) regarding obtaining ethical approvals from the respective institutions, study procedures, and entry of their data into the database. Also, she was responsible for extracting, merging, and developing analysis-ready datasets, and conducting exploratory and advanced analytics. The candidate drafted the manuscript, incorporating all relevant comments from co-authors.

For the manuscripts submitted for publication, the candidate was the lead and corresponding author on all manuscripts. She finalised and submitted the manuscripts to the journals, addressed all journal comments and submitted the corrected manuscript for publication. All authors reviewed and approved the final manuscript before submission.

1.6 Ethics

This thesis was approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (UCT-HREC REF: 797/2019). Study progress was reviewed annually, and the latest annual approval is provided in Appendix 1.1.

In addition, separate ethics approvals were sought and obtained for the GRADUATE study. Each participating site received ethical approval from their local IRB to conduct the study and submit de-identified data to the Centre for Integrated Data and Epidemiological Research (CIDER)1 at the University of Cape Town (Appendix 1.2). In addition, CIDER received ethics approval (UCT-HREC; REF: 046/2019, Appendix 1.3) to receive, merge, and analyse de-identified data related to the GRADUATE pilot study. As only de-identified data obtained during routine care was used for all analyses that use data from the IeDEA collaboration as well as for the GRADUATE study from the sites in Asia, the requirement for participant informed consent was waived as part of the ethical approvals. However, written informed consent was required for all participants from the sites in Africa (Rahima Moosa Mother and Child Hospital and Lighthouse Trust clinic) as information not routinely obtained during routine care was obtained using the questionnaires.

1.7 Structure of the thesis

This thesis consists of this introductory chapter, a literature review chapter, five results chapters, and a discussion chapter. In addition, an appendix section provides supporting materials.

The introductory chapter introduces the topic of AYLH and their transition to adulthood and covers a broad overview of HIV in adolescence, outcomes among AYLH, and transition in healthcare. This chapter also covers the rationale of the thesis, outlining its aim and objectives. It gives a description of the data sources used, data management and processing, and ethical approvals, and lays out the overview and summary of the thesis results chapters.

Chapter 2 is a literature review that provides the background to healthcare transition for AYLH. As the topic of HIV in adolescence is broad, this is not intended to be an exhaustive review but rather to present key aspects of characteristics of AYLH transitioning to adult-oriented HIV care within sub-Saharan Africa, literature on the core elements of healthcare transition within sub-Saharan Africa, and retention and virological outcomes for AYLH as they transition to adulthood. Details regarding the focus of this review are provided at the beginning of the chapter.

Five results chapters are included (Chapters 3 to 7), which present the empirical studies included in the dissertation. These map to the objectives, exploring and discussing the key research questions and findings. Broadly, the studies showcase the characteristics and long-term outcomes of AYLH in Southern Africa at

[1] *Previously called the Centre of Infections Disease Epidemiology and Research until December 2024*

various stages along the adolescent transition cascade. They highlight key variables that can be used to measure transition-related processes and outcomes for AYLH and highlight key areas for further research.

All results chapters are manuscripts that are either published or being prepared for submission (Table 1.1):

- Objective 1 is addressed in Chapter 3 which shows that it is feasible for analysts to use simple models using basic variables that are routinely available in data to improve on classifying likely mode of infection when missing.
- Objective 2 is covered in Chapter 4, 5, and 6. Chapter 4 sets the scene by describing the characteristics and outcomes of adolescents living with HIV receiving routine HIV care services in six Southern African countries, over an extended period. Chapter 5 assesses the characteristics and outcomes of youth receiving care in a youth-dedicated clinic within South Africa, comparing those receiving care in a differentiated model of care with those in routine care. Chapter 6 notes the patterns of gaps in care and virologic outcomes before and after AYLH transition, using age as a proxy for when transition occurs.
- Central to assessing and comparing transition outcomes is knowing how to optimally measure these outcomes and implementing data collection across different settings. Objective 3 is addressed in Chapter 7, with the results showing that it is feasible to develop tools for collecting data on variables for measuring transition readiness, processes, and outcomes. These tools can be valuable resources across varying geographic areas and care delivery models.

Chapter 8 summarizes the empirical findings of the thesis and considers its public health implications. The candidate's interpretation and contextualisation of the results is used to identify necessary future actions including recommendations for future research. Supplementary material follows Chapter 8.

Chapter 2: Literature review

2.1 Overview

The concept of transitioning care for adolescents and young adults with HIV from paediatric to adult providers has gained prominence in the past decade, coinciding with the recognition of extended life expectancies for youth living with HIV (73). With increasing numbers of children living with perinatally acquired HIV and children and adolescents acquiring HIV non-perinatally surviving into adulthood, the management of HIV as a chronic condition throughout their lives has become a reality (15,49).

Healthcare transition encompasses the planned and purposeful movement from a child-centred to an adult-centred model of healthcare. Its goal is to enhance the young adult's capacity to independently manage their health and effectively navigate healthcare services. This process involves planning, preparation, coordination, transfer, integration into adult-centred healthcare, and post-transition care. The success of a seamless and effective transition from paediatric to adult-oriented healthcare hinges on equipping these young individuals with the necessary skills to take responsibility for their own healthcare management.

Considerable evidence exists on healthcare transition models, processes, and clinical outcomes in developed countries (54,74). In such settings, specialized paediatric facilities typically provide HIV care for children, with adolescents and young adults transitioning to adult HIV clinics as they age. However, there is a paucity of data on transition outcomes as adolescents progress into adulthood in settings where the transition to adulthood does not involve a physical transfer of care from a paediatric clinic to a distinct adult HIV clinic. This scenario is the likely experience for the majority of AYLH in sub-Saharan Africa. Furthermore, there is a lack of evidence on outcomes among AYLH in sub-Saharan Africa, which is home to the majority of this population (75). Therefore, it would be inappropriate to generalize findings from studies conducted in wealthier countries, as there are significant differences in the structuring of adolescent HIV services and transition processes.

2.2 Aim and objectives

The aim of this literature review is to present an overview of the essential characteristics of AYLH transitioning to adult-oriented HIV care in sub-Saharan Africa. Specifically, the review aims to highlight the practices associated with the core elements of healthcare transition while identifying key points and knowledge gaps within the region. It should be noted that this review is not intended to be systematic or exhaustive, but rather to provide an overview of the current understanding of the processes and outcomes related to the transition of AYLH in sub-Saharan Africa.

The specific objectives of this literature review are as follows:

i. To describe the key characteristics of AYLH as they transition to adult-oriented HIV care within sub-Saharan Africa. This includes examining demographic, clinical, and psychosocial factors that are relevant to the transition process.

ii. To illustrate the practices involved in the planning and preparation, coordination, transfer, integration, and post-transition phases of healthcare transition for AYLH in sub-Saharan Africa. This objective seeks to provide insights into the strategies, approaches, and interventions that are employed to facilitate a successful transition for AYLH within the region.

iii. To explore the retention and virological outcomes of AYLH as they progress into adulthood within sub-Saharan Africa. This objective aims to examine the factors influencing the continuity of care and the achievement of optimal virological suppression among AYLH during the transition period.

2.3 Search strategy

The Medline bibliographic database was searched using the PubMed interface (National Library of Medicine, Bethesda, MD). The following search strategy was used to identify adolescents and young adults: child* OR paediatric OR adolescen* OR youth OR young adult. The following terms were used to narrow the search to articles focused on AYLH: HIV OR AIDS OR HIV/AIDS. To only retrieve articles on transition, the search terms: transition* OR transfer were used.

The inclusion criteria for the literature review included articles published in English, articles for studies undertaken after the year 2010, and articles from sub-Saharan Africa.

The exclusion criteria for the review were studies from countries not in sub-Saharan Africa, studies from non-routine care settings such as trials, and studies undertaken prior to 2010.

2.4 Results

Overview of included studies

The initial search generated 435 studies. Titles and abstracts of identified studies were reviewed noting the inclusion/exclusion criteria and duplicates removed. Full-text articles were then retrieved for 149 articles. Of these, 17 met the inclusion criteria, 6 qualitative studies, 10 quantitative studies, and 1 mixed-methods study (Table 2.1). Two qualitative studies were subsequently merged resulting in a total of 16 studies being included in the review.

Table 2.1 Characteristics of studies of adolescents and young adults living with HIV (AYLH) transitioning to adult-oriented care in routine care settings in sub-Saharan Africa published from 2010 to 2023

Author	Year	Location	Study type	Participants	Females (%)	Mode of HIV acquisition	Median age at ART start (years)	Median age at transition (years)	Data source
Abaka et.al. (76)	2021	Ghana	Qualitative	10 AYLH	50%	NR	NR	Age range at enrolment: 13-18	Interviews
Agambire, et. al. (77)	2022	Ghana	Qualitative	13 AYLH	50%	NR	NR	17 (IQR 13-25)	Interviews
Ashaba et. al. (78,79)	2022	Uganda	Qualitative	30 AYLH 10 caregivers 10 healthcare providers	47%	100% perinatally acquired	Mean 6.6. (SD 5.2)	Mean 20 (SD 3.1)	Interviews
Brostrom et. al. (80)	2020	Ethiopia	Retrospective cohort	1072 adolescents	60%	NR	NR	16 (IQR 15-18)	Routine medical records
Castelnuovo et. al. (81)	2018	Uganda	Retrospective cohort	907 AYLH	83%	NR	NR	21 (IQR 20-22)	Routine medical records
Davies et al. (82)	2017	South Africa	Retrospective cohort	460 adolescents	53%	90% considered perinatally acquired	8 (IQR 5-11)	13 (IQR (11-15)	Routine medical records
Haghighat et. al. (83)	2019	South Africa	Prospective cohort	951 adolescents, healthcare providers	54%	26% non-perinatally infected	9 (IQR 6-12)	14 (IQR 11-15)	Medical records and interviews
Kranzer et. al. (84)	2017	Zimbabwe	Prospective cohort	2273 AYLH	49%	NR	NR	N/A	Routine medical records
Kung et. al. 2016 (85)	2016	South Africa	Qualitative	50 healthcare providers	N/A	N/A	N/A	N/A	Interviews and questionnaires
Masese et. al. (86)	2019	Tanzania	Qualitative	19 AYLH	53%	79% perinatally acquired	NR	Mean at enrolment 24 (IQR 22-26)	Interviews and review of medical records

Table 2.1 Characteristics of studies of adolescents and young adults living with HIV (AYLH) transitioning to adult-oriented care in routine care settings in sub-Saharan Africa published from 2010 to 2023

Author	Year	Location	Study type	Participants	Females (%)	Mode of HIV acquisition	Median age at ART start (years)	Median age at transition (years)	Data source
						21% unknown			
Ouedraogo at et. al. (87)	2023	Burkina Faso	Retrospective cohort	73 AYLH	47%	96%	10 (IQR 8-14)	17 (IQR 16-18)	Medical records
Ramirez-Avila et. al. (88)	2017	South Africa	Retrospective cohort	341 adolescents	51%	NR	NR	13 (IQR 12-15)	Telephonic interview and medical records
Teasdale et.al. (89)	2017	South Africa	Retrospective cohort	644 adolescents	47%	NR	4 (IQR 1-8)	8 (IQR 5-11)	Medical records and tracing records
Zanoni et.al. (90)	2020	South Africa	Retrospective cohort	180 AYLH	54%	100% perinatally acquired	NR	12 years	Medical records
Zanoni et. al. (91)	2021	South Africa	Mixed methods: Prospective cohort + qualitative	30 AYLH 11 healthcare providers	42%	NR	NR	16.5 (IQR 16-17)	Medical records and interviews
Zanoni et. al. (92)	2022	South Africa	Prospective cohort	199 AYLH	49%	100% perinatally acquired	8 (IQR 5-9)	15 (IQR 12-21)	Medical records and questionnaire

AYLH – adolescents and young adults living with HIV; ART – antiretroviral therapy; IQR – interquartile range; SD – standard deviation; N/A – not applicable; NR – not recorded

The characteristics of the eligible studies are summarized in Table 2.1. There were nine studies conducted in Southern Africa (82–85,88–92), four in East Africa (78–81,86), and three in West Africa (76,77,87). However, no studies were included from Central Africa. The study designs varied and included qualitative, quantitative, and mixed methods approaches. Among the quantitative studies, seven were retrospective cohort studies and four were prospective studies. The studies were published between 2016 and 2023.

The majority of study participants were adolescents and youth living with HIV. Only four studies included healthcare providers of AYLH (78,79,83,85,91) and one study included caregivers (78,79). With two exceptions, the included studies had an equal distribution of males and females, with the proportion of females ranging between 42% and 54%. The exceptions were a study in Ethiopia, where 60% of the participants were female (80) and a transitional clinic enrolling youth aged 18-25 years, where 80% of the participants were females (81).

The mode of HIV acquisition was not recorded in nearly sixty percent of the included studies. Where recorded, most participants had acquired HIV perinatally (78,79,83,86,90,92). One study assumed perinatal acquisition among those enrolled into HIV care aged less than 13 years (82). The average age at ART initiation was between four and 10 years in one-third of the studies that had this variable recorded. Data were extracted from routine medical records or through interviews with participants across all the included studies.

Ten studies included AYLH who had already transitioned or transferred to adult HIV services based on the processes of the respective institutions where they received care (76–80,82,83,86,87,90,91). The included studies consisted of a combination of participants who had transitioned to adult HIV care, those who had attempted but were unsuccessful in transitioning (i.e., tried to access care in the adult HIV clinic but returned to the paediatric HIV clinic), and those who had transferred out of care. Only one study attempted to use the movement across age bands as a proxy for transition as the adolescent and young adult grew older (84). Additionally, one study included youth attending a transitional clinic but had not yet transitioned to adult care (81).

Table 2.2 provides a summary of the models of HIV care, transition processes and transition outcomes reported across the included studies.

Table 2.2 Models of HIV care and transition, transition processes and outcomes among studies of adolescents and young adults living with HIV (AYLH) transitioning to adult-oriented care in routine care settings in sub-Saharan Africa published from 2010 to 2023

Author, year	Model of HIV care	Transition model	Transition process	Post-transition outcomes including linkage to care, engagement in care, and viral suppression
Abaka et.al. 2021 (76)	Paediatric clinic at a tertiary facility	Transfer from paediatric to adult HIV clinic at the same facility	Unstructured with no policy/guide No formal readiness assessment Readiness determined by age (at 13 years), ability to honour clinic appointments, and adherence to medication No prior visits or introductions to the adult HIV clinic	No follow-up visits by paediatric clinic after transition No outcome on linkage to care, engagement in care, and virologic outcomes documented
Agambire, et. al. 2022 (77)	Adult HIV clinic at a tertiary hospital with adolescents seen on Mondays	Transfer to adult HIV clinic at the same facility	Unstructured with no policy/guide No formal readiness assessment Criteria for transition/transfer determined by age (at age 13 years) No prior visits or introductions to the adult HIV clinic	No follow-up visits by paediatric clinic after transition No outcome on linkage to care, engagement in care, and virologic outcomes documented
Ashaba et. al. 2022 (78,79)	3 HIV clinics at tertiary facility: paediatric clinic for 0-9, adolescent clinics for 10-19, and young people's clinic for 20–25-year-olds	Transition involves transfer to the adult HIV clinic at the same facility	Unstructured with no policy/guide National Care transition guidelines not implemented Readiness not assessed. No preparation done prior No prior visits or introductions to the adult clinic	No follow-up visits by paediatric clinic after transition Transition outcomes: • 13% transitioned successfully • 27% attempted but were unsuccessful • 60% had not yet transitioned No virologic outcomes documented
Brostrom et. al. 2020 (80)	Paediatric care at tertiary hospitals and a health centre	Transfer from a paediatric facility to adult HIV clinics	Unstructured with no policy/guide Transition occurred between the ages of 10-22 years, with peaks at 15-16 and 18-19 years	Only 9% had transitioned care yet >40% were eligible based on age No outcome on linkage to care, engagement in care, and virologic outcomes documented

Table 2.2 Models of HIV care and transition, transition processes and outcomes among studies of adolescents and young adults living with HIV (AYLH) transitioning to adult-oriented care in routine care settings in sub-Saharan Africa published from 2010 to 2023

Author, year	Model of HIV care	Transition model	Transition process	Post-transition outcomes including linkage to care, engagement in care, and viral suppression
Castelnuovo et. al. 2018 (81)	Accessing care at a transitional clinic with youth-friendly services for AYLH aged 18-25 years	Model of transition not recorded	Process of transition not recorded, however, over the period of follow up, 24% of adolescents transferred care	29% disengaged from care before transferring • 40% had initiated ART and 49% had not initiated ART Those with advanced stage of HIV were more likely to be lost from care No VL data available – VL monitoring not yet implemented in Uganda at the time of the study
Davies et al. 2017 (82)	Tertiary and primary care facilities	Transfer from tertiary care and transfer from primary care facilities	Transfer process unknown Followed adolescents who had transferred care through linked data 79% transferred from tertiary and 21% from primary care facilities 72% transferred aged <15 years and 28% aged 15-19 years	81% transferred successfully • 95% linked to the transfer site within 18 months Retention was 90% 1 year after transfer, 88% at year 2, and 84% at year 3 • Retention was lower in 15–19-year-olds vs. 10–14-year-olds at year 1 (81% vs. 93%) and year 2 (85% vs. 90%) • Retention among 15–19-year-olds higher at year 2 (85%) and year 3 (84%) than year 1 (81%) More likely to transfer successfully: transferring out of tertiary care, virologically suppressed at transfer, and aged >15 years 81% had VL<400 at transfer • 80% had a VL<400 copies/mL in year 1, 81% in year 2, and 75% in year 3 • Proportion with missing VL measures increased from 11% at 1 year to 17% at year 2 to 20% at year 3 post-transfer Proportion with viral load <400 copies was lower in 15–19-year-olds vs. 10–14-year-olds at year 1 (69% vs. 83%), year 2 (67% vs. 85%), and year 3 (63% vs. 78%)

Table 2.2 Models of HIV care and transition, transition processes and outcomes among studies of adolescents and young adults living with HIV (AYLH) transitioning to adult-oriented care in routine care settings in sub-Saharan Africa published from 2010 to 2023

Author, year	Model of HIV care	Transition model	Transition process	Post-transition outcomes including linkage to care, engagement in care, and viral suppression
Haghighat et. al. 2019 (83)	58% initiated ART in paediatric care while 42% initiated in non-paediatric care	Of those in paediatric care • 35% transitioned out • 65% remained Of those in non-paediatric care • 6% transitioned to paediatric care • 94% remained in paediatric care	Classical transition: transition from paediatric care to specialized adult clinics • 43% Down referral: transition out of paediatric care to primary health care clinics • 57% Cyclical transition: at least 1 repeated movement between paediatric and non-paediatric care • 27% of those who transitioned either way experienced cyclical transition	Mortality – 3%, LTFU – 9% Of the 35% that transitioned, 91% were retained at 18 months and 9% LTFU VL data available for 92% Virologic failure was 30% at last VL test • Classical transition – 35% had viral failure • Down referral – 8.2% had viral failure • Those transferring by down referral less likely to demonstrate viral failure (aOR 0.25, CI 0.12-0.53) Older age (aOR 1.76, CI 1.25-2.48) and virally unsuppressed (aOR 3.64, CI 2.55-5.20) associated with viral failure Of those who transitioned out of paediatric care, 73% had VL availability pre- and post-transition
Kranzer et. al. 2017 (84)	Paediatric clinic	Examined movement across age bands	Transition considered as movement to the next age group (from childhood to young adolescence to older adolescence to young adulthood)	Overall, 8.4% of individuals LTFU LTFU for those initiating ART aged 10-14 was 1.5 times higher after moving to 15–19-year group Moving from adolescence into young adulthood increased the risk of LTFU by nearly two-fold LTFU became higher with increasing age with those who initiated ART aged 15-19 years having higher LTFU after transitioning to ages 20-24 years No viral load data available

Table 2.2 Models of HIV care and transition, transition processes and outcomes among studies of adolescents and young adults living with HIV (AYLH) transitioning to adult-oriented care in routine care settings in sub-Saharan Africa published from 2010 to 2023

Author, year	Model of HIV care	Transition model	Transition process	Post-transition outcomes including linkage to care, engagement in care, and viral suppression
Kung et. al. 2016 (85)	Paediatric/ adolescent facility	Transfer to adult HIV clinic	Unstructured with no policy/guide Pointers used to start the process: age (16-25 years), pregnancy, completion of high school, request to move to adult care, and completion of the traditional manhood initiation ritual No communication between adolescent and adult care physicians No specific provider to transition to	No follow-up conducted after transfer
Masese et. al. 2019 (86)	Adolescent-specific HIV clinic (Teen club) within a tertiary hospital	Transfer to adult clinic or PMTCT clinic (as referred to in the paper)	Unstructured with no policy/guide Criteria for transition: age 25 years, pregnancy, getting married, exhibiting behaviour considered to have a negative influence on peers No formal readiness assessment No prior visits to the adult HIV clinic	Transition outcomes • 50% successfully transitioned - 20% to adult clinic and 30% to PMTCT clinic (as referred to in the paper) • 20% attempted transition but were unsuccessful • 30% soon to transition No follow-up conducted by paediatric clinic after transition 72% virally suppressed at most recent VL • 92% of those who transitioned successfully - 100% transitioned to adult HIV clinic and 83% to PMTCT • 71% among those whose transition was unsuccessful
Ouedraogo at et. al. 2023 (87)	Paediatric HIV clinic	Transfer from a paediatric clinic to adult clinic at same tertiary facility	Structured transition process with individual assessments and planning prior to transition Eligible if aged >13 years, fully disclosed, and compliant Close collaboration between caregiver and paediatric and adult healthcare providers Peer groups transferred together – with 49% having transitioned in groups	Peer groups continue in the adult clinic Paediatric healthcare provider attends first visit post-transfer Retention 96% within 1 year of transitioning and 93% at 2 years post-transition Mortality one year post transition – 1.4% Virologic outcomes not documented

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Ramirez-Avila et. al. 2017 (88)	Paediatric clinic at a tertiary semi-private paediatric clinic	Transfer from paediatric HIV clinic to the public sector	Mandatory transfer from a state-subsidized hospital-based, PEPFAR-funded paediatric HIV clinic to the public sector due to operational reasons Structured • Eligible if aged 11-18 years • Caregivers involved • Given 1 month notice before referral • Transferred to either a PHC clinic, community health centres, or hospital-based clinics	52% transferred to the assigned clinic 48% attended an alternate clinic to the one assigned Linked to care 7 months after transfer: • Based on caregiver reports: 98% • After validation - 88% (95%CI 77-97%) • Assuming all unreached patients failed to link - 69%. Mortality 0.65% At last measured VL, 77% had undetectable VL (no value)
Teasdale et.al. 2017 (89)	Paediatric care at a tertiary hospital	Transfer from a paediatric facility to primary and community health clinics as part of decentralization of care	Unstructured with no policy/guide Median age at transfer: 8 years (5-11)	63% transferred successfully. • 0.5% died • 18% subsequently transferred to another facility • 63% still active in care • 33% had unsuccessful transfer - 62% subsequently had lab data after LTFU, 5% within 18 months of last visit • 20% subsequently LTFU after 31 months - 47% subsequently had lab data after LTFU, 31% within 18 months of last visit At last VL for all who transferred, 82% had VL<400

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Author, year	Model of HIV care	Transition model	Transition process	Post-transition outcomes including linkage to care, engagement in care, and viral suppression
Zanoni et.al. 2020 (90)	Paediatric clinic at a tertiary hospital	Transfer from a paediatric clinic o adult clinic at same tertiary facility	Prior to 2011 – transitioned to the adult care at age 12 years once disclosed. • Unstructured with no policy/guide • N=35 After 2011 – new policy allowed them to remain at the paediatric clinic. • N=145	Retention after 1-year for those who transferred was 49% vs. 92% in those who did not • Remained lower after adjusting (ARR 0.59; 95%CI 0.43–0.82) No difference in viral suppression between those who remained in paediatric care (80%) and those who transitioned to adult care (83%) after 1 year. Adjusted ARR 1.06; 95%CI 0.89-1.26 At most recent viral load, still no difference in viral suppression between those who remained in paediatric care (78%) and those who transitioned to adult care (74%) % with missing viral loads was high among those who remained in paediatric care (13%) and those who transitioned to adult care (14%)
Zanoni et. al. 2021 (91)	Paediatric HIV clinic	Transfer from a paediatric clinic to adult clinic at same tertiary facility Study followed adolescents deemed eligible to transition	Eligibility for transition: Aged 15 years, fully disclose, and taking a fixed drug combination ART regimen Timing determined by physician There are no support groups or additional services available for adolescents in the adult clinic 63% transferred to adult clinic and 37% remained in paediatric clinic	18 months after enrolment, 63% had successfully transitioned and 37% had remained in paediatric care even though all enrolled were deemed eligible for transition • 30 months after enrolment, 4 adolescents remained in paediatric care Of those that transitioned 58% were engaged in care after 12 months vs. 100% among those that remained in paediatric care At enrolment, 97% were virally suppressed Of those that transitioned, 37% were virally suppressed within 12 months and 58% did not have a viral load measurement for >1 year after transition

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Author, year	Model of HIV care	Transition model	Transition process	Post-transition outcomes including linkage to care, engagement in care, and viral suppression
Zanoni et. al. 2022 (92)	Paediatric HIV clinic	Transfer to the adult clinic remaining in specialized care	Transition occurs after the 12th birthday but may occur later based on clinician judgement	Viral suppression • 74% prior to transition • 42% 1 year after transition Higher odds of viral suppression seen in those who scored highly on a transition ready score, were on 1st line ART, status disclosure documented Females (aOR 0.40 CI 0.19-0.85)), older at ART start, ever used alcohol had a lower odd of viral suppression

ARR – adjusted risk ratio; aOR – adjusted odds ratio; ART – antiretroviral therapy; AYLH – adolescents and young adults living with HIV; CI – confidence interval; LTFU – lost to follow up; PHC – primary health care; PMTCT – prevention of mother to child transmission (this is as referred to in the paper); VL – viral load

Models of HIV care

In sub-Saharan Africa, the provision of healthcare for children living with HIV follows a decentralized approach, where non-specialist primary care facilities play a major role. This decentralization aims to expand access to ART and has been recommended by organizations such as WHO, UNAIDS, and the President's Emergency Plan for AIDS Relief (PEPFAR) since 2008 (93). Consequently, not all children living with HIV receive ART in specialized paediatric facilities. Instead, most receive care in decentralized, integrated primary care clinics where healthcare providers attend to adults, adolescents, and children with HIV in the same setting (75). The implementation of nurse-initiated and managed ART in primary health care, for patients of all ages, has resulted in a growing number of children and adolescents being initiated on ART in non-paediatric primary healthcare clinics, even at a young age. A study conducted in South Africa revealed that approximately 60% of adolescents had initiated ART in paediatric care, while 40% started treatment in non-paediatric care settings (83). By initiating and continuing to receive care within non-paediatric primary healthcare clinics, adolescents may never enter paediatric HIV care, eliminating the need to transition out of it.

While some children continue to receive HIV care in these settings throughout their paediatric and adolescent years, others undergo a transition to different care settings during adolescence. The studies reviewed described various models of HIV care for AYLH. Although not the most prevalent approach in sub-Saharan Africa overall, the majority of AYLH within the published studies reviewed received care in specialized paediatric facilities or clinics that specifically catered to adolescents and youth (76–80,86–88,90,91). This could likely be because those researching and publishing on adolescent transition are involved in the care of AYLH at specialized facilities/clinics. One study included adolescents accessing care at a transitional clinic offering youth-friendly services to support the transitioning process (81), and two studies included adolescents receiving care in primary care settings (82,83).

In resource-limited settings, most health facilities face challenges such as overcrowding, high patient volume, and limited flexibility in appointment times. Consequently, patients are required to endure long waiting times at each stage of the service process, including collecting medical records, having clinical consultations with healthcare providers, and obtaining medication from the pharmacy (48,94). However, the experience of adolescents receiving HIV care in the reviewed studies differed from this typical scenario. In addition to routine clinical care and medication refills, AYLH had access to various additional support services. These included peer support groups, weekend clinics, expedited medication collection, sexual and reproductive health services, therapists (including psychologists), educational sessions, social events, meals, and dedicated recreational spaces (84–87,90,91,95). These findings align with other studies that have noted clinics' efforts to segregate adolescent HIV care by designating specific days for dedicated children and adolescent HIV care, establishing a dedicated group of

healthcare providers for adolescent services, and dedicating a section of the facility for adolescent care (75,96).

Transition pathways

The model of HIV care impacts the transition process for adolescents and young adults. A survey conducted in Nigeria confirmed the variation in healthcare transition experiences across Africa (97). While several healthcare transition models have been developed in high-resource settings, they may not be directly applicable to the continent due to factors such as high disease burden, cost, workforce constraints, and cultural and contextual differences. It is necessary to shift the thinking around adolescent HIV transition to reflect the realities of the sub-Saharan African context. This involves moving beyond the linear, one-time movement from specialized paediatric care to adult care observed in Europe and North America (83). Our review highlights the existence of multiple transition pathways in this context.

Firstly, in cases where adolescent HIV care is accessed within specialized paediatric facilities, the transition typically involves moving from specialist paediatric care to an adult clinic within the same premises or at a different facility, while remaining within secondary or tertiary care settings. This pathway was the most observed transition in the studies reviewed (76–80,86,87,90–92). Although adolescents still retain familiarity with the facility itself, they experience a loss of familiarity with the environment, and the healthcare providers involved are often different. For adolescents who acquired HIV perinatally and received care at the facility throughout their childhood and adolescence, this transition can be challenging (12). This sentiment was expressed by adolescents in the studies, noting a preference for their paediatric care providers whom they had known since childhood (77–79).

Secondly, another transition pathway for those receiving care in paediatric facilities involves referral to primary or community care facilities closest to their homes. This type of transfer is a result of the decentralized and differentiated HIV care model prevalent in this setting, which is driven by high disease burden and limited resources. While this transition may coincide with later adolescence and the transition to adulthood, it often occurs during childhood or early adolescence. Haghighat and colleagues demonstrated that most of the adolescents initially experienced transition out of paediatric care through this "down- referral" pathway (83). In cohorts that are part of the IeDEA Southern Africa Collaboration, only a small number of adolescents receive care in specialized paediatric tertiary institutes, transferring care to primary healthcare facilities during early adolescence or even earlier once they are clinically stable on ART (82). Another study in South Africa found that nearly 60% of transitioning adolescents underwent this type of transition (down-referral) at a young age, with some as young as 8 years old (83,88,89). Additionally, in a survey of healthcare providers caring for AYLH who were transitioning

care, it was observed that adolescents receiving care within tertiary hospitals were transferred to primary healthcare clinics closer to their homes (85).

Thirdly, there are transitional clinics that offer youth-friendly services and a structured transition to adult care for older adolescents and young adults (81).

Fourthly, for adolescents in integrated clinics, transition may involve adopting an adult approach to care, such as independently attending the clinic, scheduling their own appointments, and being responsible for medication collection, without any changes in healthcare providers or facility. One of the included studies analysed outcomes for this group using age band transition as a proxy for transitioning to adulthood, without an actual transfer of care (84).

Additionally, the period of transitioning to adulthood may also coincide with a transfer from one primary care facility to another due to patient migration or preference. When adolescents already receiving ART within primary healthcare services transitioned, their main destination for adult care was another primary healthcare clinic (85).

Lastly, cyclical transition has also been observed, where there is repeated movement between paediatric and non-paediatric care. These non-linear events are more common among adolescents receiving care at primary care clinics, observed in nearly a third of participants in one study, and may indicate either unsuccessful transition attempts or fluctuations in patient stability or treatment outcomes, resulting in upward and downward referrals as needed (83). Transfer of care can also be an ongoing process, as seen in a study that followed adolescents transferred out of care and found that of those who transferred successfully, 18% subsequently transferred onwards from the transfer clinic as well (89).

In contrast to developed countries, where transition to adult care from paediatric care typically occurs around 18-25 years of age, coinciding with the developmental shift towards adulthood and referred to as "adolescent transition," the transfer from paediatric to adult care for those in HIV care at specialized paediatric facilities in developing settings occurs earlier, during childhood or early in adolescence, once stability on ART is achieved. In South Africa, an analysis of transfers revealed that over 70% of transfers occurred before the age of 15 years (82). Similarly, in cohorts that are part of IeDEA-Southern Africa, where clinics are largely integrated, one in four adolescents transferred care between the ages of 10-13 (98). However, transferring care in early adolescence does not necessarily align with the time when transition to adulthood takes place, and adolescents are expected to assume responsibility for their own self-care. It cannot be equated to transition to adult care. The stage of development influences the extent to which parents and guardians are involved in healthcare. Even after transfer from paediatric care in early adolescence, children continue to be accompanied to clinic appointments by their parents or guardians, who also support medication adherence. The precise timing of gradual transition of responsibility for care remains unclear.

Planning and preparation

The concept of healthcare transition emphasizes the need for an intentional, organized, purposeful, and planned nature to improve healthcare access for adolescents living with HIV (99). However, the studies reviewed consistently described the transition process as unstructured, abrupt, and rushed, lacking clear guidelines or a defined process (76–80,85,86,100).

Transition policies exist in the literature outlining key elements such as the development of transition protocols, preparation for transition, collaboration between paediatric/adolescent clinics and adult clinics, and continuous evaluation of transition strategies (59). Nevertheless, these protocols mostly developed in high-resource settings may not directly translate to developing countries due to resource constraints and fundamental differences (73,75,101–103). Notably, only one study among those included reported the routine use of policies or guidelines for transition. Even where guidelines existed, they were not implemented (78,79). This highlights the lack of established evidence-informed guidelines specific to the sub-Saharan African context at the facility level (85,97,104). The absence of structured transition processes and guidelines has significant implications, as observed in one study where only a small proportion of adolescents had been transferred despite reaching the recommended age for transition (80).

Transition readiness, defined as an adolescent's ability to prepare for, initiate, and complete the transition process in collaboration with their support networks, is a key part of the transition process (105,106). Assessing readiness before transitioning care is recommended to ensure a comprehensive evaluation beyond age alone, especially among those with perinatally acquired HIV. However, readiness assessments were rarely conducted in the reviewed studies, except for one study that noted formal assessments (87). Adolescents had varying perspectives on readiness, with some lacking awareness of what readiness entails (76). It is worth noting that most HIV care settings in sub-Saharan Africa lack validated scales for assessing readiness (107), although recent efforts have been made to develop and validate tools encompassing relevant domains (92,108). The application of these tools across the setting is yet to be determined, with the expectation that comprehensive assessments of developmental, behavioural, and psychological readiness will be conducted before transitioning adolescents to adult HIV care (78,79,102,109,110).

Transition preparation emerged as a significant gap in the reviewed studies. Only one study detailed the preparation process for adolescents following completion of the disclosure process, involving sessions with the adolescent, their caregiver, and the adult HIV care provider (87). In contrast, most studies lacked any form of preparation for transition, with healthcare providers largely directing the transition process (76,78,79,85,86,90). Some adolescents mentioned being simply told to go to the adult clinic by their caregivers or healthcare providers (76–79,86). This approach contradicts expert recommendations calling for collaborative planning and preparation involving adolescents, caregivers, and healthcare

providers to ensure a structured transition process (59,103). The absence of a structured process not only jeopardizes the adolescents' informed decision-making and understanding but also misses the opportunity to equip them with the necessary skills and knowledge to navigate the transition, increasing the likelihood of unsuccessful outcomes (99,111,112). Effective preparation for healthcare transition entails providing adolescents with the information they need about their disease and the transition process. This includes developing structured transition processes that incorporate feasible interventions (76,85,86). Additionally, empowering adolescents to take charge of their health involves equipping them with self-advocacy skills to navigate the HIV clinic, communicate their needs to healthcare providers, and advocate for themselves (76,78,79).

Unsurprisingly, age was commonly used as the primary criterion for transitioning adolescents, typically based on the assumption that it reflects developmental maturity. However, there was considerable variation in the age thresholds used, ranging from 12 to 25 years (76,77,80,85–87,90,91). This wide range was evident not only across different studies but also within individual studies (80). Interestingly, facilities without an intermediary adolescent clinic tended to transition adolescents to adult care at a younger age, often before 15 years of age (76,77,90), whereas those with a dedicated adolescent-focused model of care were able to delay the transition to adult care until late adolescence or early adulthood. Furthermore, in studies from more recent years adolescents transitioned later than in studies form earlier years (87,90). Chronological age is not a sufficient measure of maturity and age cutoffs are not recommended as a sole yardstick for defining transition readiness and transition readiness (91,113).

Reassuringly, factors beyond chronological age were considered in determining the timing of transition in the reviewed studies. HIV status disclosure, clinical stability, compliance with appointments and medication, independence in attending appointments unaccompanied, and markers of societal maturity such as completing high school, pregnancy, marriage, or traditional manhood initiation rituals were considered (76,78,79,83,85–87,90,91). Also, willingness to transition was considered (78,79,83,85). However, the ultimate decision on when to transition remained at the discretion of healthcare providers (91). While these factors provided some guidance, the lack of validated tools for objective assessment resulted in challenges in determining the appropriate timing for transitioning (85).

Importantly, one study highlighted the concerning issue of transitioning adolescents before disclosing their HIV status, indicating persistent challenges with disclosure within the continent. A situational analysis of facilities across Africa identified status disclosure as the second-largest challenge in caring for adolescents (104).

The involvement of caregivers in the transition process was evident, even in cases where the transfer occurred for operational reasons and there was minimal preparation (76,77,87,88). Caregivers have played a crucial role in supporting adolescents living with HIV, particularly those with perinatally acquired HIV (107), and caregivers can be used as facilitators to the transition process. While caregiver

support is valuable, it should not hinder direct communication between healthcare providers and adolescents (115,116). In planning the transition, collaboration among paediatric and adult care providers, caregivers, and adolescents is essential for enhancing the process and achieving successful outcomes (79,86). The positive impact of family support on the transition to adult care was acknowledged by adolescents (76).

Coordination, integration, and transfer

Most of the studies revealed a lack of coordination between the paediatric and adult clinics during the transition process. In most cases, there were no scheduled meetings or introductions between the healthcare providers, leaving adolescents to meet the adult healthcare providers for the first time upon arrival at the adult clinic (76–79,85,86). This lack of coordination resulted in challenges for the adolescents, who navigated unfamiliar territory and approached healthcare providers without prior introductions (78).

The absence of bonding opportunities between the healthcare providers and the adolescents during the transition left them unprepared for the depersonalized and congested adult clinics, causing anxiety and discomfort (76,78,79). The potential role of a navigator to assist with the logistics of transition was mentioned as a possible support to alleviate anxiety (91). However, coordinating visits between the paediatric and adult healthcare providers becomes challenging when the transition is not to a specific physician but to the adult clinic within a primary healthcare facility (85). Additionally, resource limitations and the congested nature of health facilities in many settings make it difficult for receiving healthcare providers to allocate time for these engagements (48,94). While some instances saw nurses or caregivers accompanying the adolescent to the adult clinic to assist with navigation, this practice was not well communicated (76).

Only one study conducted in Burkina Faso reported a well-coordinated process between paediatric and adult care providers, where the transition occurred after all parties agreed on the adolescent's readiness and the next appointment, attended by the paediatric provider, was scheduled at the adult clinic (87).

Duration of the transition process was reported in four studies. In three of the of these studies, transfer took place during the subsequent visit following the session where adolescents were informed about the transition (76,86,88), while in one study, the transfer occurred after two consecutive preparation sessions (87).

Post-transition ongoing care

In most studies, there was a lack of follow-up visits by the paediatric healthcare providers to assess the success of the transition process (76,78,79,85,86). Previous research has emphasized the importance of

peer support in facilitating successful transition and building resilience (91,117). Connecting adolescents with peers who share similar experiences can alleviate feelings of loneliness and foster a sense of belonging (114). Interacting with peers provides strength, hope, and encouragement. However, the absence of peer support initiatives within adult care settings made the transition to adult care daunting for many participants in the studies (73,75,118). To make the transition process more manageable, AYLH who have already transitioned recommended incorporating some of the adolescent or youth-friendly services from paediatric and adolescent clinics into adult clinics, such as peer support initiatives and dedicated clinics for adolescents (76,86). However, this approach may limit opportunities for youth to learn and interact with older patients (114).

There has been significant advocacy for youth-friendly services in HIV clinics in facilities providing paediatric and adolescent care. However, as these adolescents age and transition to adult care, a challenge they face is the lack of these services in adult HIV clinics. For example, some facilities do not offer weekend access to HIV care for adults, even in facilities that provide such alternatives for adolescents (90). Considering that adolescents have experienced the convenience of accessing HIV care on weekends, it is important for adult clinics to offer similar options to accommodate their schooling or work schedules (76,77).

Linkage, engagement in care, and virologic outcomes post-transition

There was considerable variation in how successful transition was defined across studies. Some studies considered successful transition based on recorded HIV visits, clinical appointments, laboratory tests, or medication pick-up after transfer. Others considered successful transition as being retained in care with viral suppression one year after the transfer (82,88–91). Similarly, engagement in care was defined differently across studies, including keeping clinic visits within specific timeframes or having any evidence of clinic contact within a specified period (81–84,90)that provide such alternatives for adolescents (90). Considering that adolescents have experienced the convenience of accessing HIV care on weekends, it is important for adult clinics to offer similar options to accommodate their schooling or work schedules (76,77).

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differently across studies, including keeping clinic visits within specific timeframes or having any evidence of clinic contact within a specified period (81–84,90).

Limited data were available on post-transition outcomes in the included studies. Some studies did not mention linkage and retention, while others reported successful transition attempts, unsuccessful transitions, and subsequent movements back to paediatric care without providing specific numbers. Quantitative studies reported retention rates ranging from as low as 49% to over 90% (81–84,87,88,90). Retention rates declined with longer follow-up duration, particularly for older adolescents, for example from 90% at year 1 to 84% at year 3 (82).

The model of transition used appeared to have an impact on outcomes. Remaining in the same facility tended to have better results compared to transferring to a different facility, and studies that implemented comprehensive planning and preparation phases, as well as group transfers, reported higher retention rates (87,89,90). For example, one study showed that retention was lower among those who transferred care to adult HIV clinics compared to those who remained in paediatric clinics within the same facility (49% vs. 92%, respectively) (90). This is in keeping with evidence from the UK that showed that retention of adolescents transitioning to adult care was lower in those moving to a new facility (119). An exception with high post-transition retention rates (>90% after 2 years) involved a comprehensive planning and preparation phase and implemented group transfers (87). Studies suggested that leveraging peer support groups during the transition process could provide psychological support, as adolescents expressed a sense of loss when transitioning and valued the support from their peers (91).

In the transition model where AYLH were referred from paediatric to primary care facilities closest to their homes, two-thirds successfully transferred and 18% of these subsequently transferred to another facility (89). Limited data were available on outcomes for adolescents transitioning to adult care from adolescent transition clinics. In Uganda, a quarter of young adults attending an adolescent transitional clinic disengaged while still in care before transitioning (81). No outcomes were available after transferring from this care. Analysing engagement in care and viral suppression as adolescents aged up from childhood to young adulthood helped account for outcomes among those in integrated care who did not transfer to a different healthcare facility (84). Age at which ART was initiated and transitioning to a higher age band both had effects on dis-engagement, with adolescents who initiated ART as children or young adolescents having lower rates of disengaging from care when aging t compared to those who initiated ART as older adolescents.

Also, data sources used to determine transition success affected how outcomes were reported. Depending on the data source used (visit records, laboratory records, or a combination of both), different rates of successful transfer were reported, and the reported delay between transfer and evidence of contact at the receiving facility varied depending on data source used (75).

Furthermore, inadequate readiness assessments were associated with unsuccessful transition outcomes. A study based on inadequate readiness criteria found that more than a third of eligible youth were still accessing care within paediatric care even after 18 months, and those who transitioned to adult care had poorer engagement rates (58%) compared to those who remained (100%) after 12-months (91). Delayed transition was attributed to various reasons including clinical, psychosocial, logistical, and structural issues such as lack of appropriate ART formulations in adult clinics (91).

The effect of age and the model of transition used were challenging to distinguish using observational data, as younger age groups were more likely to be transferred due to down referral to primary healthcare facilities. However, studies showed that transferring out of paediatric care at an older age (between 15 to 19 years) was associated with a higher risk of virologic failure and loss to follow-up (82). Also, a study from Zimbabwe reported that disengaging from care among those who started ART as older adolescents (15-19 years) doubled as they aged up to 20-24 years (84).

In a study from South Africa examining risk of dis-engaging from care among children on ART during transfer, by linking routine cohort data to laboratory data, up to two-thirds of individuals deemed to have unsuccessfully transferred and nearly half considered to have disengaged from care were found to have engaged with care at a later point based on the laboratory records. It is possible that participants self-transferred to another health facility or that their referral to a different facility was not recorded at the original one (89).

Viral suppression

Viral load outcomes were reported in a limited number of studies, revealing several important findings. Firstly, there was a decline in the availability of viral load measures over time. Studies noted that viral load data were missing for a varying proportion of participants, ranging from 11% to 58% following transfer (82,91). The proportion of missing viral load data did not significantly differ between those who remained in paediatric care and those who transitioned to adult HIV care (13% and 14%, respectively), in one study at the last viral load assessment (90).

Secondly, proportions of adolescent with viral suppression (with definition of viral suppression varying across studies as <200, <400 or <1000 copies/mL) varied across studies, ranging from as low as 37% (91) to as high as 70-90% (82,83,88–90). None of the studies reported viral suppression proportions exceeding the target of 90% set by UNAIDS. One study comparing viral suppression before and after transition found a decrease from 74% suppressed prior to transition to 42% one year after transition (79). However, another study found no significant differences in viral suppression rates between those who remained in paediatric care (80%) and those who transitioned to adult care (83%) one-year post-transition or 74% vs. 78% at the most recent viral load assessment (90). It is worth noting that viral load monitoring occurs annually, while retention measures are based on more frequent activities such as

clinic visits and pharmacy refills. Also, viral load measures are only conducted on those who are retained hence if retention drops, those still engaged in care are more likely to be suppressed. This may explain why rates of viral suppression did not differ significantly between the two groups, despite significant differences in retention rates (90). These findings support the notion of a cyclical cascade due to intermittent engagements in care for AYLH.

Lastly, viral suppression was poorer among older adolescents (82) and became poorer with increasing duration of follow up. For example, one study reported a decrease in viral suppression rates from 80% to 75% from one to three years post-transfer (82).

Experiences with the process of transitioning

Views regarding the transition experience varied widely across the studies. In two studies where a formal transition process was lacking, adolescents expressed overall satisfaction with the transition and were content with having made the transition, particularly in cases where the transition was prompted by pregnancy (76,86). Being at the adult clinic provided them with a sense of reassurance as they saw older patients living with HIV, which gave them hope for the future. Additionally, transitioning to the adult clinic was seen as a part of personal growth and separation from childhood. Transitioning closer to home also resulted in reduced transportation costs, making it more convenient (76,91). The anticipation of receiving additional services, such as sexual and reproductive health support, various ART delivery options, and information on safe sex, employment, and life skills, was seen as a positive aspect of transitioning to adult care (100).

Negative experiences during the transition process sometimes led to adolescents refusing to transition or returning to paediatric care after transitioning (77,91). Some adolescents expressed dissatisfaction with feeling unprepared, feeling rushed through the process, and being informed about their HIV status shortly before the transition (76,77). Lack of availability of adult clinics on weekends created difficulties for adolescents who had previously benefited from weekend clinic visits. This required them to miss school or work to attend their monthly appointments (77–79,86,91,100). High patient volumes and long waiting hours at adult clinics also posed challenges, particularly for adolescents with school schedules (78,79,86,100), in addition to inflexible clinic hours and rigid scheduling (81).

The loss of interpersonal relationships and support from peers, paediatric healthcare providers, and caregivers was highlighted as a significant challenge (77–79,91). Adolescents expressed concerns about losing support from caregivers after the transition, as they feared being seen as fully independent adults (78,79). Stigmatization experiences, especially when accessing services outside of the HIV clinic, were also reported by adolescents (77,85,86). Congestion and long waiting hours at the adult HIV clinic were mentioned as sources of frustration (78,91). Inflexible hours and rigid scheduling, that interfered with

schooling activities with many of them still in school, resulted in them either missing classes or needing to visit facility more than once for a healthcare visit and to collect their medications (91).

2.5 Discussion

The goal of HIV transitioning is to ensure that adolescents and young adults living with HIV continue to receive appropriate, uninterrupted, and developmentally appropriate healthcare as they age from adolescence to young adulthood. This review highlights the commonalities and outcomes in the healthcare transition process for AYLH in sub-Saharan Africa.

Transition models should consider the unique challenges and needs of adolescents in sub-Saharan Africa, as traditional models from high-resource settings may not directly apply. Multiple transition pathways exist in the region including transitioning from specialized paediatric care to adult clinics within the same or different facilities, down-referral to primary or community care facilities, transfers between primary care facilities, transfers from transitional clinics offering youth-friendly services, and adopting adult care approaches within integrated clinics. In addition, some adolescents experience cyclical transitions between paediatric and non-paediatric care. Furthermore, the timing of transition differs from developed countries, occurring earlier during childhood or early adolescence usually as part of decentralization of care.

Inadequate preparation for transition, poor communication between paediatric and adult healthcare providers, ineffective assessment of transition readiness, lack of a transition plan, and an unclear and unstructured transition process were identified as key challenges. To improve treatment outcomes, adolescents should be prepared for transition and equipped with health literacy and self-advocacy skills to navigate adult HIV clinics. Communication between healthcare providers in paediatric and adult clinics, as well as with caregivers, is crucial for successful transition preparation.

The age of the adolescent was found to be less relevant than the need for a well-planned transition process involving the adolescents themselves and collaboration among stakeholders. Quantitative outcomes are limited, with viral load monitoring post-transition largely lacking.

It is essential to consider the unique challenges and needs of adolescents in sub-Saharan Africa when designing transition models. Further research is needed to determine the optimal timing and approach for successful transitions to adult care in this context. This research needs to include development of pragmatic tools to distinguish between adolescents with perinatally and non-perinatally acquired HIV in analyses of routine data. Most of the reviewed papers did not report on it or inferred mode using only age at first visit as a proxy. Mode of HIV acquisition influences clinical management, however, may be information that is difficult to enquire from the AYLH. For some analyses it may be important to distinguish between these groups using variables commonly available in routine data. National

governments should develop context-specific policy guidelines to support effective healthcare transition practices for AYLH and monitor their outcomes. Such monitoring requires standardized definitions and assessments of successful transition, which are currently lacking. Improved data sources and tracking methods are necessary to accurately capture transition outcomes and identify areas for intervention to ensure continuity of care for adolescents.

Chapter 3: Improving Methods to Classify Perinatal Vs. Non-Perinatal HIV Acquisition in Young Adolescents 10–14 Years of Age

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3.1 Chapter overview and contribution to thesis

Adolescents living with HIV are a heterogeneous group, distinguished in part by their mode of HIV acquisition. While some characteristics may overlap, adolescents with perinatally acquired HIV often have distinct clinical profiles shaped by prolonged periods of untreated HIV and its associated complications. While many children with perinatal HIV enter care early, a subset, particularly slow progressors, may survive into adolescence without treatment. Modelling suggests that children who acquired HIV after infancy can survive up to 14 years without ART, making it plausible that adolescents aged 10–14 years entering care for the first time may have acquired HIV either perinatally or non-perinatally. In resource-limited settings, the mode of acquisition is rarely documented in routine clinical data, making classification difficult. Age at enrolment is often used as a proxy, commonly <10 or <15 years for perinatal acquisition, but this approach can lead to substantial misclassification.

To improve classification, predictive models can improve the accuracy of classification of AYLH presenting for HIV care between the ages of 10-15 years. this chapter addresses objective 1 of the PhD thesis: the development of a predictive algorithm to determine the likely mode of HIV acquisition among adolescents aged 10-15 years entering HIV care.

Role of the candidate

The candidate conceptualized the study and wrote the study concept, under the guidance of the supervisor. The candidate was solely responsible for conducting all the data cleaning and analyses, drafting the manuscript, incorporating all relevant comments from co-authors, and finalising and submitting the manuscript to the journal. In addition, the candidate subsequently addressed all journal comments and submitted the corrected manuscript for publication. All authors reviewed and approved the final manuscript before submission.

The candidate presented the findings of this analysis at the 22nd International Workshop on HIV and Hepatitis Observational Databases (IWHOD), Fuengirola Spain and 10th International Workshop on HIV Pediatrics 2018, Amsterdam, Netherlands.

Publication status

Published: Pediatric Infectious Disease Journal. 2021 May 1;40(5):453-456.

3.2 Abstract

Mode of HIV acquisition for adolescents with HIV is often not recorded within routine healthcare databases. Hence, age at enrolment in HIV care is often used as a proxy for perinatal vs. non-perinatal HIV acquisition. Using routine cohort data from adolescents presenting for HIV care 10–14 years of age, we developed logistic regression models to predict likely mode of HIV acquisition.

3.3 Introduction

The population of adolescents living with HIV is comprised of those with both perinatally and non-perinatally acquired HIV. While similar in some ways, adolescents with perinatally acquired HIV have differing socio-demographic and disease characteristics, vulnerabilities, and risk behaviours when compared to those with more recent HIV acquisition. Adolescents with perinatally acquired HIV have longstanding HIV, and those presenting for HIV care for the first-time during adolescence would have lived with untreated HIV for prolonged periods (15).

While most children with perinatally acquired HIV are expected to have presented for the first time for HIV care as infants or children, up to a third may have slow-progressing disease and could survive into adolescence without treatment (43). The Spectrum AIDS Impact Model has estimated median survival for children acquiring HIV after the first year of life of up to 14 years in the absence of any antiretroviral treatment (120,121). This means for adolescents presenting for the first time for HIV care between the ages of 10–14 years, perinatal and non-perinatal HIV acquisition are both plausible. In resource-limited settings, however, the mode of acquisition of children and adolescents is frequently not ascertained or captured within routine healthcare databases. In an effort to distinguish these two sub-groups within data, a number of analyses have used age cut-offs at enrolment as a proxy to categorize the likely mode of HIV acquisition, with those entering HIV care at specific ages, such as <10 (31,122) or <15 years (30), assumed to have perinatally acquired HIV. The optimal age threshold to use in such situations is unclear and using age cut-offs alone could result in substantial misclassification.

Using data from IeDEA Southern Africa, IeDEA Asia-Pacific and CCASAnet cohorts, we aimed to determine characteristics of adolescents with HIV 10–14 years of age at enrolment into routine HIV care that could predict and better distinguish likely mode of HIV acquisition.

3.4 Methods

We conducted an analysis on prospectively collected data of adolescents who enrolled into HIV care 10–14 years of age within the IeDEA Southern Africa, IeDEA Asia-Pacific and CCASAnet cohorts, from 1990–2017. IeDEA is an international research consortium of seven regional collaborations of HIV observational databases (www.iedea.org). Each regional collaboration combines routine

observational data from HIV care and treatment programs from several countries in their respective regions. Characteristics and outcomes of adolescents with HIV across the IeDEA collaboration have been described elsewhere (30,123,124).

Ethics

All IeDEA participating sites have ethics approval from their local IRB to contribute de-identified, anonymized, individual patient data to their IeDEA regional data centres. Each data centre has its own IRB approval to receive, combine and analyse this data. Patients/caregivers either provided informed consent for inclusion of their data in the respective regional databases or regional IRBs have granted consent waivers.

Measurements and outcomes

Characteristics of adolescents presenting for HIV care 10–14 years of age included demographic, anthropometric, and recorded mode of acquisition. Recorded mode of acquisition was categorized as perinatal, non-perinatal, and unknown. Perinatally acquired HIV was as reported by the sites, and included acquisition of HIV in utero, during labour, and delivery, or postnatally through breastfeeding. All other means of HIV acquisition were included as non-perinatally acquired HIV. Height measures were converted to age and sex specific height-for-age z-scores (HAZ) using the "who2007" Stata macro (125). The main outcome of interest was the mode of HIV acquisition, categorized as perinatal and non-perinatal.

Statistical analysis

Characteristics of adolescents enrolling into HIV care 10–14 years of age were described by mode of HIV acquisition (perinatal vs. non-perinatal vs. unknown) using medians with interquartile ranges (IQRs) and frequency distributions. To describe characteristics at entry into care, measurements from the date closest to the date of entry into care up to 6 months after were used. Using patient characteristics of adolescents with a documented mode of acquisition, logistic regression models to predict the likely mode of acquisition were developed. The predictive ability of the different models generated were compared using sensitivity, specificity, and area under the receiver operating characteristic curve (AUROC). As our model was aimed at prediction, variable and model selection was based on goodness-of-fit statistics. The different predictive models were then used to classify mode of HIV acquisition in those with an undocumented mode of acquisition and the classification results from models with different combinations of patient characteristics (age alone vs. age with HAZ and sex vs. age with HAZ, sex, and CD4 count) compared.

Statistical analyses were done using Stata 15.0 (StataCorp, College Station, TX, USA).

3.5 Results

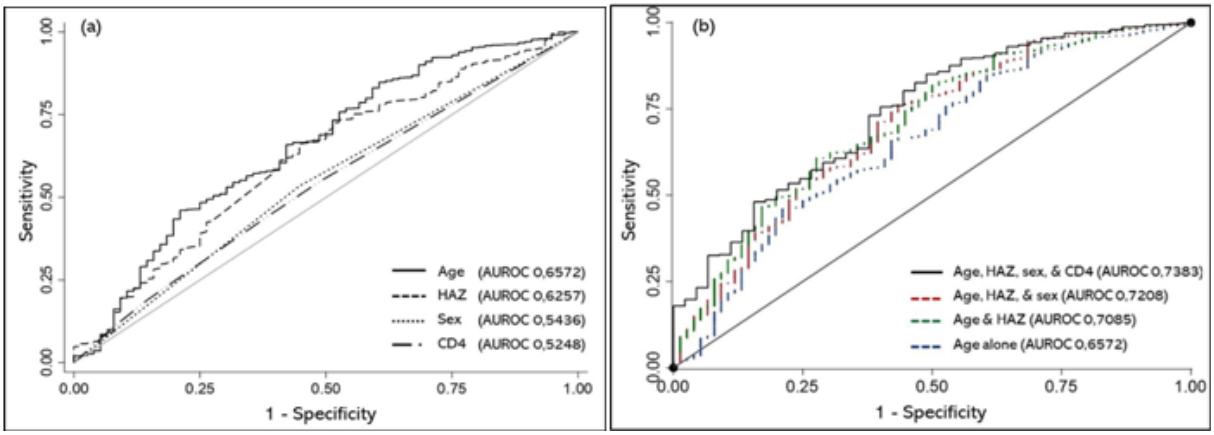
We included 10,349 adolescents (54% female) from 16 countries (9402 from IeDEA Southern Africa, 718 from IeDEA Asia-Pacific, 229 from CCASAnet. About two-thirds (65%) were <13 years of age at entry into HIV care (median [IQR] age 12.2 years [11.1;13.5]). Mode of HIV acquisition was documented in 20% (n=2,076); among these: 2,000 (96%) acquired HIV perinatally (53% female), and 76 (4%) acquired HIV non-perinatally (45% female). Adolescents with perinatally acquired HIV, when compared to those with documented non-perinatally acquired HIV, were more likely to be female (53% vs. 45%), slightly younger (median age 11.8 [10.8;13.0] vs. 12.7 [11.7;14.2] years), and had lower HAZ (median HAZ −2.27 [−3.10;−1.46] vs. −1.60 [−2.58;−0.82]) at enrolment into HIV care. There were no differences observed with regards to the median CD4 count at entry into care (186 [55;415] vs. 190 [54;431] cells/μL).

In multivariable logistic regression models using characteristics of adolescents with a documented mode of acquisition, perinatal HIV acquisition was associated with younger age at presentation (adjusted odds ratio [aOR] for each increasing year 0.62, 95%CI 0.52;0.75), lower HAZ (aOR for a 1 unit increase 0.65, 95% CI 0.53;0.79), and being female (aOR 1.64, 95% CI 0.99;2.72). CD4 count at first presentation was not predictive of perinatal HIV acquisition.

When considering only one predictive variable using models of characteristics of adolescents with documented mode of acquisition, a model with age alone (AUROC 0.6572, 95% CI 0.5903;0.7241) had the highest predictive ability when compared to models with only HAZ (AUROC 0.6257, 95% CI 0.5568;0.6946), sex (AUROC 0.5436, 95% CI 0.4863;0.6009), or CD4 count (AUROC 0.5248, 95% CI 0.4427;0.6070) (Figure 3.1). The model including age and HAZ had a higher AUROC (0.7085; 95% CI 0.6420;0.7749), with a further increase in predictive ability after adding sex (0.7208; 95% CI 0.6577;0.7839) and CD4 count (0.7383; 95% CI 0.6635;0.81304) (Figure 3.1).

When using a model based on age alone, 75% (95% CI 74;76) of adolescents 10–14 years of age with unknown mode of acquisition were classified as having perinatally acquired HIV. This proportion decreased to 65% (95% CI 64;66) with the addition of HAZ and sex to the model. However, these additions increased the proportion that could not be classified due to missing HAZ data (14%, 95% CI 13;15%). Further addition of CD4 count to the model decreased the proportion classified as perinatally acquired to 35% (95% CI 34;36) and increased the proportion that could not be classified to 56% (95% CI 55;57%).

Figure 3.1: Areas under the Receiver Operating Curves (ROC) for a) models with individual covariates and b) models with different covariates for predicting perinatal HIV acquisition among adolescents living with HIV presenting for HIV care 10–14 years of age



3.6 Discussion

Among adolescents living with HIV presenting for HIV care 10–14 years of age, only <20% of adolescents had documented mode of acquisition, highlighting the need for predictive models to address this data gap. Among those with a recorded mode of acquisition, <5% were reported as having acquired HIV non-perinatally, suggesting that the majority had acquired HIV perinatally. An age threshold of <10 years at enrolment as a proxy for perinatal acquisition in this population would thus have misclassified 97% of these adolescents. Raising the threshold to 15 years from 10 years recognizes the younger adolescents presenting very late for care, with severely suppressed immune systems and stunting. These adolescents are often a neglected group which may not fit in with paediatric clinics but also might not fit with older adolescent clinics where most patients have non-perinatally acquired HIV.

Predictive models of mode of HIV acquisition based on age, sex, and HAZ had a much higher AUROC than a model using age alone and misclassified considerably fewer adolescents compared to using an arbitrary age threshold of <10 years as a proxy for likely perinatally acquired HIV. Importantly, in our routinely collected data, mode of HIV acquisition could be classified in 86% of adolescents using age, sex and HAZ. This information provides a basis on which to test additional variables and build a more reliable algorithm.

Our study is limited by a relatively small proportion of adolescents having documented mode of acquisition and limited additional predictor variables (e.g., no data on parental death). There is also a risk of misclassification for those incorrectly reported as not having perinatally acquired HIV due to the lack of parental HIV information. Also, our study may have limited generalizability as the adolescents included in these analyses are those presenting for HIV care in health facilities that are part of research collaborations that routinely collected data on key variables required for the analysis, and our models

were developed using data from those with a documented mode of HIV acquisition. This group may not be representative of all adolescents with HIV or even all adolescents presenting for HIV care in other contexts. Furthermore, as the aim of this analysis was exploratory, focused on descriptive prediction rather than rigorous model comparison, formal statistical comparisons of AUROC values were not conducted. This limits the ability to determine whether observed differences in AUROC values between models were statistically significant or simply due to random variation. As such, caution is warranted in interpreting small differences in AUROC.

Lastly, this analysis assumes shared predictor relationships between those with and without known acquisition mode. Given that only a small proportion of adolescents had documented mode of acquisition and that this was limited to particular countries and cohorts, the associations with mode of acquisition identified in our predictive models may have been driven by the associations present in the subset of adolescents from countries and cohorts that had data on mode of acquisition, and these associations may not be generalizable. Unmeasured predictors, such as parental HIV information, clinical stage at presentation, differences in care-seeking behaviour, and socio-economic status may have biased classification.

Nonetheless, predictive models based on a small number of variables that are routinely available may be useful for analysts wanting to include likely mode of HIV acquisition when the mode of HIV acquisition is not recorded. If age alone is used as a proxy for mode of HIV acquisition due to missing data on predictor variables, careful consideration should be given to the appropriate age threshold for assuming likely perinatally acquired HIV in different contexts.

3.7 Conclusion

Using age alone as a proxy for mode of HIV acquisition is more likely to result in misclassifications among adolescents presenting for HIV care between the ages of 10-14 years. Analysts should consider using simple predictive models to determine likely mode of HIV acquisition when this is missing in data.

Chapter 4: Characteristics and outcomes of adolescents living with perinatally acquired HIV within Southern Africa

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4.1 Chapter overview and contribution to thesis

This chapter addresses objective 2 which seeks to evaluate the characteristics and outcomes of adolescents living with HIV in Southern Africa and ascertain the determinants that influence these outcomes. It offers a comprehensive analysis of the characteristics, outcomes, and determinants of care for over 25,000 adolescents accessing routine HIV care data within 15 healthcare facilities in Lesotho, Malawi, Mozambique, South Africa, Zambia, and Zimbabwe. The key demographic and clinical characteristics of these adolescents are presented at various stages of care, capturing a longitudinal perspective. In addition, retention in care, mortality, and viral suppression outcomes are assessed, shedding light on the factors influencing survival in this population.

One significant contribution of this study is the consideration of adolescents who entered HIV care between the ages of 10 and 13 years as having perinatally acquired HIV. This unique subgroup provides valuable insights into the outcomes and challenges faced by adolescents living with perinatally acquired HIV who are slow progressors and initiate care during early adolescence, as compared to those who enter care before the age of 10 years. The inclusion of adolescents entering care during adolescence provides novel insights that were previously unexplored. Previous research in Southern Africa typically focused on individuals who were assumed to have perinatally acquired HIV and entered care before the age of 10 years. By expanding the age range and considering the outcomes of those entering care during adolescence, this study reveals the substantially worse outcomes experienced by this subgroup, highlighting the importance of early HIV diagnosis and intervention.

Gaining insights into the treatment experiences and health status of adolescents living with HIV could inform the designing of effective transition strategies to adult HIV care. Our regional analysis reveals that the majority of those currently transitioning to adulthood in this setting often presented for HIV care in advanced stages of disease and initiated ART before the adoption of universal treatment policies. As a result, many were exposed to prolonged periods of untreated HIV during early childhood, placing them at risk for chronic immune activation and complications from delayed treatment.

We also observed limited catch-up growth during adolescence. Despite long-term ART, many adolescents exhibited persistent linear growth impairment, with minimal recovery over time. This suggests that AYLH in these settings may not achieve their full developmental potential. Such physical stunting can have lasting psychosocial effects, including internalized stigma, reduced self-esteem, and

social isolation, which may further undermine engagement in care, particularly during the critical transition to adult services. Addressing growth and its psychosocial consequences must be part of holistic transition support strategies.

As programmes prepare AYLH for transition, it is crucial to recognize the long-term effects of historical treatment access and to tailor support accordingly. Multidisciplinary approaches that integrate clinical, psychosocial, and developmental support will be necessary. Over the next decade, we can expect to see improved adolescent outcomes as children who started ART early in life mature, but for now, services must be adapted to the lived experiences of those who did not benefit from early intervention.

Role of the candidate

The candidate and supervisor conceptualized the concept and designed the study. The candidate wrote the study concept. The candidate was solely responsible for conducting all the data cleaning and analyses, drafting the manuscript, incorporating all relevant comments from co-authors, and finalising and submitting the manuscript to the journal. In addition, the candidate subsequently addressed all journal comments and submitted the corrected manuscript for publication. All authors reviewed and approved the final manuscript before submission.

The candidate presented the study findings at the 23rd International Workshop on HIV and Hepatitis Observational Databases (IWHOD), March 2019, Athens, Greece, the 11th International Workshop on HIV Pediatrics, July 2019, Mexico City, Mexico – for which the candidate received the award for best oral presentation by an early-stage investigator, and the 10th IAS Conference on HIV Science, July 2019, Mexico City, Mexico.

Publication status

Published: AIDS. 2020 December 1;34(15):2275-2284.

4.2 Abstract

Background

Using data from 15 IeDEA Southern Africa sites, we compared the characteristics and outcomes of adolescents living with perinatally acquired HIV.

Methods

We included adolescents living with perinatally acquired HIV entering care aged <13 years with ≥1 HIV care visit during adolescence (10–19 years). We compared the characteristics and cross-sectional outcomes: transfer out, loss to follow-up (LTFU: no visit in the 12 months prior to database closure), mortality, and retention between those who entered care aged <10 vs. aged 10–13 years; and explored predictors of mortality after age 13 years using Cox Proportional Hazards models.

Results

Overall, 16,229 (50% female) adolescents who entered HIV care aged <10 years and 8897 (54% female) aged 10–13 years were included and followed for 152,574 person-years. During follow-up, 94.1% initiated ART, with those who entered care aged <10 more likely to have initiated ART (97.9%, 95% CI 97.6;98.1%) than those who presented aged 10–13 years (87.3%, 95% CI 88.6;88.0%). At the end of follow-up, 3% had died (entered care aged <10 vs. 10–13 years; 1.4% vs. 5.1%), 22% were LTFU (16.2% vs. 33.4%), and 59% (66.4% vs. 45.4%) were retained. There was no difference in the risk of dying after the age of 13 years between adolescents entering care aged <10 vs. 10–13 years (adjusted hazard ratio [aHR] 0.72; 95% CI 0.36;1.42).

Conclusion

Retention outcomes for adolescents living with perinatally acquired HIV progressively worsened with increasing age, with these outcomes substantially worse among adolescents entering HIV care aged 10–13 vs. <10 years.

4.3 Introduction

Southern Africa is home to nearly 40% of the estimated 1.6 million adolescents aged 10–19 years living with HIV globally (5,126,127). This population is comprised of adolescents living with perinatally acquired HIV as well as those who acquired HIV non-perinatally during childhood or adolescence. Adolescents with perinatally acquired HIV have longstanding HIV acquired at a time when their immune systems were not fully developed and experience the rapid physical, mental, and psychosocial changes characteristic of adolescence while living with a chronic, often stigmatized disease (4,15,21).

Current evidence has shown that in comparison to adults and young children living with HIV, adolescents generally have poorer outcomes (29,32,128). They are underserved by the current HIV care services, have lower access to ART, are more likely to be LTFU, and have poorer growth and adherence to treatment (37,38,129). Previous research examining outcomes of adolescents living with perinatally acquired HIV within Southern Africa assumed perinatal acquisition among those entering care before the age of 10 years and examined outcomes of younger adolescents (10–14 years of age) (31). While most children with perinatally acquired HIV present for care as infants or children, up to a third have slow-progressing disease and survive into adolescence without treatment (120,130–135). Data are lacking on the exact numbers of adolescents in this category, their characteristics, or how their outcomes differ from those presenting earlier.

Using data merged from 15 cohorts in the IeDEA-Southern Africa collaboration, we compared the characteristics (demographic, clinical, anthropometric) and outcomes (transfer out [TFO], LTFU, mortality, and retention) of adolescents who entered care aged <10 years vs. aged 10–13 years; and explored the predictors of mortality after the age of 13 years.

4.4 Methods

Study population and design

We conducted an analysis of prospectively collected data of adolescents living with perinatally acquired HIV in care within sites contributing data to the IeDEA Southern Africa collaboration between January 2004 and December 2017. IeDEA Southern Africa is the Southern African regional collaboration of the IeDEA consortium. It combines routine, observational, prospectively collected, individual patient data from ART programs in six Southern Africa countries: Lesotho, Malawi, Mozambique, South Africa, Zambia, and Zimbabwe. Cohorts within IeDEA Southern Africa range in size, are predominantly government-funded and follow national HIV treatment guidelines. Each participating site transfers anonymized data to the IeDEA Southern Africa data centres at the University of Cape Town in South Africa and the University of Bern in Switzerland at regular intervals (approximately annually) using a standard data transfer and exchange standard for inclusion in combined analyses (67).

Ethics

All participating sites have institutional ethical approval from the Institutional Review Boards (IRBs) to contribute anonymized individual patient data to the IeDEA Southern Africa data centres. The Data centres have ethical approval to receive and analyse anonymized patient data from the individual sites. Most local IRBs waived the need for informed consent for analysis of de-identified routine patient data, but where the IRB required informed consent, this was obtained from the caregiver with verbal assent from the child.

Measurements and outcomes

As mode of HIV acquisition was not routinely reported in the data, we used age of entry into HIV care <13 years as a proxy for perinatal acquisition, unless a non-perinatal mode was recorded. We included adolescents who entered care aged 10–13 years to capture those children with slow-progressing disease who survive into adolescence without treatment. Adolescents with perinatally acquired HIV were thus defined as patients who entered HIV care aged <13 years, with no documentation of non-perinatal causes of acquiring HIV, and with >=1 HIV care visit during adolescence. We excluded participants with missing data on sex or with <6 months of potential follow-up from entry into care until database closure.

We defined entry into HIV care and into our study as the first recorded HIV care visit in the respective cohort. We defined ART initiation as the earliest date recorded in the databases when a triple-drug ART regimen was dispensed. Characteristics of adolescents with perinatally acquired HIV at entry into HIV care, at ART initiation, across various ages during adolescence, and at last visit included demographic (age, sex, calendar year, and country); clinical (WHO clinical staging, ART regimens, CD4 absolute cell count and percentage, and HIV-RNA viral load); and anthropometric (height and body mass index [BMI]) variables. To describe characteristics at entry into care, measurements from the date closest to the date of entry into care up to 1 month after were used. Measurements closest to the date of ART initiation, birthday of interest, and last visit within a window of ±6 months were used to describe the characteristics at ART start, across various ages during adolescence, and at last visit, respectively. In assessing viral suppression, only adolescents in care within sites offering routine (at least annual) viral load measurements were included. HIV-RNA viral load measures from the date closest to each respective birthday, within a window of ±9 months, were used to describe viral suppression across the various ages during adolescence. We used an 18-month window to assess viral suppression, as routine viral load testing is recommended annually, and we wanted to allow enough time on either side of the date of each birthday for a viral load to be done and recorded. Viral suppression was considered as an HIV-RNA <400 copies/ml.

Age at entry into HIV care was categorized as <10 years and 10–13 years. Severe immunosuppression was defined where the CD4 absolute cell count or percentage met classification as per WHO immunologic classifications for established HIV (136). Height, and BMI measures were converted to age and sex-specific z-scores (height-for-age z-score [HAZ] and BMI-for-age z-score [BAZ]) using the WHO "igrowup_restricted" Stata macro (137) for up to 5 years of age and the "who2007" Stata macro (125) from 5 to 19 years of age. HAZ and BAZ were further categorized as >−2, ≤−2 to >−3, and ≤−3.

The outcomes of this analysis included LTFU, TFO, mortality, and retention. We defined LTFU as having no recorded visit in the 12 months prior to the individual cohort database closure, with no record of having died or transferred care. The date of being LTFU was set as the date of last contact with the site. TFO was defined as any documented transfer of care. Mortality included all-cause mortality recorded in the dataset. We defined retention as having a recorded visit in the 12 months prior to database closure with no record of having died or been TFO.

Statistical analysis

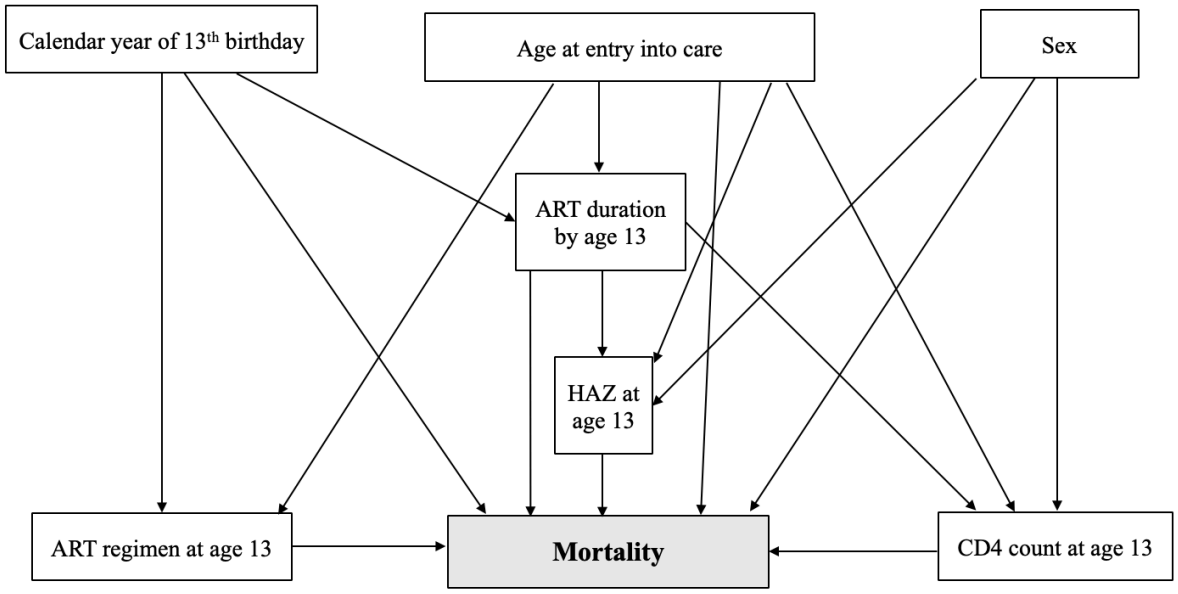
Participants entered the analysis on the date of their first visit and exited on the earliest date of death, TFO, LTFU, or their 22nd birthday. Cross-sectional immunological, virologic, and anthropometric characteristics of adolescents as well as mortality, LTFU, TFO, and retention outcomes are presented by age of entry into care (<10 years vs. 10–13 years).

In addition, separate cumulative incidence estimates for mortality, LTFU, TFO, and corresponding retention are calculated using competing risks analysis. For adolescents who entered care aged <10 years, person-time for cumulative incidence estimates started on the date of their 10th birthday and ended on the date of death, TFO, LTFU, or 22nd birthday, whichever occurred first. Person-time for cumulative incidence estimates for adolescents who entered care aged 10–13 years started on the date of their first visit and ended on the date of death, TFO, LTFU, or 22nd birthday, whichever occurred first.

We used Cox proportional hazards models to identify predictors of mortality following the 13th birthday with. This semi-parametric regression method estimates the risk of death at a given time point, while adjusting for potential confounding variables. The model assumes proportionality of hazards over time, meaning the relative risk between comparison groups remains constant throughout the follow-up period. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to assess the strength and direction of associations between covariates and mortality risk. The proportional hazards assumption was assessed using Schoenfeld residuals and graphical methods. Variables that violated this assumption were either stratified or interacted with time to account for non-proportionality.

Models only included adolescents who had initiated ART by their 13th birthday and were still alive and in care at the age of 13 years, as participants started contributing person-time from the date of their 13th birthday. Models were adjusted for the following characteristics, which were known or assumed to be potential confounders associated with mortality as guided by the directed acyclic graph (DAG) shown in Figure 4.1: age at entry into care (aged <10 vs. 10–13), sex (male vs. female), ART duration and regimen by 13th birthday, calendar year of 13th birthday, CD4 count at 13th birthday, and HAZ at 13th birthday. Furthermore, we conducted a sensitivity analysis including only those who had been on ART for ≥1 year by the age of 13 years to exclude those with a very high mortality after ART initiation.

Figure 4.1: Directed acyclic graph (DAG) illustrating the assumed causal relationships between variables included in the analysis to identify predictors of mortality of adolescents and youth living with HIV (AYLH) following their 13th birthday



All statistical analyses were done using Stata 15.0 (StataCorp, College Station, TX, USA).

4.5 Results

Of the 25,496 adolescents within the IeDEA Southern Africa database who met our eligibility criteria, we excluded 22 with missing data on sex and 348 with <6 months of potential follow-up. In total, 25,126 adolescents (51.5% female) from 15 IeDEA Southern Africa sites in six Southern African countries were thus included (Table 3.1).

Baseline characteristics at entry into HIV care

Approximately two-thirds (n=16,229) of adolescents in our analysis entered HIV care before the age of 10 years, at a median (IQR) age of 6.7 (4.4;8.4) years. The median (IQR) age at first visit among those who entered care between the ages of 10–13 years (n=8897) was 11.4 (10.6;12.1) years (Table 4.1). Among those with measurements at their first visit, just over half presented for care severely immunosuppressed, with no difference observed between those presenting aged <10 years vs. aged 10–13 years.

Table 4.1: Characteristics of adolescents living with perinatally acquired HIV at entry into HIV care

Characteristic	First visit aged <10 years	First visit aged 10–13 years	All
Total number, n (%)	16,229 (64.6%)	8897 (35.4%)	25,126 (100%)
Sex: Male, n (%)	8070 (49.7%)	4115 (46.2%)	12,185 (48.5%)
Female, n (%)	8159 (50.3%)	4782 (53.8%)	12,941 (51.5%)
Year of birth, median (IQR)	2002 (2000; 2004)	1999 (1996; 2001)	2001 (1998; 2004)
Country, n (%)			
Lesotho	232 (1.4%)	134 (1.5%)	366 (1.5%)
Malawi	2003 (12.3%)	1402 (15.8%)	3405 (13.5%)
Mozambique	65 (0.4%)	50 (0.6%)	115 (0.5%)
South Africa	7758 (47.8%)	3243 (36.4%)	11,001 (43.8%)
Zambia	4980 (30.7%)	3181 (35.7%)	8161 (32.5%)
Zimbabwe	1191 (7.3%)	887 (10.0%)	2078 (8.3%)
Age (years) at first visit, median (IQR)	6.7 (4.4; 8.4)	11.4 (10.6; 12.1)	8.6 (5.8; 10.8)
Year of first visit, median (IQR)	2008 (2006; 2010)	2010 (2008; 2013)	2009 (2006; 2011)
2004 to 2006, n (%)	5108 (31.5%)	1389 (15.6%)	6497 (25.9%)
2007 to 2010, n (%)	7733 (47.6%)	3433 (38.6%)	11,166 (44.4%)
2011 to 2017, n (%)	3388 (20.9%)	4075 (45.8%)	7463 (29.7%)
Severely immunosuppressed‡, n/N	11,195/ 16,229	5795/ 8897	16,990/25,126
n (%)	5778 (51.6%)	2954 (51.0%)	8732 (51.4%)
CD4 percentage§, n/N	2918/4862	–	2918/4862
median (IQR)	16 (11.0; 23.0)	–	16 (11.0; 23.0)
CD4 cell count (cells/μL)§, n/N	6812/ 11,367	5360/ 8897	12,172/ 20,264
median (IQR)	351 (175; 606)	283 (123; 488)	321 (148; 553)
<350, n (%)	3380 (49.6%)	3219 (60.1%)	6599 (54.2%)
350 to 500, n (%)	1166 (17.1%)	861 (16.1%)	2027 (16.6%)
>500, n (%)	2266 (33.3%)	1280 (23.9%)	3546 (29.1%)
Height-for-age z-score (HAZ), n/N	8570/ 16,229	5245/ 8897	13,815/25,126

Characteristic	First visit aged <10 years	First visit aged 10–13 years	All
median (IQR)	−2.11 (−3.05; −1.19)	−2.20 (−3.05; −1.30)	−2.15 (−3.05; −1.23)
>−2, n (%)	3992 (46.6%)	2319 (44.2%)	6311 (45.7%)
≤−2 to >−3, n (%)	2316 (27.0%)	1540 (29.4%)	3856 (27.9%)
≤−3, n (%)	2262 (26.4%)	1386 (26.4%)	3648 (26.4%)
Body mass index-for-age z-score (BAZ), n/N	8738 / 16,229	5296/ 8897	14,034/25,126
median (IQR)	−0.41 (−1.34; 0.44)	−1.07 (−2.01; −0.27)	−0.67 (−1.62; 0.21)
Body mass index (kg/m^2), n/N	8615 / 16,229	5189/ 8897	13,804/25,126
median (IQR)	15.1 (14.1; 16.4)	15.5 (14.3; 16.9)	15.3 (14.1; 16.6)

‡As defined in the WHO 2006 guidelines criteria; §CD4 percentage assessed in adolescents that entered care aged <5 years; CD4 cell count assessed in adolescents that entered care aged ≥5 years

n/N – number of non-missing observations/total eligible; ART – antiretroviral therapy; IQR – interquartile range;

Median HAZ was below the −1 z-score and median BAZ below the 0 z-score (Table 4.1). There were no differences observed in the HAZ and BMI between those presenting aged <10 years vs. aged 10–13 years (Table 4.1).

Patient characteristics at ART initiation

In total, 94.1% of all adolescents initiated ART during follow-up, with those who entered care aged <10 years more likely to have initiated ART (97.9%, 95% CI 97.6;98.1%) compared to those who presented aged 10–13 years (87.3%, 95% CI 88.6;88.0%; Table 4.2). Median (IQR) age at ART start for adolescents who entered care aged <10 years was 7.2 (4.8;8.9) years vs. 11.6 (10.8;12.3) years for those who entered aged 10–13 years. Approximately two-thirds of adolescents with data available were classified as WHO clinical stage 3 or 4, 54.6% (95% CI 53.8;55.4%) as severely immunosuppressed, 55.1% (95% CI 54.2;56.0%) as stunted (HAZ ≤ −2), and 16.9% (95% CI 16.3;17.6%) as wasted (BAZ ≤−2). Median (IQR) CD4 counts, HAZ, and BAZ at ART start were generally higher among those who entered care aged <10 years compared to those who entered aged 10–13 years (Table 4.2).

Table 4.2 Characteristics of adolescents living with perinatally acquired HIV at antiretroviral therapy start

Characteristic	First visit aged <10 years	First visit aged 10–13 years	All
Ever initiated ART, n (%)	15,883 (97.9%)	7770 (87.3%)	23,653 (94.1%)
Age (years) at ART start, median (IQR)	7.2 (4.8; 8.9)	11.6 (10.8; 12.3)	8.9 (6.1; 10.9)

Characteristic	First visit aged <10 years	First visit aged 10–13 years	All
0 to 4.9, n (%)	4142 (26.1%)	–	4142 (17.5%)
5 to 9.9, n (%)	10,701 (67.4%)	–	10,701 (45.2%)
≥10, n (%)	1040 (6.5%)	7770 (100)	8810 (37.3%)
Year of ART start, median (IQR)	2008 (2006; 2011)	2010 (2008; 2013)	2009 (2007; 2011)
Severely immunosuppressed‡, n/N	10,823/ 15,883	4994/ 7770	15,817/23,653
n (%)	5850 (54.0%)	2791 (55.9%)	8641 (54.6%)
CD4 percentage§, n/N	2510/4142		2510/4142
Median (IQR)	15.0 (10.0; 21.1)	–	15.0 (10.0; 21.1)
CD4 cell count (cells/μL)§, n/N	7001/ 11,741	4562/ 7770	11,563/19,511
Median (IQR)	329 (170; 568)	251 (109; 423)	297 (142; 505)
<350, n (%)	3710 (53.0%)	3025 (66.3%)	6735 (58.2%)
350 to 500, n (%)	1204 (17.2%)	703 (15.4%)	1907 (16.5%)
>500, n (%)	2087 (29.8%)	834 (18.3%)	2921 (25.3%)
Height-for-age z-score (HAZ), n/N	8702/ 15,883	4597/ 7770	13,299/23,653
Median (IQR)	−2.12 (−3.03; −1.22)	−2.24 (−3.06; −1.36)	−2.16 (−3.05; −1.27)
>−2, n (%)	4021 (46.2%)	1949 (42.4%)	5970 (44.9%)
≤−2 to >−3, n (%)	2443 (28.1%)	1409 (30.6%)	3852 (29.0%)
≤−3, n (%)	2238 (25.7%)	1239 (27.0%)	3477 (26.1%)
Body mass index-for-age z-score (BAZ), n/N	8860/ 15,883	4659/ 7770	13,519/23,653
Median (IQR)	−0.40 (−1.30; 0.44)	−1.02 (−1.93; −0.24)	−0.62 (−1.54; 0.24)
Body mass index (kg/m2), n/N	8765/ 15,883	4583/ 7770	13,348/23,653
Median (IQR)	15.3 (14.1; 16.6)	15.7 (14.5; 17.1)	15.4 (14.2; 16.8)
WHO stage, n/N	11,028/ 15,883	5623/ 7770	16,651/23,653
1 or 2, n (%)	3909 (35.5)	2319 (41.2)	6228 (37.4)
3 or 4, n (%)	7119 (64.5)	3304 (58.8)	10,423 (62.6)
First line regimen, n/N	14,784/ 15,883	7263/ 7770	22,047/23,653
2 NRTI + EFV, n (%)	7074 (47.8)	3760 (51.8)	10,834 (49.1)
2 NRTI + NVP, n (%)	6438 (43.5)	3362 (46.3)	9800 (44.4)
2 NRTI + PI, n (%)	1272 (8.6)	141 (1.9)	1413 (6.4)

‡As defined in the WHO 2006 guidelines criteria; §CD4 percentage assessed in adolescents that entered care aged <5 years; CD4 cell count assessed in adolescents that entered care aged ≥5 years

ART – Antiretroviral therapy; EFV – Efavirenz; IQR – Interquartile range; NNRTI - Nucleoside reverse transcriptase inhibitor; NVP – Nevirapine; PI – Protease Inhibitor; n/N – number of non-missing observations/total eligible; IQR – interquartile range;

Patient characteristics at various ages during adolescence

Among the 16,229 adolescents who entered care before the age of 10 years, approximately 91.9% had initiated ART by their 10th birthday (Table 4.3). At age 10 years, median (IQR) CD4 count was 716 (465;1009) cells/μL, with 71.5% of adolescents having a CD4 count >500 cells/μL; duration on ART 3.1 (1.4;5.3) years; with 89.5% on a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen; and 10.5% on a protease inhibitor (PI)-based regimen. Among those on a PI-based regimen at age 10 years, 37.2% (95% CI 34.6;40.0%) had been previously switched from an NNRTI (Table 4.3). Among adolescents in care within facilities offering routine annual HIV-RNA viral load testing and on ART by the age of 10 years (n=7331), 72.7% (95% CI 71.6;73.7%) had a documented viral load measurement at age 10 years, and among these, 78.0% (95% CI 76.9;79.1%) were virally suppressed.

Table 4.3: Characteristics at entry into adolescence (at age 10 years) in adolescents living with perinatally acquired HIV who entered HIV care before the age of 10 years (N=16,229)

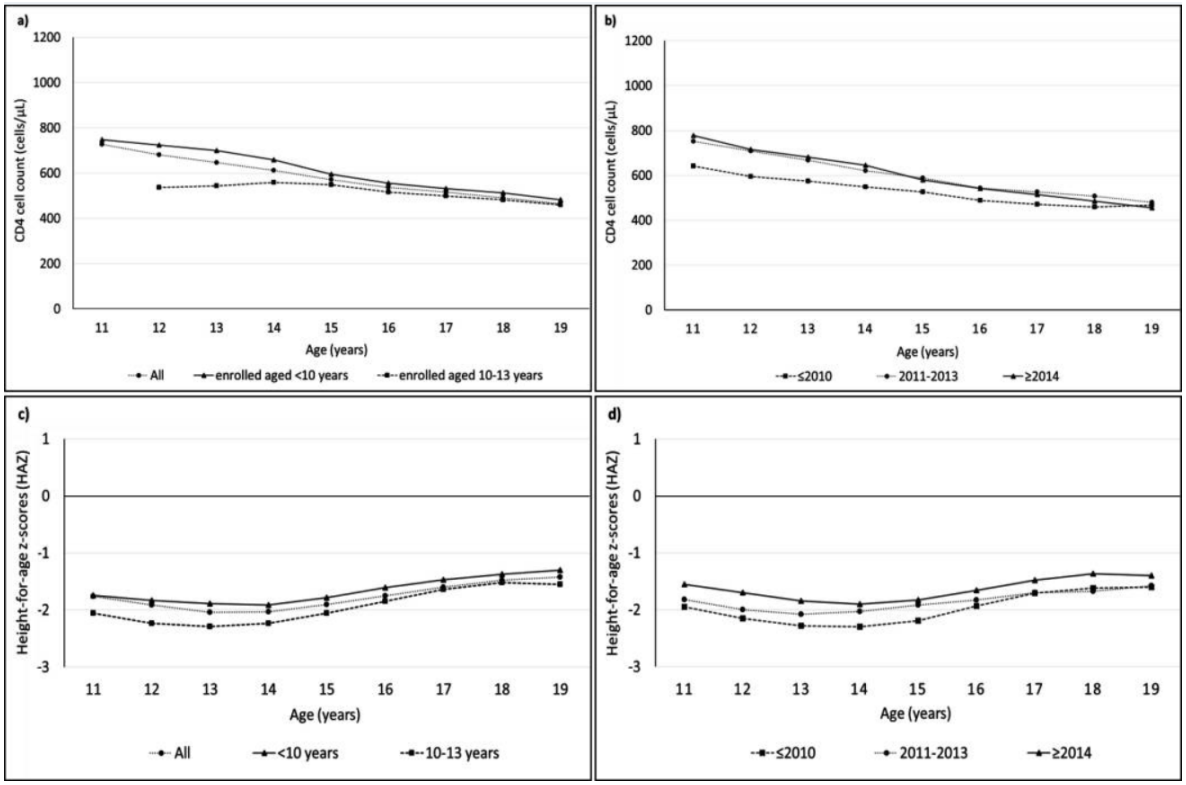
Characteristics at entry into adolescence	n/N*	First visit aged <10 years
Year of 10th birthday, median (IQR)	16,229/16,229	2012 (2010 – 2014)
<2010, n (%)	16,229/16,229	3668 (22.6)
2010 to 2013, n (%)	16,229/16,229	6902 (42.5)
2014 to 2018, n (%)	16,229/16,229	5659 (34.9)
Initiated ART by age 10 years, n (%)	16,229/16,229	14,913 (91.9)
Duration on ART (years), median (IQR)	14,913/14,913	3.1 (1.4 – 5.3)
<2, n (%)		5124 (34.4)
2 to 5, n (%)		5584 (37.4)
>5, n (%)		4205 (28.2)
Regimen at age 10 years, n (%)	12,463/14,913	
EFV-based		6210 (49.8)
NVP-based		4944 (39.7)
PI-based		1309 (10.5)
Among those on a PI-based regimen at age 10 years, proportion switched to PI-based regimen before age 10 years, n (%)	1265**/1309	471 (37.2)
CD4 cell count (cells/μL), median (IQR)	8311/16,229	716 (465 – 1009)
<350, n (%)		1325 (15.9)
350 to 500, n (%)		1041 (12.5)
>500, n (%)		5945 (71.5)
Height-for-age z-score (HAZ), median (IQR)	8459/16,229	-1.64 (-2.41 – -0.91)
≤-2, n (%)		3199 (37.8)

Characteristics at entry into adolescence	n/N*	First visit aged <10 years
Weight-for-age z-score (WAZ), median (IQR)	9381/16,229	-1.33 (-2.07 – -0.63)
≤-2, n (%)		2549 (27.2)
Body mass index-for-age z-score (BAZ), median (IQR)	8483/16,229	-0.45 (-1.14 – 0.21)
≤-2, n (%)		732 (8.6)
Body mass index (kg/m2), median (IQR)	8455/16,229	15.7 (14.7 – 16.9)
HIV-RNA viral load done***, n (%)	7331/7331	5327 (72.7)
HIV-RNA viral load*** (copies/mL), n (%)	5327/7331	
≤400		4157 (78.0)
>400		1170 (22.0)

ART – Antiretroviral Therapy; EFV – Efavirenz; NVP – Nevirapine; PI – Protease inhibitor
*n/N – number with non-missing observations in which measure assessed over total number that should be assessed
** Proportion assessed in adolescents on PI-based regimen at 10 years of age and with regimen data available at ART start and at age 10 years
*** proportion with HIV-RNA viral load measures assessed only in adolescents on ART by the age of 10 years and in care within facilities with routine annual viral load testing

Comparing characteristics of adolescents across various ages during adolescence, median CD4 counts for younger adolescents (10–14 years) were generally higher than for older adolescents (15–19 years). Also, across adolescence, median CD4 counts for adolescents who entered care aged <10 years were generally higher when compared to those for adolescents who entered care aged 10–13 years. This trend was similarly observed in a separate analysis restricted to those who had been on ART for ≥1 year. Furthermore, median CD4 counts for adolescents in care from 2014 onwards were generally higher than those from the previous years (Figure 4.2).

Figure 4.2 Median CD4 cell counts and height-for-age z-scores among adolescents living with perinatally acquired HIV on ART for at least 1 year across various ages by age of enrolment into HIV care and by calendar period of respective birthdays.



a. Median CD4 cell counts among adolescents living with perinatally acquired HIV across various ages by age of enrolment into HIV care
b. Median CD4 cell counts among adolescents living with perinatally acquired HIV across various ages by calendar period of respective birthdays
c. Median height-for-age z-scores (HAZ) among adolescents living with perinatally acquired HIV across various ages by age of enrolment into HIV care
d. Median height-for-age z-scores (HAZ) among adolescents living with perinatally acquired HIV across various ages by calendar period of respective birthdays

Patient characteristics at last visit

Characteristics of adolescents at last visit are shown in Table 4.4. Participants contributed 152,574 person-years of follow-up (median 6.2, IQR 3.1;8.8 years), of which 91,619 person-years was during adolescence (median 3.1, IQR 1.2;5.6 years). At last visit, the median (IQR) age was 13.6 (11.7;16.1) years, with 3210 (12.8%) aged >18 years. The median (IQR) duration of follow-up for adolescents living with perinatally acquired HIV who entered care aged <10 years was 7.5 (5.1;9.7) years compared to 3.1 (0.9;6.1) years for those who entered care aged 10–13 years.

Table 4.4 Characteristics of adolescents living with perinatally acquired HIV at last visit

Characteristic	First visit aged <10 years (N=16,229)	First visit aged 10–13 years (N=8897)	All (N=25,126)
Age (years) at last visit, median (IQR)	13.1 (11.4; 15.3)	14.4 (12.5; 17.6)	13.6 (11.7; 16.1)
10 to 13.9, n (%)	9935 (61.2)	3978 (44.7)	13,913 (55.4)
14 to 17.9, n (%)	5067 (31.2)	2936 (33.0)	8003 (31,8)
18 to 22, n (%)	1227 (7.6)	1983 (22.3)	3210 (12.8)
Duration of follow-up (years), median (IQR)	7.5 (5.1; 9.7)	3.1 (0.9; 6.1)	6.2 (3.1; 8.8)
Total person-years	119,156	33,418	152,574
Duration of follow-up (years) during adolescence (between 10–19 years); median (IQR)	3.1 (1.4; 5.3)	3.1 (0.9; 6.1)	3.1 (1.2; 5.6)
Total person-years	58,201	33,418	91,619
ART duration (years): median (IQR)	7.0 (4.4 – 9.3)	3.4 (1.3 – 6.3)	6.0 (3.1 – 8.6)
CD4 cell count (cells/μL), n/N	7804/ 16,229	4704/ 8897	12,508/ 25,126
Median (IQR)	649.5 (418; 907)	456 (247.5; 684)	573 (341; 828)
Height-for-age z-score (HAZ), n/N	9055/ 16,229	4726/ 8897	13,781/ 25,126
Median (IQR)	−1.66 (−2.49; −0.87)	−2.00 (−2.91; −1.12)	−1.77 (−2.64; −0.94)
Body mass index-for-age z-score (BAZ), n/N	9098/ 16,229	4767/ 8897	13,865/ 25,126
Median (IQR)	−0.65 (−1.43; 0.07)	−0.86 (−1.79; −0.06)	−0.72 (−1.54; 0.03)
Body mass index (kg/m2), n/N	9062/ 16,229	4706/ 8897	13,768/ 25,126
Median (IQR)	17.0 (15.5; 19.0)	17.2 (15.4; 19.4)	17.1 (15.5; 19.1)
Outcomes, n (%)			
Died	229 (1.4%))	455 (5.1%)	684 (2.7%)
Lost to follow-up (LTFU)	2638 (16.2%)	2970 (33.4%)	5608 (22.3%)
Transferred out (TFO)	2590 (16.0)	1436 (16.1%)	4026 (16.0%)
Retained	10,772 (66.4%)	4036 (45.4%)	14,808 (58.9%)

ART – Antiretroviral therapy; IQR – interquartile range

Outcomes

At the end of follow-up, 684 (2.7%) adolescents had died, 4026 (16.0%) had transferred care, 5608 (22.3%) had been LTFU, and 14,808 (58.9%) were still actively in care. Compared to those that entered care aged <10 years, a higher proportion of adolescents entering care aged 10– 13 years died (1.4% vs. 5.1%) and were LTFU (16.2% vs. 33.4%), while a lower proportion were retained in care (66.4% vs. 45.4%). at the end of follow-up (Table 4.4). For adolescents who entered care aged <10 years, cumulative 5-year incidence estimates (95% CI) from the age of 10 years were 1.5% (1.3;1.7%) for mortality; 17.8% (17.1;18.4%) for LTFU; and 17.6% (17.0;18.3%) for TFO. Corresponding 5-year cumulative probability for being retained was 63.1% (61.6;64.6%). For adolescents who entered care

aged 10–13 years, cumulative 5-year incidence estimates (95% CI) from first visit were 4.7% (4.2;5.1%) for mortality; 28.0% (27.1;28.9%) for LTFU; and 13.9% (13.2;14.7%) for TFO. Corresponding 5-year cumulative probability of being retained was 53.4% (51.4; 55.5%).

In the adjusted regression model, characteristics at age 13 years associated with having a decreased risk of dying after the age of 13 years were: reaching age 13 years in more recent calendar years (aHR per increasing year 0.91; 95% CI 0.84;0.99); having a CD4 count between 350 and 500 cells/μL (aHR 0.37; 95% CI 0.21;0.63) or >500 cells/μL (aHR 0.14; 95% CI 0.09;0.23) compared to a CD4 count <350 cells/ and HAZ>−2 (aHR 0.57, 95% CI 0.36;0.91) or ≤−2 to >−3: 0.61, 95% CI 0.38;0.98 vs. HAZ≥−3) (Table 4.5, Multivariate Model A). Increasing age of entry into HIV care, sex, ART duration, and ART regimen were not associated with mortality. Similar results were obtained in a sensitivity analysis restricted to adolescents living with perinatally acquired HIV who had been on ART for ≥1 year by age 13 years (Table 4.5, Multivariate Model B).

Table 4.5 Cox-proportional hazards model for predictors of mortality following the 13th birthday among adolescents living with perinatally acquired HIV initiated ART by age 13 years and still in care after the age of 13 years (N=13,470)

Characteristic	Univariate models HR (95% CI)	Multivariate model A aHR‡ (95% CI)	Multivariate model B aHR‡ (95% CI)
Age of entry into HIV care (years)			
<10	0.45 (0.35 – 0.59)	0.72 (0.36 – 1.43)	0.72 (0.34 – 1.52)
10–13	ref	ref	ref
Sex			
Female	0.99 (0.78 – 1.25)	1.34 (0.91 – 1.98)	1.19 (0.73 – 1.96)
Male	ref	ref	ref
ART duration (years) at age 13 years (per 1-year increase)	0.80 (0.75 – 0.85)	0.92 (0.77 – 1.10)	0.85 (0.67 – 1.09)
ART regimen at age 13 years			
Efavirenz-based	ref	ref	ref
Nevirapine based	1.37 (1.03 – 1.83)	0.88 (0.50 – 1.55)	1.17 (0.54 – 2.51)
Protease inhibitor-based	1.56 (0.97 – 2.52)	1.42 (0.74 – 2.73)	1.52 (0.72 – 3.17)
Other	3.70 (1.17 – 11.71)	1.50 (0.34 – 6.67)	9.62 (1.17 – 78.92)
Calendar year of 13th birthday (per 1-unit increase)	0.84 (0.80 – 0.88)	0.91 (0.83 – 0.99)	0.97 (0.86 –1.09)
CD4 cell count (cells/μL) at age 13 years			
<350	ref	ref	ref
350 to 500	0.42 (0.27 – 0.65)	0.37 (0.22 – 0.64)	0.37 (0.19 – 0.72)

Characteristic	Univariate models HR (95% CI)	Multivariate model A aHR‡ (95% CI)	Multivariate model B aHR‡ (95% CI)
>500	0.14 (0.10 – 0.21)	0.15 (0.09 – 0.25)	0.12 (0.06 – 0.22)
HAZ at age 13 years			
>−2	0.43 (0.29 – 0.64)	0.57 (0.36 – 0.91)	0.46 (0.24 – 0.86)
≤−2 to >−3	0.49 (0.32 – 0.75)	0.61 (0.38 – 0.98)	0.71 (0.39 – 1.29)
≥−3	ref	ref	ref

‡Models also adjusted for country
ART – antiretroviral therapy; HR – Hazard ratio; aHR – adjusted hazard ratio; 95% CI – confidence interval; HAZ – height-for-age z-score
Multivariate Model A – includes adolescents living with perinatally acquired HIV initiated ART by age 13 years and still in care after the age of 13 years.

4.6 Discussion

This analysis presents the HIV treatment outcomes of over 25,000 adolescents within Southern Africa, from as early as 2004 up to 2017. We found that increasing numbers of adolescents had suboptimal outcomes during adolescence, with these outcomes substantially worse among adolescents entering HIV care during adolescence versus before age 10 years.

In this analysis, perinatal HIV acquisition was assumed in all adolescents who had entered care before the age of 13 years without documentation of non-perinatal HIV acquisition. We used this age threshold to capture those children with slow-progressing disease who survive into adolescence without treatment and present for care during early adolescence. We found no differences in the proportion of males vs. females (48.5% vs. 51.5%) in our overall sample after increasing this age threshold, supporting the notion of a perinatal route of transmission among this group. Had those presenting between the ages of 10–13 years acquired HIV non-perinatally; we would have expected the proportion of females to be substantially higher due to the well described increased risk of acquiring HIV in adolescence among young females in our region (138). In addition, those who entered care aged 10–13 years showed poor HAZ during adolescence, similar to levels seen in those who entered care before the age of 10 years. Reduced height is one of the hallmarks for longstanding HIV in childhood due to perinatal HIV acquisition (5,133,139,140).

Adolescents in our analysis who entered care before the age of 10 years-initiated ART at a median age of 7.2 years. Also, a large number were severely immunosuppressed at ART initiation. This highlights the substantial delay in ART initiation. This could be partially explained by the fact that these adolescents were children at a time when ART treatment services were limited and the criteria for ART initiation restrictive, with guidelines requiring prior immunologic and clinical deterioration before ART start (18,19,141). In addition, socio-economic factors could have played a role. While the numbers of adolescents are expected to decline in the future owing to decreasing numbers of children acquiring

HIV perinatally, the next wave of adolescents may have initiated ART earlier. However, the benefit of universal ART will only be realized when all children with perinatally-acquired HIV initiate ART in infancy.

Regardless of age of entry into care, our study noted a steady decline in the median CD4 count with increasing age, even when restricted to those who had been on ART for at least 1 year by the respective birthday. Although some age-related drop in CD4 cell count is expected as adolescents age up, the decline we report is worrying as older adolescents are maturing and expected to be gaining increasing independence in preparation for early adulthood. The absence of adherence data mean that we were unable to establish the extent to which poor adherence and treatment failure may have influenced this finding. In contrast, as the adolescents aged, we observed improvements in the median HAZ as shown by other research (142,143). Though these scores improved over time, they generally remained below the −1 z-score across the adolescent ages, confirming earlier research that adolescents within resource-limited settings may not reach their full height potentials (144,145). Compared to earlier calendar years, we found improvements in the CD4 counts and HAZ in more recent calendar years, reflecting the positive effects that the changing HIV treatment guidelines, such as allowing ART to be initiated earlier, could be having (146).

We noted that overall, a substantially high proportion of adolescents were LTFU, with overall retention at the end of the study period being less than 60%. This elevated rate of LTFU is a significant concern, particularly in the context of interpreting mortality outcomes. In many settings, a considerable proportion of individuals categorized as LTFU may in fact have died. However, due to routine health data systems not being linked to national vital registration systems, such deaths go unrecorded. As a result, this may imply an under-ascertainment of mortality in our analysis. This underestimation biases mortality estimates downward and may obscure important differences between subgroups. Additionally, LTFU is unlikely to occur at random and may be associated with factors also linked to mortality, such as advanced illness and socioeconomic barriers to care. These complexities further limit the interpretation of both mortality and retention outcomes. Therefore, findings related to these outcomes should be interpreted with caution.

These rates of LTFU also highlight the challenges of retaining adolescents in care as they age. One study in Zimbabwe which showed better retention rates among adolescents (41) who had adolescent friendly services including peer and non-peer counselling within their public sector cohort. In our study, LTFU was also considerably greater among adolescents who presented to care aged 10–13 years compared to those who presented before the age of 10 years. This underscores the urgent need to recognize this population of late presenters or slow progressors and identify optimal interventions to keep then retained, particularly in the early years of engaging with care.

Cross-sectionally at the end of follow-up, mortality was substantially higher among adolescents who entered care aged 10–13 years compared to those who entered aged <10 years. This could be attributed to the fact that those who presented earlier needed to have reached adolescence to be included in this analysis, making this a group limited to those who survived childhood with HIV. Among the adolescents who died after the age of 13 years, median age at death was 15.5 years. Immunosuppression and impaired anthropometric measures were associated with mortality, as has been shown in other studies (41,147).

The study's limitations include that mode of HIV acquisition was assumed based on age of entry into HIV care and non-reporting of other modes of acquisition (5,148). We had missing data on critical measures such as CD4 count, HIV-RNA, WHO clinical staging, and anthropometric measures, particularly among older adolescents. Laboratory testing and anthropometric evaluations could have been obtained more frequently among those at higher risk of poor outcomes, which may have biased our results. In addition, we used routinely collected data in our analyses, which did not include key information on adherence, disclosure, and other social measures of well-being that would be needed to more fully characterize reasons for positive or negative outcomes during adolescence. Assessment of viral load outcomes was limited to the cohorts offering routine (annual) viral load measurements. LTFU was assumed for all adolescents with an unknown outcome, which may have resulted in an underestimate of mortality. Our data were obtained from facilities providing data to the IeDEA Southern Africa collaboration; hence, results may not be generalizable to all adolescents within the region. Lastly, reasons for TFO were not documented within the database.

4.7 Conclusions

This analysis shows outcomes of adolescents living with perinatally acquired HIV in sites offering routine HIV care services across six Southern African countries, over extended periods of time. Adolescents in our cohort had progressively worsening retention with increasing age. These outcomes were substantially worse among adolescents entering HIV care during adolescence vs. those entering care before age 10 years. Interventions tailored to improving treatment outcomes in this population need attention to ensure optimal health outcomes for this population.

Chapter 5: Characteristics and outcomes among youth living with HIV receiving care in youth clubs vs. standard care at a Youth Clinic in Cape Town, South Africa

5.1 Chapter overview and contribution to thesis

Even though providing differentiated care approaches for people accessing HIV care is widely recognised and encouraged, data on healthcare outcomes for young people receiving differentiated care within youth-focused care models remain limited. This chapter addresses objective 2, comparing the characteristics and outcomes of AYLH receiving HIV care and transitioning to adulthood either within a differentiated model of care (a youth club) or receiving routine care at the same facility during the same period. This analysis uses data from a primary health care facility in a high HIV burden sub-district in South Africa. The facility offers comprehensive sexual and reproductive health services in addition to HIV care to all adolescents and youth aged 12-25 years.

This analysis contributes to the thesis by highlighting the positive impact of differentiated models of care, revealing higher rates of transition to adult HIV care, lower rates of attrition, and higher completion of viral load assessments and suppression rates compared to routine care. It also shows the feasibility of integrating sexual and reproductive health services in a differentiated model of care for AYLH. The youth club also supported retention in care for young people transitioning from youth to adult care through organizing group transfers within youth clubs to the adult clubs offered by the adult clinic, providing a supportive approach preferred by young people.

Role of the candidate

The candidate and supervisor developed the concept and designed the study. The candidate wrote the study concept. The candidate was solely responsible for conducting all the data cleaning and analyses, drafting the manuscript, incorporating all relevant comments from co-authors, and finalising and submitting the manuscript to the journal. In addition, the candidate subsequently addressed all journal comments and submitted the corrected manuscript for publication. All authors reviewed and approved the final manuscript before submission.

Publication status

Being prepared for submission.

5.2 Abstract

Background

Differentiated service delivery throughout the HIV care continuum is a key strategy to address the challenges in providing comprehensive HIV care for AYLH who are widely recognized to have poorer ART outcomes than adults.

Methods

We conducted a retrospective observational cohort analysis focusing on youth who received care at a dedicated youth clinic in Cape Town, South Africa, between January 2015 to June 2019. We used data captured in the facility's electronic monitoring systems and linked to city-wide laboratory and service access through the Western Cape PHDC – a province-wide health information exchange linking data for those using public sector health services. We describe the characteristics and outcomes (retention, and viral suppression defined as <400 copies/ml) of youth ever receiving care within youth clubs (i.e. groups for approximately 20 young people aged between 15-25 years living with HIV, facilitated by lay counsellors with structured session guides) and a comparative group of youth who received care at the same facility during the study period but were never enrolled in the youth clubs.,

Results

Of the 1934 youth (87% female), contributing 4526 person years of follow up (median 2.1; IQR 1.0; 3.8), 397 (20.5%) were ever enrolled in youth clubs. There were no differences between youth enrolled into youth clubs vs. those that did not on proportion female sex (87% vs. 87%; diff -0.003, p<0.01), median age of first presentation to HIV care (20 vs. 21 years, p<0.01), and age at ART initiation (21 vs. 22 years, p<0.01), respectively.

By analysis closure, 28% (95% CI 26;30%) of youth were lost to care, with a higher proportion of those who never enrolled in youth clubs being lost to care compared to those enrolled (33% vs. 9%, difference 24.5%, p<0.01). A higher proportion of those who had not enrolled into youth clubs died (1% vs. 0.8%; difference 0.6, p=0.33), though not statistically significant. In total, 60% (95%CI 58;62%) of youth transferred care, with a higher proportion of transfers noted among those who enrolled in clubs compared to those who did not (71% vs. 60%, difference 14%, p<0.01). Of those who transferred care, 61% transferred to the adult HIV clinic on the same premises as the Youth Clinic.

In the 13 months before analysis closure, among youth who had been on ART for at least 12 months, a higher proportion of those enrolled vs. not in clubs were virally suppressed (94% [95% CI 91;96.5%] vs. 85% [95% CI 82;88%], difference 9% [95% CI 5;13%]; p<0.01).

Conclusion

The positive outcomes observed in youth clubs, such as lower attrition and higher viral load suppression, suggest the potential benefits of differentiated care models.

5.3 Introduction

Despite substantial progress in the global HIV response, AYLH continue to be the age group with poorer outcomes. Treatment coverage for AYLH continues to lag, with only two-thirds of adolescents aged 10 to 19 years living with HIV receiving ART in 2022 (149). AYLH have also been reported to experience poorer viral suppression, higher rates of treatment failure, and higher rates of disengaging from care compared to other groups (29–40). AYLH continue to face challenges in accessing testing, treatment, and achieving viral suppression, exhibiting poorer retention outcomes compared to adults in South Africa (150). Addressing these gaps is necessary to improving the overall health outcomes for this population.

A key strategy to address the challenges in providing comprehensive HIV care is the implementation of DSD models throughout the HIV care continuum. This approach aims to simplify and adapt services to better meet the preferences and expectations of diverse groups at risk of or living with HIV. In 2016, WHO acknowledged the importance of adapting ART services to cater to the varied clinical needs of people living with HIV (146). However, it was not until 2017 that the recognition extended to children and adolescents, acknowledging the potential benefits of client differentiated ART delivery models (151).

Since the WHO's endorsement of a differentiated care approach in 2016, research on DSD models has increased, primarily focusing on outcomes for adults and those stable on ART (47). South African guidelines support a differentiated approach for young people living with HIV (150). While examples of successful adolescent-friendly health services exist, documentation is often limited, scalability a concern, and the quality and standards vary widely across service delivery points (152). Reviews have repeatedly highlighted the need for more adolescent and youth-focused DSD studies (153). A situational analysis conducted by the Paediatric-Adolescent Treatment Africa (PATA) and the South African Young Positives (SAY+) highlighted scarcity of evidence on DSDs for adolescents and young people within east and southern Africa, the regions most affected by the HIV pandemic (154). Many adolescents living with HIV still lack access to adolescent-friendly health services, with 69% obtaining ART medication from a clinic pharmacy and only 41% considering the services they receive from healthcare providers as "adolescent friendly". A review by Maskew and colleagues (153) showed similar retention between AYLH attending adherence clubs and those not attending across several cohorts within Africa, even in settings where adherence clubs showed superior retention rates among adults.

In resource-limited settings, data on healthcare outcomes for young people within youth-focused care models remain limited (55). We aimed to describe the characteristics, retention and virologic outcomes of youth receiving HIV care in a dedicated youth clinic who were ever enrolled in a youth-focused DSD model (youth clubs) and those receiving care at the same clinic who were not enrolled.

5.4 Methods

We conducted a retrospective observational cohort analysis focusing on AYLH who received care at a dedicated youth clinic in Cape Town, South Africa, between January 2015 and June 2019. We describe the characteristics and outcomes of youth receiving care within youth clubs, and a comparative group of youth who received care at the same facility during the study period but were never enrolled in the youth clubs.

Setting

The youth clinic is situated within Khayelitsha, a large township in the City of Cape Town district in South Africa with one of the oldest and largest ART treatment programs in South Africa (155). The youth clinic plays a pivotal role in attracting and retaining youth in HIV care. It offers a range of healthcare services, including contraception, diagnosis and treatment of sexually transmitted infections (STIs), HIV counselling and testing, ART initiation and management, medical termination of pregnancy, tuberculosis screening and treatment, and general curative care.

Youth Clubs

In 2012, Médecins Sans Frontières (MSF) partnered with the City of Cape Town Health Department (City Health) to pilot Youth Clubs - a facility-based group intervention designed for youth aged 15 to 25 years living with HIV. This youth-focused intervention targeted patient losses along the treatment journey for youth living with HIV. It had a specific focus on retaining youth both before and after initiating ART, ensuring timely ART initiation, and preventing losses post-initiation.

Youth clubs are closed membership groups of approximately 15-20 individuals living with HIV, aged between 15-25 years. Eligibility criteria for club participation include being aged 15-25 years, awareness of HIV diagnosis, absence of active tuberculosis, and no medical conditions requiring regular clinical follow up. Eligibility was much less restrictive than that for adult clubs as youth not initiated on ART and those on ART but not virally suppressed were eligible to join.

Club meetings occur monthly for the initial six months and then bi-monthly thereafter. Services provided during these sessions include HIV clinical management, ART refills, contraception, and

psychosocial support. The groups incorporate members at different stages in the HIV cascade, enabling mutual learning and support between those not yet on ART, newly initiated, and those on ART for longer. The club sessions are facilitated by trained lay counsellors, responsible for retrieving patient folders, collecting pre-packed ART refills, conducting weight checks, and screening for various health concerns. They also facilitate a structured discussion covering key topics such as disclosure, adherence, and stigma. A club nurse supports the lay counsellor, administering contraception, conducting clinical consultations, and facilitating blood draws for viral load investigations.

Each youth club maintains a paper-based register documenting attendance, weight, and referrals during each visit. Data from these registers are subsequently entered into the facility's electronic monitoring system by clinic data clerks (156).

Upon reaching 26 years (no longer eligible for youth clinic care), patients are transferred to the neighbouring Community Health Centre (CHC) for adult HIV care. While located on the same premises as the Youth Clinic, the CHC operates independently, with separate buildings and staff. Run by the Western Cape Provincial Government Department of Health and Wellness, the CHC offers comprehensive primary health care services to the community.

Measurements and outcomes

In the Western Cape Province of South Africa, the Western Cape Provincial Government Department of Health and Wellness has implemented electronic patient administration systems across all fixed public sector services and facilities, including primary care clinics, secondary and tertiary level hospitals. The province also established a unique patient identifier which facilitates linkage of medical records across various health facility patient information systems. This includes primary care and hospital visits and admissions, the National Health Laboratory Service (NHLS) which conducts all laboratory testing, and electronic pharmacy management systems. This unique patient identifier enhances the integration of health data in a patient-level interlinked health information exchange, the Provincial Health Data Centre (PHDC). The PHDC consolidates data from multiple routine electronic clinical, clerical, and administrative databases across the province, resulting in the creation of an individual-level database of those using public sector health services (68–72). All PHDC data linkages using identified data were performed by PHDC staff who are bound by South African provincial and national requirements around protection of patient confidentiality.

For the purposes of this analysis, de-identified data pertaining to youth accessing care within youth clubs at the specified facility between January 2015 and June 2019 were obtained from the PHDC. Additionally, a comparative group of youth accessing care at the same facility during the same period but not enrolled in youth clubs, matched based on age, sex, and duration on ART at time of matching, was also obtained. For inclusion in the comparison group youth had to have had an initial encounter

with the youth clinic after 1 June 2015 and before end June 2019. For both groups, youth entered the analysis at their initial encounter with the youth clinic after 1 June 2015 and exited at the date of analysis closure (30 June 2019), date of outcome, date of their 25th birthday, or date of censoring, whichever occurred first. Youth had to either been on ART at the initial visit or initiated ART at some point in the period. Data on clinic encounters, ART refills, laboratory results (CD4 and HIV-RNA viral load), and pharmacy data were extracted for analysis.

We defined entry into youth clubs care as the first recorded HIV care visit in a youth club, after 1 January 2015. We defined entry into the analysis as the first recorded HIV care visit in the youth clinic after 1 January 2015. Date of ART initiation was the earliest date recorded in the databases when a triple-drug ART regimen was dispensed. Characteristics of youth at first visit to the youth clinic, at first presentation to HIV care, at ART initiation, and at enrolment into a youth club were described.

In assessing viral load measurements, only youth on ART for at least 6 months were included. The first viral load assessment and viral load result conducted within the analysis period was assessed, and then 12-monthly thereafter. In addition, cross-sectional analyses were done of the proportion of patients with a viral load assessment and the corresponding viral load results within 13 months prior to study closure (January 2019 -January 2020) or analysis exit. HIV-RNA viral load measures from the date closest to each period, within a window of ±9 months, were used. Viral suppression was considered as an HIV-RNA <400 copies/ml. Results are summarized using percentages with binomial 95% confidence intervals (CIs).

Statistical analysis

The primary outcomes of interest were:

- The proportion of youth still actively in care, either at the same facility or elsewhere, defined as having a recorded contact (visit or HIV-related laboratory test or pharmacy pick-up) in the dataset within the six months following analysis closure (from 1 July 2019 to 1 January 2020).
- The proportion of youth transferring care, defined as having a recorded contact (visit or HIV-related laboratory test or pharmacy pick-up) at a different facility within the six months following analysis closure (including patients that transferred to adult HIV care).
- The proportion of youth virally unsuppressed (defined as first viral load >400 copies/ml) and of these, the proportion with a subsequent viral load, proportion that suppressed at subsequent viral load assessment, and 12-monthly thereafter.
- The proportion of youth virally suppressed within the last 13-month period of their analysis i.e., within the last 13-month period before they were censored, exited the analysis, or analysis closure.

Patient characteristics were described using medians with interquartile ranges (IQRs) and proportions, accordingly. Characteristics were compared between those enrolled in youth clubs and those who were not using Wilcoxon rank-sum test for continuous variables and McNemar and Cochrane Q tests for categorical variables.

Data were analysed using Stata 13.0 (STATA Corporation, College Station, TX, USA).

Ethics

This analysis was approved by the UCT-HREC as part of a nested analysis on the characteristics and outcomes of adolescents living with HIV transitioning to adulthood in different health care models across Southern Africa (UCT-HREC REF 797/2019). The requirement for individual patient consent was waived as this was a retrospective analysis of de-identified routinely collected data.

5.5 Results

We included 1934 youth in care at the Youth Clinic, contributing 4390 person-years of follow-up (median 2.1; IQR, 1.0; 3.8). Among them, 397 (20.5%) enrolled in youth clubs and 1537 (79.5%) did not. Youth that enrolled in clubs contributed 1168 person-years of follow-up (median 3.1: IQR 1.8; 4.3) while those that did contributed 3223 person-years of follow-up (median 1.8: IQR 0.7; 3.6).

There were no differences observed between youth that enrolled into youth clubs vs. those that did not for female sex (87% [95% CI 83;90%] vs. 87% [95% CI 85;89%]; diff -0.3, p=0.87) and age at first presentation to HIV care (20 [IQR 18;22] vs. 21 [IQR 18;23] years, p<0.01), at first visit to the youth clinic (21 [IQR 18; 22] vs 22 [20;23] years, p<0.01), and at ART initiation (21 [IQR 18;22] vs. 22 [19;23] years, p<0.01), respectively (Table 5.1). While fewer youth enrolled into clubs were on ART at entry into the youth clinic (24% [95% CI 20;28%] compared to those who did not (27% [95% CI 25;30%], difference 3.5%, p=0.16) and had been on ART for longer at their first visit to the youth clinic (1.7 [IQR 0.3;6.3] vs. 1.5 [IQR 0.4;3.9] years, p= 0.51), respectively, these differences were not statistically significant.

Table 5.1. Description of youth receiving care in youth clubs vs. standard care at a Youth Clinic

Characteristic	Enrolled in Youth Clubs	Not enrolled in Youth Clubs
Number	397	1537
Female, n (%)	344 (87%)	1337 (87%)
Median (IQR) age at first presentation to HIV care, years	20 (18; 22)	21 (18; 23)

Characteristic	Enrolled in Youth Clubs	Not enrolled in Youth Clubs
0 to 9, n (%)	28 (7%)	62 (4%)
10 to 19, n (%)	144 (36%)	487 (32%)
20 to 24, n (%)	225 (57%)	988 (64%)
Median (IQR) year of presentation to HIV care	2015 (2013; 2017)	2015 (2013; 2017)
≤2010, n (%)	49 (12%)	172 (11%)
2011 to 2014, n (%)	101 (25%)	423 (28%)
2015 to 2019, n (%)	247 (62%)	942 (61%)
Median (IQR) age at first visit to the youth clinic, years	21 (18; 22)	22 (20; 23)
13 to 19, n (%)	144 (36%)	372 (24%)
20 to 22, n (%)	184 (46%)	577 (38%)
23 to 25, n (%)	69 (17%)	588 (38%)
Ever initiated ART, n (%)	397 (100%)	1444 (94%)
Age at ART initiation, years	*n=397*	*n=1444*
Median (IQR)	21 (18; 22)	22 (19; 23)
0 to 9, n (%)	25 (6%)	55 (4%)
10 to 19, n (%)	115 (29%)	317 (22%)
20 to 25, n (%)	257 (65%)	1030 (71%)
>25, n (%)	0	42 (3%)
On ART at entry into the youth clinic, n (%)	95 (24%)	396 (27%)
Duration on ART at entry into youth clinic, years	*n=95*	*n=396*
Median (IQR)	1.7 (0.3; 6.3)	1.5 (0.4; 3.9)
<6 months, n (%)	28 (29%)	114 (29%)
6 months to <1 year, n (%)	11 (12%)	50 (13%)
1 to 2 years, n (%)	22 (23%)	105 (27%)
≥3 years, n (%)	34 (36%)	127 (32%)
Year of club enrolment		
2015, n (%)	3 (1%)	-
2016, n (%)	104 (26%)	-
2017, n (%)	166 (42%)	-
2018, n (%)	103 (26%)	-
2019, n (%)	21 (5%)	-
Median (IQR) age at club enrolment, years	22 (20; 23)	-
14 to 19, n (%)	71 (18%)	-
20 to 22, n (%)	156 (39%)	-
23 to 25, n (%)	170 (43%)	-
Median (IQR) duration on ART at entry into club, years	1.2 (0.4; 2.4)	-

Characteristic	Enrolled in Youth Clubs	Not enrolled in Youth Clubs
<6 months, n (%)	106 (27%)	-
6 months to <1 year, n (%)	76 (19%)	-
1 to 2 years, n (%)	134 (34%)	-
≥3 years, n (%)	81 (20%)	-

ART – antiretroviral therapy; IQR – interquartile range,

At analysis closure, 72% (95% CI 70;74%) of youth were retained (had a recorded contact at analysis closure), with a higher proportion retained among those enrolled in clubs compared those not enrolled (91% [95% CI 88;94%] vs. 67% [95% CI 64;69%], difference 24% [95%CI 21-28%], p<0.01). Also, 28% (95%CI 26-30%) of youth were lost to care, with a higher proportion among youth not enrolled in clubs lost to care compared to those enrolled (32% [95% CI 30-35] vs. 9% [95% CI 6-11%]; difference 24% [95%CI 20-27%], p<0.01) (Table 5.2).

Table 5.2. Cross-sectional outcomes of youth receiving care in youth clubs vs. standard care at a Youth Clinic at analysis closure

Characteristic	Enrolled in Youth Clubs (n=397)	Not enrolled in Youth clubs (n=1537)
Total person-years of follow-up (person-years)	1168	3223
Median, (IQR)	3.1 (1.8;4.3)	1.8 (0.7;3.6)
Still in care, n (%)	362 (91%)	1025 (67%)
At the same facility	79 (22%)	149 (15%)
Transferred care, n (%)	283 (71%)	876 (57%)
Transferred to the adult HIV clinic within the same premises, n (%)	215 (76%)	487 (56%)
Lost to follow-up, n (%)	34 (9%)	498 (32%)
Died, n (%)	3 (1%)	21 (1%)

IQR – interquartile range

By analysis closure, 24 youth (1.2%, 95% CI 0.8;1.8%) were reported to have died, a higher proportion among those not enrolled into youth clubs vs. those in clubs, but this was not statistically significant (1.4% [95% CI 0.8;2.1%] vs. 0.8% [95% CI 0.2;2.2%]; difference 0.6, p=0.33).

Overall, 60% (95% CI 58;62%) of youth transferred care, with more than half of those that transferred (61%, 95% CI 58;63%) transferring to the adult HIV clinic on the same premises as the Youth Clinic

(the CHC). When comparing youth in clubs with those not enrolled, no difference was observed in the overall proportion that transferred (45% vs. 50%, p=0.22). However, a marked difference emerged in the proportion transferring to the adult CHC on the same premises, with a higher percentage of youth in clubs transferring to the adult CHC on the same premises compared to their non-enrolled counterparts (76% [95% CI 71;81%] vs. 56%, [95% CI 52;59%]; difference 20% [95% CI 14;26%], p<0.01).

Overall, 74% (95% CI 72;76%) of youth had at least one viral load assessment during the analysis period, regardless of duration on ART, with a higher proportion of youth enrolled in clubs having a viral load assessment (97%, 95% CI 96;99%) compared to those not enrolled (69%, 95% CI 66;71%; difference 27%, 95% CI 26;31%, p<0.01) (Table 5.3). Among youth with any viral load assessment, 88% (95% CI 86;89%) were virally suppressed (at <400 copies/mL) at the first viral load measurement recorded within the analysis period, with a higher proportion of youth enrolled into clubs 95% (95% CI 92;97%) being virally suppressed compared to those not enrolled (85%, 95% CI 83;87; difference 9% [95%CI 6;12]; p<0.01).

Table 5.3. Viral load completeness and results of youth receiving care in youth clubs vs. standard care at a Youth Clinic during the analysis period

Characteristic	Enrolled in Youth Clubs	Not enrolled in Youth clubs
Number	397	1537
Any viral load test performed during analysis, n (%)	386 (97%)	1054 (69%)
Results (copies/mL), n (%)		
<400	365 (95%)	898 (85%)
400 to 1000	4 (1%)	37 (4%)
>1000	17 (4%)	119 (11%)
Elevated viral load (≥400 copies/mL), N	*N=21*	*N=156*
Repeat viral load done, n (%)	16/21 (76%)	97/156 (62%)
Results (copies/mL), n (%)		
<400	7 (44%)	47 (48%)
400 to 1000	2 (13%)	3 (3%)
>1000	7 (44%)	47 (48%)
Last 13 months of follow-up*, N	388	1268
Viral load done, n (%)	309/388 (80%)	585/1268 (46%)
Results (copies/mL), n (%)		

Characteristic	Enrolled in Youth Clubs	Not enrolled in Youth clubs
<400	291 (94%)	499 (85%)
400 to 1000	5 (2%)	17 (3%)
>1000	13 (4%)	69 (12%)

*Only among youth that had been on antiretroviral therapy for ≥12 months and had a visit in the 13 months before analysis closure

or the subset of youth with a viral load ≥400 copies/mL (n=177) at their first viral load measurement recorded within the analysis period, 64% (95% CI 56;71%) had a subsequent viral load assessment, with a higher proportion among those in clubs (76% [95% CI 58;94%]) having a subsequent viral load assessment compared to those not in clubs (62% [95% CI 55;70%]; difference 14% [95% CI 6;34]; p=0.21). Among those with a subsequent assessment, 48% (95% CI 35;51%) achieved viral suppression to <400 copies/mL, with no differences observed between those in clubs compared to those not enrolled (44% [95% CI 19;68%] vs. 48% [95% CI 39;58%]; difference 5% [95% CI -0.22;31%], p=73), respectively.

In a cross-sectional assessment of viral load assessments in the 13-months prior to analysis closure among youth who had been on ART for at least 12 months before analysis closure, youth enrolled in clubs had a significantly higher viral load coverage (80%, 95% CI 76;84%) compared to those not enrolled (46%, 95% CI 43;49%; difference 34%, 95% CI 28;38%; p<0.01). Also, there were higher proportions of virally suppressed youth among those enrolled in clubs when compared to those not enrolled (94%, 95% CI 92;97% vs. 85%, 95% CI 82;88%; difference 9%, 95% CI 3;5%; p<0.01).

5.6 Discussion

While the provision of differentiated services for adolescents and young people living with HIV is widely recommended, very few studies have systematically compared the characteristics and outcomes of youth receiving differentiated care to those in routine care within the same environment. This study underscores the positive impact of youth clubs, revealing youths enrolled in youth clubs having lower rates of attrition (91% still in care vs. 67%), higher completion of viral load assessments (97% vs. 69%) and higher suppression rates (95% vs. 85%) compared to routine care, respectively.

Patients who become non-suppressed within DSD models could be referred to routine care. In our analysis, a higher proportion of youth virally non-suppressed while accessing care within youth clubs had a subsequent viral load assessment compared to those not in clubs (76% vs. 62%). Also, no difference was observed in the proportions subsequently virally suppressed between those in clubs

compared to those not enrolled. This may show that the interventions employed once youth are unsuppressed can also be implemented within DSD models of care, suggesting that it may not be necessary to remove immediately refer patients out of DSD models should they become non-suppressed.

While there was not enough information provided as to the circumstances surrounding transfer of care for those that transferred, having access to the youth club supported an effective approach for the transition from youth to adult care. The youth club model also proved effective in facilitating the transition from youth to adult care. As youth in dedicated paediatric, adolescent, and/or youth facilities age, transitioning to adult HIV services becomes crucial. It was notable that in our analysis, those in youth clubs were more inclined to transfer care to the adult clinic on the same premises rather than being lost to follow-up. This could be due to the Youth Clinic organizing group transfers within youth clubs to the adult youth clubs offered by the adult clinic, providing a supportive approach preferred by young people and potentially contributing to the observed success in the transition process. Though specific details on the enrolment the transferred youth into the adult ART clubs were not available, existence of adult clubs at the adult clinic and organisation of group transfers prepares youth for DSD in adult care as well.

A growing body of evidence suggests improved retention and viral load outcomes among adolescents in differentiated models of care. Nevertheless, research on interventions for youth and young adults remains limited and yields mixed results. A comprehensive review by Casale et. al. (157) highlights the variability of the impact of “youth-friendly” clinics or services within existing facilities. While some studies demonstrate positive effects on retention and viral suppression (158,159), others show no significant impact (160,161). In South Africa, youth clinics have demonstrated a protective effect against attrition among young people living with HIV (162). Similarly, a study in Malawi revealed that attending a teen club significantly reduced attrition among adolescents, emphasizing the importance of dedicated clinic time, services, and peer support (158). A randomized trial in Zimbabwe demonstrated improved virological outcomes and attendance through an intensive treatment support program, incorporating elements like treatment supporters, group support, text messages, calls, home visits and clinic-based counselling (163). In contrast, a Kenyan intervention, despite including support groups, peer education, and dedicated clinic time, failed to show improvement in youth ART outcomes.

There are several strengths to this study. Our analysis is from routine services, portraying the effectiveness of youth clubs as part of healthcare facilities' everyday operations rather than within a controlled research setting. This enhances the generalizability of the results to other healthcare facilities within the region. The results of this study, conducted through linked data across the district, contribute to a more comprehensive understanding of youth outcomes. The ability to track outcomes beyond the primary facility, including viral load results from other facilities, prevents misclassification of silent

transfers as lost to follow-up and ensures completeness of viral load data. The use of linked data allowed for the tracking of youth who transferred care, shedding light on where they accessed care and the likelihood of the movement being associated with their transition to adulthood.

Some limitations need to be considered in the interpretation of these findings. The analysis was limited to the variables routinely captured in the facility's electronic monitoring system. Key variables such as the date of club exit, disclosure, comorbidities, pregnancies, adherence, and transition processes were not available for assessment, limiting a more nuanced understanding of the factors influencing outcomes. While the study provides valuable insights, the applicability of findings from youth clubs run in designated youth clinics may not extend universally to many resource-limited settings without a youth clinic. Despite analysing data spanning several years, the median follow-up time was relatively short. This may be attributed to the recent initiation of patients into youth clubs or improved capturing of club visits in more recent years. There could have been some misclassification of some of the club patients whose club visits were not captured as club visits. This could result in the findings of non-club-patients being affected. However, given the general better outcomes noted among club participants and differences in the outcomes noted, we expect that this was minimal.

To be eligible for youth clubs, participants had to be free of any medical conditions requiring regular clinical follow-up or co-infections. This selection criterion likely contributed to the better outcomes observed among club members. However, this was minimal as youth clubs have less restrictive eligibility compared to adult clubs. The study included predominantly female youth entering HIV care and mostly starting ART in young adulthood, potentially limiting the generalizability of findings to those with recent HIV acquisition or not yet on ART. Further research is needed to assess the effectiveness of differentiated care models for populations living with perinatally-acquired HIV, particularly as they age.

Due to the criteria for joining a club, the study could not ascertain reasons for individuals who met club eligibility criteria but did not join, hindering a comprehensive comparison between those groups. The non-club comparison group is a mix of those who eligible to join a club but chose not to and those who weren’t eligible and were probably sicker.

We had no additional data from tracing or death registry linkage on outcomes of those "lost to follow-up" which included all patients with an unknown outcome, including under-ascertained mortality, which might affect the accuracy of the findings. This analysis was conducted from 2015 to 2019, at the start of the "Treat All" era hence the results may not be generalizable to the current treatment context. In addition, dolutegravir was not available during the period, limiting the applicability of our analysis on viral suppression rates to the current era.

5.7 Conclusion

Our study offers important descriptive insights into the role of youth clubs within routine healthcare services for youth living with HIV. While not designed to establish causality, the observed associations, such as lower attrition rates and higher viral load monitoring among youth club participants, highlight the potential benefits of differentiated service delivery models. In addition, the study also shows the feasibility and relevance of tailored approaches in supporting care continuity during the transition process. By tracking outcomes beyond the primary facility, this analysis contributes to a more nuanced understanding of care engagement patterns. Youth clubs may serve as a promising model for supporting long-term HIV care among young people in similar settings.

Chapter 6: Characterizing the double-sided cascade of care for adolescents living with HIV transitioning to adulthood across Southern Africa

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6.1 Chapter overview and contribution to thesis

Across Southern Africa, paediatric HIV care is mostly provided in decentralized, non-specialist primary care clinics, where "transition" to adult care usually does not include transfer to another clinic but entails becoming more autonomous for one's HIV care. This manuscript address's objective 2 of the PhD thesis which seeks to evaluate the characteristics and outcomes of adolescents living with HIV in Southern Africa and ascertain the determinants that influence these outcomes. Using different age proxies for when transition might occur, this publication seeks to investigate the influence of aging up to adulthood on gaps in care and virologic outcomes of AYLH. To the best of our knowledge, this was the first analysis to examine gaps in care and viral suppression outcomes in the pre- and post-transition periods for AYLH HIV transitioning to adulthood without transferring care within facilities in Southern Africa. We demonstrate that across multiple transition-age thresholds, retention of youth in care declined after transition. This highlights that adolescents and young adults are at an increased risk of disengaging from care as they reach the ages when they are expected to take responsibility for their own care and be managed as "adults."

Role of the candidate

Davies MA, Sohn AH, Judd A, Collins IJ, and the candidate conceptualized the study. The candidate designed the study and wrote the study concept. The candidate was solely responsible for conducting all the data cleaning and analyses, writing, and managing all the versions of the manuscript, incorporating suggestions from co-authors, and submitting it to the journal. All authors reviewed and approved the final manuscript before submission.

The candidate presented the study findings at the 22nd International Workshop on HIV and Hepatitis Observational Databases (IWHOD), 22-24 March 2018, Fuengirola Spain and 10th International Workshop on HIV Pediatrics 2018, 18-21 July 2018. Amsterdam, Netherlands.

Publication status

Published: Journal of the International AIDS Society. 2020 Jan; 23(1): e25447.

6.2 Abstract

Background

As AYLH age, they face a "transition cascade," a series of steps associated with transitions in their care as they become responsible for their own healthcare. In high-income countries, this usually includes transfer from predominantly paediatric/adolescent to adult clinics. In sub-Saharan Africa, paediatric HIV care is mostly provided in decentralized, non-specialist primary care clinics, where "transition" may not necessarily include transfer of care but entails becoming more autonomous for one's HIV care. Using different age thresholds as proxies for when "transition" to autonomy might occur, we evaluated pre- and post-transition outcomes among AYLH.

Methods

We included AYLH aged <16 years at enrolment, receiving ART within IeDEA Southern Africa sites (2004 to 2017) with no history of transferring care. Using the ages of 16, 18, 20 and 22 years as proxies for "transition to autonomy," we compared the outcomes: no gap in care (≥2 clinic visits) and viral suppression (HIV-RNA <400 copies/mL) in the 12 months before and after each age threshold. Using log-binomial regression, we examined factors associated with no gap in care (retention) in the 12 months post-transition.

Results

A total of 5516 AYLH from 16 sites were included at "transition" age 16 (transition-16y), 3864 at 18 (transition-18y), 1463 at 20 (transition-20y) and 440 at 22 years (transition-22y). At transition-18y, in the 12 months pre- and post-transition, 83% versus 74% of AYLH had no gap in care (difference 9.3 (95% CI 7.8;10.9)); while 65% versus 62% were virally suppressed (difference 2.7 (95% CI −1.0;6.5%)). The strongest predictor of being retained post-transition was having no gap in the preceding year, across all transition age thresholds (transition-16y: adjusted risk ratio (aRR) 1.72; 95% CI (1.60;1.86); transition-18y: aRR 1.76 (1.61;1.92); transition-20y: aRR 1.75 (1.53;2.01); transition-22y: aRR 1.47; (1.21;1.78)).

Conclusion

AYLH with gaps in care need targeted support to prevent non-retention as they take on greater responsibility for their healthcare. Interventions to increase virologic suppression rates are necessary for all AYLH ageing to adulthood.

6.3 Introduction

There is a growing cohort of AYLH, largely due to the increasing number of children with perinatally acquired HIV surviving into adolescence and adulthood, combined with a growing number of youth with non-perinatally acquired HIV. In 2017, nearly three million youth (aged 15 to 24 years) were living with HIV in sub-Saharan Africa (127). As these young people become adults, they are increasingly expected to become responsible for their own healthcare and progressively required to start setting up their own clinic appointments and be responsible for collecting and taking their ART.

Clinical outcomes and retention among AYLH have generally been poorer when compared to young children and older adults (36,38,128,164,165). In settings where paediatric HIV care is provided within specialized paediatric facilities, adolescents and young adults must be transferred out to adult HIV clinics as they age. Research from North America and Europe has shown that during this process, not all youth transferred to adult clinics successfully continue care (74,119,166–168). There are very limited data on transition outcomes among AYLH in sub-Saharan Africa (75) and a paucity of evidence as to the outcomes of adolescents as they grow older in settings where transition to adulthood necessitates taking on greater responsibility for one's healthcare but is *not* accompanied by physical transfer of care from a paediatric/adolescent clinic to a distinct adult HIV clinic. This could be the most common scenario within sub-Saharan Africa as only a third of facilities included in a situational analysis of facilities within sub-Saharan Africa reported attending to adolescents separately from adult and/or paediatric patients (104). Also, most studies have reported on outcomes *after* transition, with few studies (53,169) describing engagement in care among transitioning youth in the period *before* transition. Because they often have an extended period of HIV care and ART prior to transition, unlike conventional HIV cascades that start after diagnosis, the adolescent transition cascade needs to be double-sided, comparing outcomes both before and after transition.

We sought to evaluate gaps in care and viral suppression in AYLH in the year before and after their 16th, 18th, 20th and 22nd birthdays, using these different age thresholds as proxies for when "transition" to autonomy may occur in the context where adolescents remain at the same facility through to adulthood.

6.4 Methods

Study population

We analysed prospectively collected data of AYLH who were receiving ART within IeDEA Southern Africa sites between 2004 and 2017. The IeDEA Southern Africa cohort is a collaboration which collects de-identified routine patient data on demographics, antiretroviral drugs, clinical contacts and laboratory tests from cohorts within six Southern African countries: Lesotho, Malawi, Mozambique,

South Africa, Zambia and Zimbabwe. These data are transferred annually to the IeDEA Southern Africa data centres at the Universities of Cape Town, South Africa, and Bern, Switzerland, for inclusion in combined analyses using a standard data transfer format.

Ethics

All cohorts contributing data to IeDEA Southern Africa have ethics approval to contribute de-identified data to the IeDEA Southern Africa Data Centres. Their respective IRBs have granted waivers of informed consent as the analyses use data collected as part of routine patient care. The IeDEA Southern Africa Data Centres have ethics approval to combine and conduct analyses on the de-identified data.

Outcomes and analysis

We assessed "transition" at the ages of 16, 18, 20 and 22 years, with a special focus on the age of 18 years, as this is the legal age of adulthood in most Southern African countries. For this analysis, age was used as a proxy for "transition" to adulthood because in most facilities included, growing up into adulthood is not usually accompanied by physical transfer of care to a distinct adult HIV clinic. To be included in the analysis of "transition" at age 18 years (transition-18y), patients had to have been enrolled into HIV care before the age of 16 years, as patients enrolling at older ages (e.g. at the age of 20 years) would be responsible for their own healthcare at enrolment in routine care settings; have at least one visit at the age of 18 years within a window of six months before and after their 18th birthday (i.e. have at least one visit between the ages of 17.5 to 18.4 years); been on ART by their 18th birthday; and not transferred to a different facility as they aged up. In addition, the date of a patient's 18th birthday had to be at least one year before the closure of their cohort database to allow for evaluation of retention at one-year post-transition (Figure 6.1a). These criteria were adjusted accordingly for the analyses at 16 years (transition-16y), at 20 years (transition-20y) and at 22 years (transition-22y) (Figures 6.1a and 6.1b). While the transition-18y, transition-20y and transition-22y analyses included patients enrolled into HIV care before the age of 16 years, the transition-16y analysis only included patients enrolled into care before the age of 14 years so that engagement in the year prior to transition could be assessed. When assessing viral suppression outcomes, we only included patients in care within facilities with routine annual viral load testing.

The primary objectives were to compare the proportion of patients (a) with no gap in care in the 12 months before and 12 months after the respective age threshold, and (b) virally suppressed in the 18 months before and 18 months after each transition-age threshold. No gap in care was defined as having at least two clinic visits more than two months apart in the ± 12-month period. Viral suppression was defined as an HIV-RNA viral load <400 copies/mL in the ±18-month period. We used an 18-month

Figure 6.1a Flow diagram for inclusion in: (i) "transition at 16 years" and (ii) "transition at 18 years" analyses.

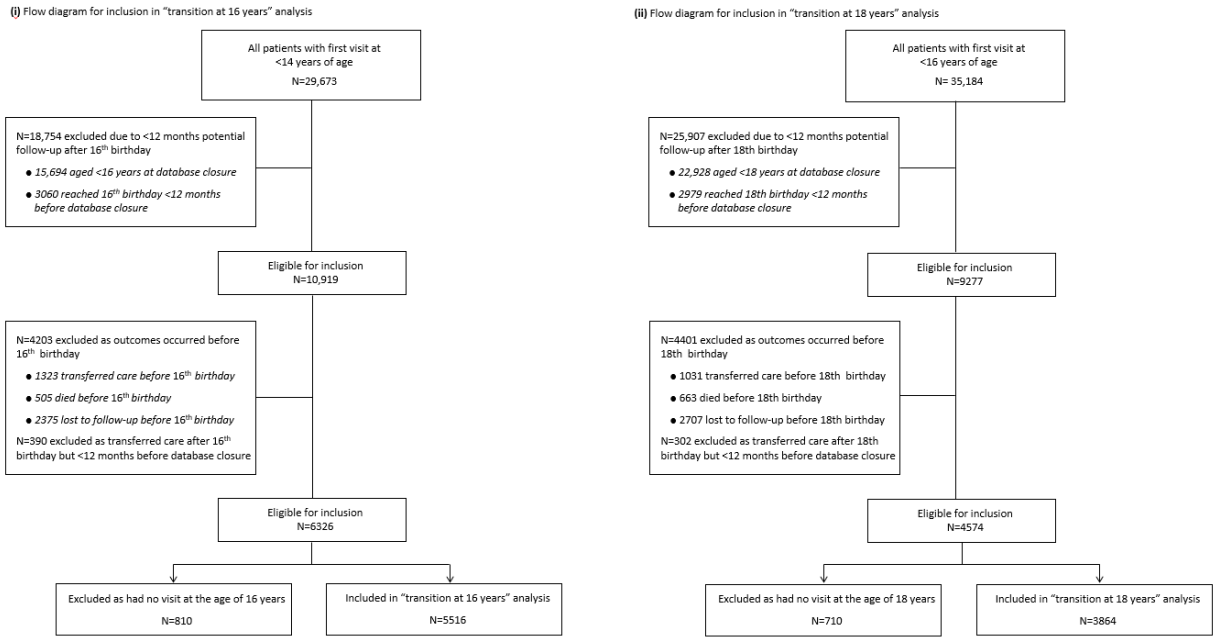
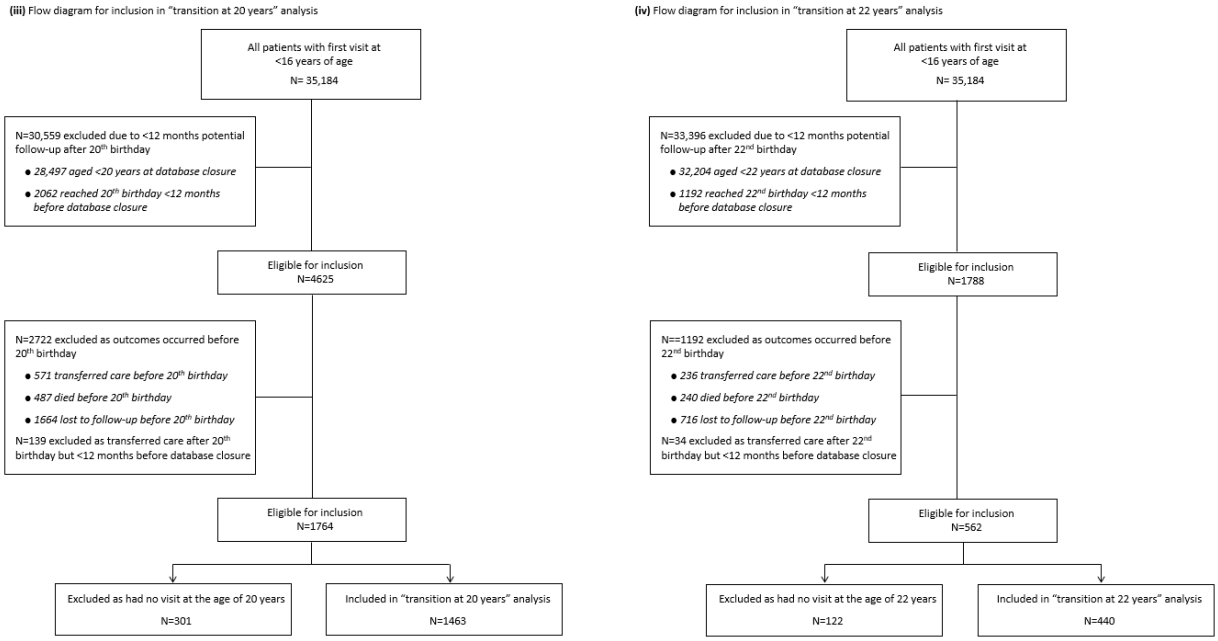


Figure 6.1b Flow diagram for inclusion in: (iii) "transition at 20 years" and (iv) "transition at 22 years" analyses.



window to assess viral suppression as routine viral load testing is recommended annually and we wanted to allow enough time on either side of the transition age for a viral load to be done and documented. Secondary objectives were to assess changes in the proportion of patients with no gap in care in the 12-

month period post-transition as the age of enrolment into HIV care increased (<10, 10 to 14, and 15 to 16 years), and to evaluate predictors of having no gap in care in the post-transition period. Adolescents with no gap in care after the respective transition-age threshold were considered "retained." As our primary analysis may have favoured the pre-transition period since adolescents had to have a visit within a year of the relevant age threshold to be included, sensitivity analyses examining these outcomes among only AYLH retained at the time of database closure were conducted. In addition, an analysis assuming "transition" at the age of 15 years (transition-15y) was conducted given that the age of 15 years is often used as the cut-off point by many national governments when reporting HIV data.

Characteristics of AYLH for each analysis were described by frequencies for categorical variables and as medians and inter-quartile ranges for continuous variables. As the mode of acquisition was not available in our data, we conducted stratified analyses comparing those who enrolled into care at <10 years, 10–14 years, and 15–16 years to explore outcomes across the different age-at-enrolment groups cut-offs commonly used to make assumptions for likely mode of HIV acquisition (31). We investigated whether there were any differences in the proportion of patients with no gap in care and proportion virally suppressed *before* and *after* each respective age threshold which we termed as the pre- and post-transition periods. Predictors of being retained in the 12 months post-transition were assessed using log-binomial regression models. In the adjusted models we included the following pre-determined covariates: sex (male or female), age at first entry into HIV care (<10, 10 to 14, or 15 to 16 years), total number of patients transitioning at the same time in the clinic (≤50, 51 to 100, 101 to 200, or >200) and having a gap in care in the 12-month period pre-transition (gap in care vs. no gap in care).

All statistical analyses were conducted in Stata 15.0 (STATA Corporation, College Station, Texas, USA).

6.5 Results

The analyses included 5516 (51% female) AYLH at transition-16y, 3864 (53% female) at transition-18y, 1463 (54% female) at transition-20y and 440 (59% female) at transition-22y thresholds (Table 6.1 and Figures 6.1a and 6.1b). Across transition-age cohorts, the majority enrolled into HIV care (61% to 68%) and started ART (50% to 67%) between the ages of 10 and 14 years. The proportion of adolescents assumed to be living with perinatally acquired HIV (enrolled into HIV care aged <10 years) decreased with increasing transition-age threshold from 34% (transition-16y) to 2% (transition-22y) (Table 6.1).

Table 6.1 Characteristics of adolescents and young adults living with HIV at different transition[a] age thresholds

Characteristics	"Transition" at 16 years	"Transition" at 18 years	"Transition" at 20 years	"Transition" at 22 years
Number	5516	3864	1463	440
Female, n (%)	2831 (51)	2044 (53)	796 (54)	258 (59)
Age at enrolment in HIV care (years), n (%)				
<10	1884 (34)	543 (14)	67 (5)	9 (2)
10 to 14	3632 (66)	2489 (64)	993 (68)	268 (61)
15 to 16	–	832 (22)	403 (27)	163 (37)
Median (IQR) age at enrolment in HIV care (years)	11.2 (9.2 to 12.7)	13.3 (11.3 to 14.8)	13.9 (12.4 to 15.1)	14.5 (13.4 to 15.3)
Year of "transition," n (%)				
<2010	687 (12)	407 (11)	63 (4)	6 (1)
2010 to 2012	2025 (37)	1453 (38)	496 (34)	109 (25)
2013 to 2014	2245 (41)	1599 (41)	757 (52)	278 (63)
2015 to 2016	559 (10)	405 (10)	147 (10)	47 (11)
Year of ART start, n (%)				
≤2004	513 (9)	321 (8)	160 (11)	66 (15)
2005 to 2009	3795 (70)	2615 (69)	1103 (76)	337 (78)
≥2010	1136 (21)	852 (23)	180 (12)	30 (7)
Age at ART start (years), n (%)				
<10	1615 (30)	444 (12)	54 (4)	4 (1)
10 to 14	3632 (67)	2330 (61)	880 (61)	218 (50)
≥15	197 (4)	1014 (27)	509 (35)	211 (49)
Median (IQR) age at ART start (years)	11.5 (9.6 to 13.1)	13.5 (11.6 to 15.1)	14.2 (12.7 to 15.5)	15.0 (13.8 to 15.8)
Median (IQR) duration on ART at time of "transition" (years)	4.5 (3.0 to 6.5)	4.5 (2.9 to 6.4)	5.8 (4.5 to 7.3)	7.1 (6.2 to 8.2)
Median (IQR) duration on ART at time of "transition" by age at enrolment in HIV care (years)				
<10	7.2 (6.3 to 8.4)	8.7 (8.0 to 9.7)	10.4 (10.0 to 11.5)	11.2 (10.0 to 12.3)
10 to 14	3.5 (2.5 to 4.6)	4.7 (3.7 to 6.0)	6.4 (5.4 to 7.5)	7.8 (7.1 to 8.7)
15 to 16	–	2.3 (2.0 to 2.6)	4.2 (3.8 to 4.6)	6.2 (5.8 to 6.6)
WHO stage at ART start, n (%)				
1 or 2	1764 (33)	1220 (33)	469 (33)	134 (31)
3 or 4	2503 (47)	1851 (50)	726 (51)	229 (54)
Missing	1097 (20)	655 (17)	239 (17)	65 (15)
Median (IQR) follow-up from first visit to "transition" (years)	4.8 (3.3 to 6.8)	4.7 (3.1 to 6.7)	6.1 (4.9 to 7.6)	7.5 (6.7 to 8.6)
Median (IQR) follow-up from first visit to "transition" by age of enrolment in HIV care (years)				
<10	7.7 (6.7 to 9.0)	9.3 (8.5 to 10.6)	11.2 (10.3 to 13.0)	12.9 (12.4 to 14.6)
10 to 14	3.7 (2.8 to 4.7)	5.0 (3.9 to 6.2)	6.7 (5.8 to 7.9)	8.2 (7.6 to 9.1)
15 to 16	–	2.4 (2.2 to 2.7)	4.4 (4.2 to 4.8)	6.5 (6.2 to 6.8)

Characteristics	"Transition" at 16 years	"Transition" at 18 years	"Transition" at 20 years	"Transition" at 22 years
Number transitioning within same year in facility, n (%)				
≤50	1469 (27)	1233 (32)	610 (42)	279 (63)
51 to 100	969 (18)	607 (16)	337 (23)	161 (37)
101 to 200	683 (12)	509 (13)	283 (19)	–
>200	2395 (43)	1515 (39)	233 (16)	–

ART, antiretroviral therapy; IQR, interquartile range.
[a]Age used as a proxy for "transition" to adulthood.

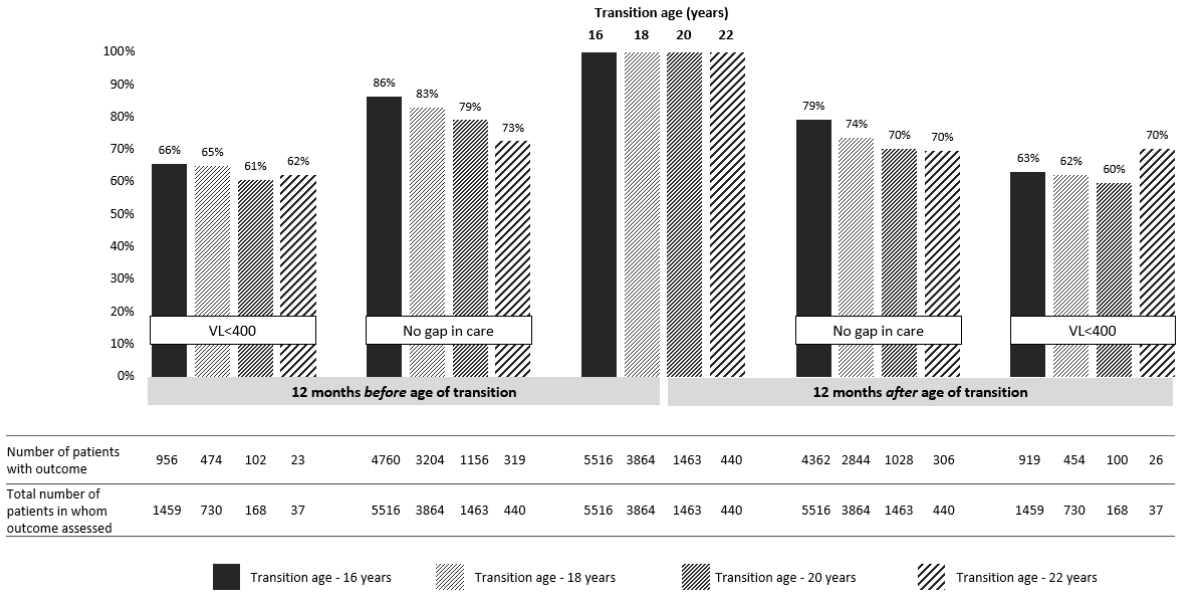
Eighty-six percent of AYLH included in the transition-16y analysis had no gap in care in the 12-month period pre-transition, 83% in the transition-18y, 79% in the transition-20y and 73% in the transition-22y age thresholds (Table 6.2 and Figure 6.2). In the 12-month period post-transition, 79% of AYLH included in the transition-16y analysis had no gap in care, 74% in the transition-18y, and 70% in both the transition-20y and transition-22y analyses (Table 6.2 and Figure 6.2).

Table 6.2 Outcomes of adolescents and young adults living with HIV across different transition age thresholds

Outcomes	"Transition" at 16 years (N = 5516)	"Transition" at 18 years (N = 3864)	"Transition" at 20 years (N = 1463)	"Transition" at 22 years (N = 440)
No gap in care 12 months *before* age of transition	86%	83%	79%	73%
No gap in care 12 months *after* age of transition	79%	74%	70%	70%
Difference (95% CI)	7.2 (6.0 to 8.4)	9.3 (7.8 to 10.9)	8.7 (6.1 to 11.4)	3.0 (−2.4 to 8.4)
HIV-RNA viral load done[a]	**(N = 1952)**	**(N = 1040)**	**(N = 280)**	**(N = 66)**
18 months *before* age of transition	84%	82%	78%	77%
18 months *after* age of transition	84%	81%	74%	68%
Difference (95% CI)	−0.05 (−2.0 to 1.9)	1.1 (−1.8 to 4.1)	3.9 (−3.1 to 10.9)	9.0 (−6.2 to 24.4)
HIV-RNA <400 copies/mL[b]	**(N = 1459)**	**(N = 730)**	**(N = 168)**	**(N = 37)**
18 months *before* age of transition	66%	65%	61%	62%
18 months *after* age of transition	63%	62%	60%	70%
Difference (95% CI)	2.5 (0.03 to 5.0)	2.7 (−1.0 to 6.5)	1.2 (−6.8 to 9.2)	−8.1 (−24.6 to 8.4)

CI, confidence interval.
[a]Limited to patients within facilities with annual routine viral load monitoring
[b]Limited to patients with viral load measurements done before and after the respective age threshold.

Figure 6.2 Outcomes of adolescents and young adults living with HIV across different transition age thresholds.



Compared to the pre-transition period, the proportion with no gap in care consistently declined post-transition, across all transition age thresholds (transition-16y: 86% vs. 79%, difference 7.2, 95% CI 6.0;8.4; transition-18y: 83% vs. 74%, difference 9.3, 95% CI 7.8;10.9; transition-20y: 79% vs. 70%, difference 8.7, 95% CI 6.1;11.4; transition-22y: 73% vs. 70%, difference 3.0, 95% CI −2.4;8.4) (Table 6.2 and Figure 6.2). Comparing the pre- and post-transition periods, we found no differences in the proportions of patients with viral load measurements (e.g., transition-18y: 82% vs. 81%, difference 1.1 (95% CI −1.8;4.1)) or proportions with viral suppression (e.g., transition-18y: 65% vs. 62%, difference 2.7 (95% CI −1.0 ;6.5)). This was observed throughout most transition age thresholds (Table 6.2 and Figure 6.2).

In the sensitivity analyses comparing the pre- and post-transition periods among patients still in care at the time of database closure, we found that the proportion with no gap in care also consistently declined post- when compare to pre-transition at the transition-16y and transition-18y thresholds (transition-16y: 89% vs. 86%, difference 2.8 (95% CI 1.6;4.0); transition-18y: 86% vs. 83%, difference 2.7 (95% CI 1.2;4.3)), but there were no differences at the transition-20y and transition-22y thresholds (transition-20y: 82% vs. 80%, difference 2.3 (95% CI −0.5;5.1); transition-22y: 77% vs. 80%, difference −3.0 (95% CI −7.7;3.6)) (Table 6.3 and Figure 6.3). Across all transition-age thresholds, there were no differences in the proportions of patients with viral load measurements or proportions virally suppressed between the pre- and post-transition periods (Table 6.3 and Figure 6.3). In further analyses assuming

transition at age 15 years, we found very similar results to those from the transition-16y analysis (Supplementary Table 6.1).

Table 6.3 Outcomes of adolescents and young adults living with HIV across different transition age thresholds to restricted to patients still in care at the end of follow-up

Outcomes	"Transition" at 16 years (N = 4341)	"Transition" at 18 years (N = 2909)	"Transition" at 20 years (N = 1126)	"Transition" at 22 years (N = 342)
No gap in care 12 months *before* age of transition	89%	86%	82%	77%
No gap in care 12 months *after* age of transition	86%	83%	80%	80%
Difference (95% CI)	2.8 (1.6 to 4.0)	2.7 (1.2 to 4.3)	2.3 (−0.5 to 5.1)	−3.0 (−7.7 to 3.6)
HIV-RNA viral load done[a]	**(N = 1706)**	**(N = 888)**	**(N = 235)**	**(N = 56)**
18 months *before* age of transition	84%	83%	78%	77%
18 months *after* age of transition	85%	82%	76%	71%
Difference (95% CI)	−0.5 (−2.6 to 1.6)	0.9 (−2.3 to 4.1)	2.1 (−5.6 to 9.9)	5.4 (−10.8 to 21.5)
HIV-RNA <400 copies/mL[b]	**(N = 1285)**	**(N = 634)**	**(N = 143)**	**(N = 33)**
18 months *before* age of transition	66%	66%	61%	64%
18 months *after* age of transition	65%	64%	60%	73%
Difference (95% CI)	1.5 (−1.2 to 4.1)	1.4 (−2.6 to 5.5)	0.7 (−8.1 to 9.5)	−9.1 (−27.5 to 9.3)

CI, confidence interval.

[a]Limited to patients within facilities with annual routine viral load monitoring

[b]Limited to patients with viral load measurements done before and after the respective age threshold.

We found no difference in the proportion of patients virally suppressed between the pre- and post-transition periods among AYLH included in this analysis with assumed perinatally acquired HIV (transition-18y: 63% vs. 58%, difference 4.7 (95% CI −2.3;11.7)) and those with non-perinatally acquired HIV (transition-18y: 66% vs. 64%, difference 1.7 (95% CI −3.4;6.7) and 68% vs. 66%, difference 2.6 (95% CI −9.0;14.2)) (Figure 6.4 and Supplementary Table 6.2). However, as with the whole cohort, proportion with no gap in care declined post-transition when compared to pre-transition in both groups (Figure 6.4 and Supplementary Table 6.2). Results for the transition-16y and transition-20y age thresholds are shown in Supplementary Table 6.2 and Supplementary Figure 6.1.

Figure 6.3 Outcomes of adolescents and young adults living with HIV across different transition age thresholds – restricted to patients still in care at the end of follow-up.

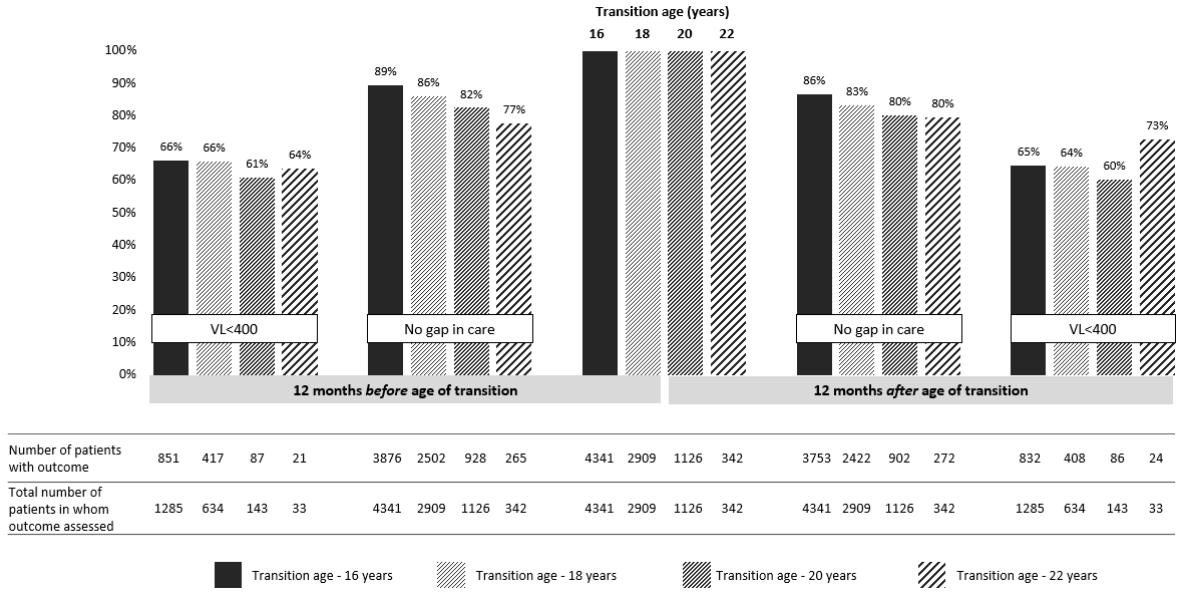
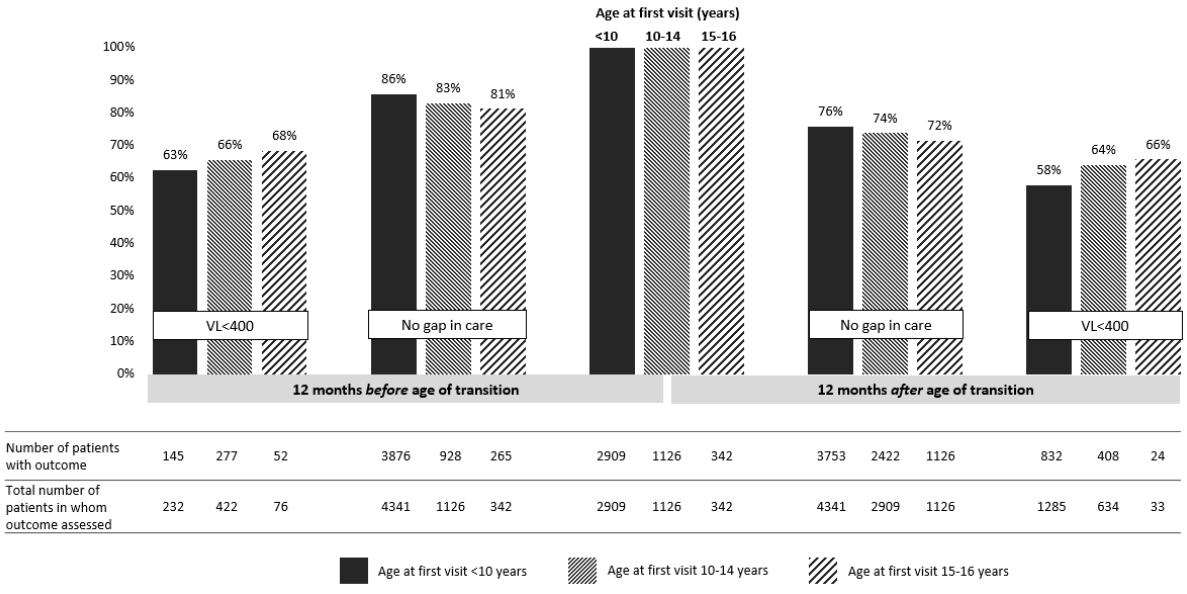


Figure 6.4 Outcomes of adolescents and young adults living with HIV in the 12 months before and 12 months after transition age 18 years, by age of enrolment into HIV care.



Using log-binomial regression, patients were consistently more likely to be retained post-transition if they had no gap in care in the preceding year, across all transition-age thresholds (transition-16y: adjusted risk ratio (aRR) 1.72 (95% CI 1.60;1.86); transition-18y: aRR 1.76 (1.61;1.92); transition-20y: aRR 1.75 (1.53;2.01); transition-22y: aRR 1.47 (1.21;1.78) (Table 6.4).

Table 6.4 Regression of predictors of retention of adolescents and young adults living with HIV in the 12 months after the age of transition across transition-age thresholds: 16, 18, 20, and 22 years

Characteristic	Transition at 16 years (N = 5516)	Transition at 18 years (N = 3864)	Transition at 20 years (N = 1463)	Transition at 22 years (N = 440)
	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)
Female (vs. male)	0.99 (0.97 to 1.01)	0.99 (0.96 to 1.02)	1.01 (0.96 to 1.07)	0.99 (0.89 to 1.11)
Age at enrolment into HIV care (years)				
<10	ref	ref	ref	ref
10 to 14	1.00 (0.98 to 1.03)	1.02 (0.98 to 1.07)	1.15 (0.98 to 1.35)	1.50 (0.76 to 2.94)
15 to 16	–	1.02 (0.97 to 1.08)	1.18 (1.00 to 1.39)	1.55 (0.79 to 3.04)
Number transitioning within same year in facility, n (%)				
≤50	ref	ref	ref	ref
51 to 100	1.06 (1.03 to 1.09)	1.04 (1.01 to 1.08)	0.95 (0.89 to 1.01)	0.85 (0.74 to 0.98)
101 to 200	1.04 (1.01 to 1.07)	0.89 (0.84 to 0.94)	0.80 (0.72 to 0.88)	–
>200	0.88 (0.85 to 0.91)	0.79 (0.76 to 0.83)	0.74 (0.66 to 0.84)	–
≥2 visits in 12 months *before* age of transition	1.72 (1.60 to 1.86)	1.76 (1.61 to 1.92)	1.75 (1.53 to 2.01)	1.47 (1.21 to 1.78)

aRR - adjusted risk ratio; CI - confidence interval.

Sex was not associated with post-transition retention throughout all transition-age thresholds. Also, for certain transition-age thresholds, the number of youth transitioning at the same time within a clinic was associated with retention. Compared to patients transitioning with ≤50 other patients within the same year in the clinic, those transitioning with 51 to 100 other patients were slightly more likely to be retained at the transition-16y (aRR 1.06 (95% CI 1.03;1.09)) and transition-18y (aRR 1.04 (1.01;1.08)) age thresholds; those transitioning with 101 to 200 other patients were less likely to be retained at the transition-18y (aRR 0.89 (0.84; 0.94)) and transition-20y (aRR 0.80 (0.72;0.88)) age thresholds, and those transitioning with >200 other patients were less likely to be retained across the transition-16y: aRR 0.88 (0.85;0.91), transition-18y: aRR 0.79 (0.76;0.83), and transition-20y: aRR 0.74 (0.66;0.84) age thresholds (Table 6.4)). Similar results were also observed in the analyses restricted to AYLH still in care at the end of follow-up (Table 6.5).

Table 6.5 Regression of predictors of retention in the 12 months after the age of transition across transition-age thresholds: 16, 18, 20 and 22 years – restricted to patients still in care at the end of follow-up

Characteristic	Transition at 16 years (N = 4341)	Transition at 18 years (N = 2909)	Transition at 20 years (N = 1126)	Transition at 22 years (N = 342)
	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)
Female (vs. male)	0.99 (0.97 to 1.01)	1.01 (0.98 to 1.03)	1.00 (0.96 to 1.05)	1.06 (0.96 to 1.18)
Age at enrolment into HIV care (years)				
<10	ref	ref	ref	ref
10 to 14	1.00 (0.98 to 1.02)	1.01 (0.97 to 1.04)	1.04 (0.92 to 1.16)	1.10 (0.71 to 1.72)
15 to 16	–	1.00 (0.96 to 1.04)	1.05 (0.93 to 1.18)	1.13 (0.73 to 1.77)
Number transitioning within same year in facility, n (%)				
≤50	ref	ref	ref	ref
51 to 100	1.06 (1.04 to 1.08)	1.02 (0.99 to 1.05)	0.91 (0.85 to 0.97)	0.87 (0.74 to 1.02)
101 to 200	0.93 (0.89 to 0.97)	0.85 (0.81 to 0.89)	0.81 (0.75 to 0.88)	–
>200	0.93 (0.90 to 0.95)	0.88 (0.85 to 0.92)	–	–
≥2 visits in 12 months *before* age of transition	1.44 (1.33 to 1.55)	1.57 (1.43 to 1.72)	1.47 (1.29 to 1.67)	1.32 (1.10 to 1.60)

aRR - adjusted risk ratio; CI - confidence interval.

6.6 Discussion

To the best of our knowledge, this is the first analysis to examine gaps in care and viral suppression outcomes in the pre-and post-transition periods for adolescents and young adults living with HIV transitioning to adulthood without transferring care within facilities in Southern Africa. We demonstrate that across multiple transition-age thresholds, retention of youth in care declined after transition, with this trend worsening as the age of transition increased from 16 to 22 years. Our data support the conclusion that adolescents and young adults are at an increased risk of disengaging from care as they reach the ages when they are expected to take responsibility for their own care and are managed as "adults."

Our findings show a decline in the proportion of youth who consistently remain in care after reaching transition ages, with 79% having no gaps in care in the 12 months after transition-16y and 70% after transition-22y. While our study used age as a proxy of transition to adulthood, our findings are consistent with studies from other cohorts that have shown sub-optimal engagement in care as adolescents enter adulthood (54,74,119,166,170). For example, one study in the Netherlands reported an increase in the mean number of individual yearly missed appointments as adolescents aged up to

young adulthood (171), while another in Zimbabwe showed that loss to follow-up among those who started ART as older adolescents (15 to 19 years) nearly doubled as they aged up to the ages of 20 to 24 years (84). Another analysis that looked at loss to follow-up rates within the US HIV Research Network (HIVRN) cohort reported that 11% of patients were lost to follow-up in the year after their 18th birthday and 20% were lost after their 22nd birthday (172). Other studies from settings were adolescents and young adults transfer to adult care as part of the transition process have reported worse outcomes (119). However, direct comparison with our results is difficult given that patients in our study remained at the same facility over time.

While post-transition virologic suppression rates were low in our cohorts (60% to 70%), they were similar to the pre-transition rates. For adolescents who have transferred to adult clinics, virologic suppression rates in adult clinics have not differed substantially from those in the paediatric setting (53). Notably, poor treatment adherence in paediatric care has been reported to be a reliable predictor of adherence in adult care(171). This emphasizes the importance of taking available opportunities to proactively address adherence issues early in care in order to improve later adherence and ensure adolescents have effective tools they can take into adult life. Also, the number of AYLH with viral load data declined as transition age increased, limiting our ability to conduct meaningful analyses for this outcome.

While the assumed mode of HIV acquisition and sex were not associated with post-transition retention, the strongest predictor of post-transition retention was prior poor engagement in care. Youth with gaps in care have been shown to be at risk of being lost to follow-up as they grow older (172). Furthermore, we found that for certain transition-age thresholds, the number of patients transitioning within the same year in the clinic impacted retention. Compared to youth transitioning with ≤50 others, youth transitioning with 51 to 100 others did better at the transition-16y and transition-18y thresholds, those transitioning with 101 to 200 others did worse at the transition-18y and transition-20y thresholds, and those transitioning with >200 other patients did worse across all transition-age thresholds. Although these results are difficult to interpret, it is possible that clinics with few transitioning patients are not adequately equipped to deal with the transition process. In contrast, clinics with too many patients may lack enough staff and time to support individualized and adolescent-friendly care for youth. An earlier survey of facilities providing care to adolescents living with HIV in sub-Saharan Africa showed that half of facilities had no guidelines or protocols for managing adolescent transition (104).

The major caveat to the interpretation of this study is that we used age as a proxy for transition to autonomy in the context of clinical care where youth remained in the same care facility as they aged and without knowing when they actually became responsible for their own individual health management. Chronological age does not reliably reflect the actual transition to self-management as autonomy is influenced by other factors besides age. Using age as a proxy may result in non-differential misclassification, where some youth classified as "autonomous" (based on age) may not have taken on

independent care responsibilities, while others below the age cut-off may have. Also, using age may lead to overgeneralized conclusions that do not take into account the diversity of adolescent experiences.

We did not include a comparison with those who were known to have been transferred out of care for other reasons, who were silently transferred (e.g. remained in care at another facility through an undocumented transfer) or who were LTFU before each respective age thresholds. Our definition of "retention" was pragmatic but relatively crude and we may have misclassified patients who had temporary gaps in care but later re-engaged with HIV care services. In addition, our analysis was limited to variables that were available in routinely collected data and we could not measure specific factors related to independence or self-management of care such as the ability to make appointments, attending clinic appointments without a parent or caregiver, and transition-related processes which may entail changes in the clinic days or times, or movements to a different section of the facility, without transfer of care. Despite these limitations, given that our analysis used routinely collected longitudinal data, our findings may be more generalizable to settings with similar transition processes. By studying engagement in care and viral suppression in the year before and after transition, we were able to more fully characterize care experiences of youth as a continuum, showing how care-related behaviours earlier in life impact those later in life.

For adolescents and young adults living with HIV, the period of healthcare transition is a particularly vulnerable one that is associated with greater risk of disengagement from care. We found that gaps in care earlier in adolescence and young adulthood are a marker for worse outcomes later. There is an urgent need for timely interventions for AYLH with gaps in care before they reach transition ages and for models of care tailored to the needs of transitioning adolescents and young adults. For AYLH managed within facilities where transition to adulthood does not entail a physical transfer of care to an adult HIV clinic, greater awareness of the risk of poorer outcomes and investment of human and technical resources are needed to ensure they successfully adapt to changing expectations for their care.

6.7 Conclusion

Our analysis demonstrates that AYLH with gaps in care need targeted support to prevent non-retention as they age and take on greater responsibility for their healthcare. We noted with concern the low virologic suppression rates both in the pre- and post-transition periods.

Chapter 7: Creating a data collection and management platform to support measurement of adolescent HIV care transition processes within low- and middle-income countries: The GRADUATE project

Tsondai PR, Davies MA, Singtoroj T, Maxwell N, Technau KG, Phiri S, Chokephaibulkit K, Lumbiganon P, Sohn AH; on behalf of the Global fRAmework of Data collection Used for Adolescent HIV Transition Evaluation (GRADUATE) Advisory Group

7.1 Chapter overview and contribution to thesis

This chapter addresses the third objective of the thesis which was to design a data collection and management platform that effectively captures transition-related processes and outcomes of adolescents and young people living with HIV within LMICs. Few national programs and research cohorts within developing countries document transition-related processes and outcomes for AYLH transitioning to adulthood. The GRADUATE project identified key data variables and data definitions that capture the process of transition, its predictors, and the outcomes across the transition period, created data tables to facilitate data collection and evaluated the feasibility and utility of the data-capturing tools to measure transition readiness, processes, and outcomes and optimally determine transition preparation activities and outcomes. Utilization of the tools in other settings could facilitate comparisons and identify gaps in the care of transitioning adolescents or concerning outcomes that need to be addressed.

Role of the candidate

Mary-Ann Davies and Annette Sohn conceptualized the study and wrote the study concept. The candidate led the study team. She was solely responsible for developing all the study materials including an online data collection platform, directing data collection, visiting study sites and ensuring all protocols were being observed, conducting all the data cleaning and analyses, writing, and managing all the versions of the manuscript, incorporating suggestions from co-authors, and submitting it to the journal. Mary-Ann Davies and Annette Sohn were responsible for overall leadership and assisted with data interpretation. All authors reviewed and approved the final manuscript before submission.

The candidate presented the study findings at the virtual 23rd International AIDS conference (AIDS 2020), 6-10 July 2020.

Publication status

Published: PLOS Glob Public Health 2024; 4(8): e0002705.

7.2 Abstract

Background

Few national programs and research cohorts within LMICs document transition-related processes and outcomes for AYLH transitioning to adulthood. The GRADUATE project aimed to create a broadly implementable open access data collection and management platform that would support measurement of adolescent HIV care transition processes and outcomes within LMICs.

Methods

Between 2017–2020, The Global fRAmework of Data collection Used for Adolescent HIV Transition Evaluation (GRADUATE) project convened a collaborative advisory group to identify key variables and definitions capturing the process, predictors, and outcomes across the transition period.

Results

In total, 114 variables identified as essential to measuring AYLH transition-related data were identified and formatted into a GRADUATE Data Exchange Standard (DES), which was added to and harmonized with the existing International epidemiology Databases to Evaluate AIDS (IeDEA) DES. In 2019, the GRADUATE DES was pilot tested at four IeDEA facilities in Malawi, South Africa, and Thailand through a cross-sectional study. Upon comparing the variables to routine medical records, available data were too limited to adequately capture transition related processes and outcomes. However, additional data collection using GRADUATE tools was feasible and improved completeness. Of the 100 (52% female) AYLH included in the pilot study, 71% had transitioned/transferred to adult care, with 42% transitioning from an adolescent-specific model of care within an integrated family clinic to having their clinic visits scheduled on a different day of the week while 58% transferred from a paediatric facility to one offering adult HIV care. While almost all (94%) had a transition-related discussion with their healthcare providers prior to the transition, we found that 69% (95% CI 49–85%) were somewhat or very satisfied/comfortable with the post-transfer clinic and the staff.

Conclusion

Utilization of the GRADUATE DES better characterized AYLH transitioning to adulthood across LMICs, and optimally measured transition preparation activities and outcomes. Utilization of the GRADUATE DES in other settings could facilitate comparisons and identify gaps in the care of transitioning adolescents that need to be addressed.

7.3 Introduction

ART has transformed HIV to a chronic illness. An increasing number of children and adolescents living with perinatally and non-perinatally acquired HIV are surviving beyond adolescence into adulthood and having to manage HIV for the rest of their lives (59). There are over three million AYLH aged 15 to 24 years in the world today (173). As these AYLH grow, they face a series of steps associated with transitions in their care and are expected to become increasingly responsible for their own healthcare. The goal of transition is to continue providing uninterrupted, high-quality, and developmentally appropriate healthcare services as an individual moves from adolescence to adulthood. In high-income countries, this frequently involves transferring care from a paediatric/adolescent setting to an adult HIV clinic, often following a systematic and structured process (54,56,59,99,101). However, in LMICs, transition to adulthood for children living with HIV may not always involve physical movement to a different clinic, or change in provider, and is often not well-defined or structured (75). Nonetheless, as they age, youth increasingly become empowered to self-manage their disease and start attending clinic visits and collecting their medications without a caregiver. The healthcare providers also begin interacting with them as adults rather than as children/adolescents, even if they are still receiving care within the same facility. This time of a person's life may also be a vulnerable period in general and with regard to ART adherence in particular, where sudden or unplanned changes may cause care interruptions or worsen outcomes (38,174).

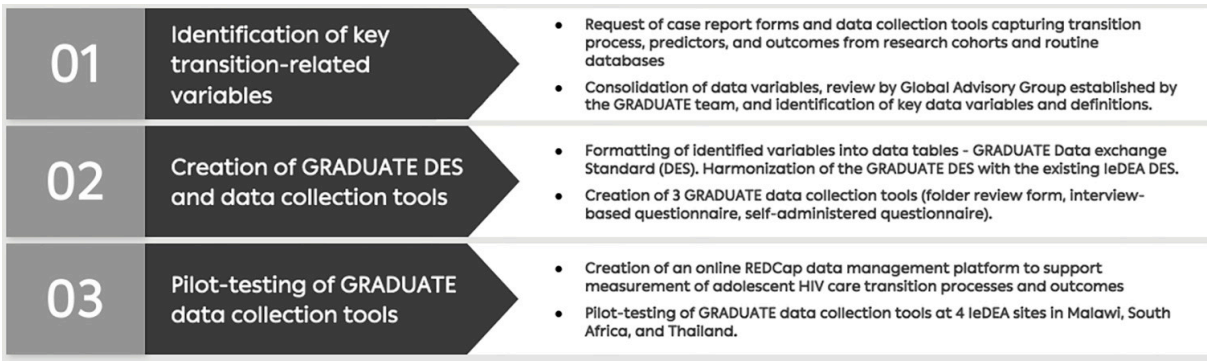
While research on the transition of AYLH into adult care has progressed in specific cohorts in the US and Europe (49,166,175,176), the field remains in early stages in LMICs, where the vast majority of AYLH reside. Few national programs or research cohorts in LMICs document the transition experience or its outcomes (55,177). Whereas high-income countries may have access to research cohorts with extensive demographic and behavioural questionnaires as well as non-routine laboratory data, cohorts within LMICs have more limited data gathered in routine care. Moreover, routine data within these settings may not yet include many of the variables needed to fully characterize this population or to adequately assess transition-related processes and outcomes. There is no standard method for tracking these outcomes across the transition period which seriously limits surveillance of these targets in adolescents. Also, central to assessing and comparing transition outcomes is knowing how to optimally measure them and implementing data collection across different settings.

The GRADUATE project aimed to create the first broadly implementable and open access data collection and management platform that would support measurement of adolescent HIV care transition processes and outcomes. We describe the processes of creating this platform, and present results from the pilot exercise conducted to assess the developed tools.

7.4 Methods

The GRADUATE project was conducted between 2017-2020 in three phases, as shown in Figure 7.1.

Figure 7.1 Phases of the GRADUATE project in creating a data collection and management platform to support measurement of adolescent HIV care transition processes and outcomes



CRFs – case report forms; DES – Data exchange Standard; GRADUATE - Global fRAmework of Data collection Used for Adolescent HIV Transition Evaluation; IeDEA - International epidemiology Databases to Evaluate AIDS

Phase 1: Identification of key transition-related variables

Case report forms and data collection tools were requested from established research cohorts and routine databases in countries across all income settings that were actively collecting transition-related data from adolescents living with HIV, namely: the Pediatric HIV/AIDS Cohort Study (PHACS) Adolescent Master Protocol's AMP Up cohort in the US (178), Adolescents and Adults Living with Perinatal HIV (AALPHI) cohort in the UK (179), Centre Maternel et Infantile sur le SIDA (CMIS) Mother-Child Cohort in Canada (180), Cape Town Adolescent Antiretroviral Cohort (CTAAC) in South Africa (181), and the Study of Transitioning Asian Youth (STAY) Cohort in Southeast Asia. In addition, the IeDEA (182) Data Exchange Standard (DES) was reviewed, which is a data model for sharing observational HIV data, designed and maintained by the IeDEA Data Harmonization Working Group (183).

Variables on key demographic, socioeconomic, clinical, and laboratory aspects relating to AYLH within the received case report forms and DES were extracted. These were presented to an advisory group composed of expert clinicians, researchers, and implementers working with children and AYLH from across various country income settings, established by the GRADUATE project. The advisory group reviewed the pooled variables. Through a prioritization exercise, they evaluated each variable, rating them to distinguish between those that were essential and optional. Subsequently, they deliberated on the ratings through a consultative process, paying particular attention to those that had been deemed optional or unnecessary and that would be excluded from the list of variables. They

reached consensus on the variables central to capturing characteristics of AYLH transitioning to adulthood across LMICs, as well as the processes, predictors, and outcomes across the transition period.

Phase 2: Creation of the GRADUATE DES and data collection tools

In phase 2, selected variables were categorized into three tiers, depending on how likely they were to already be captured or how easily they could be obtained.

- Tier one or "basic core variables" were defined as those most likely to be routinely captured by HIV programs within LMICs that could be used for surveillance and program evaluations, such as those describing ART history, anthropometric measures, missed appointments, retention, transfer of care, and immunologic and virologic markers.
- Tier two or "advanced core variables" were defined as those that may not be available within routine care but should be collected whenever possible for assessing clinical outcomes within dedicated cohorts. These include variables capturing transition preparation, disclosure, orphanhood, caregiver arrangements, housing, education, employment, co-morbidities, access to reproductive and mental health care, substance use, and pregnancy and pregnancy outcomes.
- Tier three or "research variables" were defined as those unlikely to be routinely collected and would likely need to be determined in the context of targeted research. These include variables capturing detailed mental health (e.g., depression screens), social well-being (e.g., resilience factors), sexual health, and HIV resistance data.

The selected variables were then defined, formatted, and organized into tables. These tables were added to and harmonized with the existing IeDEA DES (18) to create the GRADUATE-IeDEA DES (Supplementary information 7.1). To facilitate patient-level data collection of variables included in the GRADUATE-IeDEA DES, we designed a folder review form to abstract information from paper-based and electronic routine medical records and databases, as well as self-administered and interview-based questionnaires for completion by the participant or by the study staff while interviewing the participant, respectively.

Phase 3: Collection of transition-related information using GRADUATE data collection tools

We conducted a cross-sectional study from 1 March to 31 July 2019 of AYLH aged 18–24 years and in care at participating IeDEA sites to 1) test the utility of the GRADUATE DES and associated data collection tools within routine care, 2) evaluate the proportion of key variables in describing the processes, predictors, and outcomes of transition available in routine medical records, 3) examine the

proportion of these variables not available that can be obtained from additional data collection efforts, such as through questionnaires, and 4) compare the completeness and quality of transition-related data across participating sites. The study was implemented at sites with a clearly delineated process for transitioning youth to adult HIV care: one primary care clinic (Lighthouse Trust Clinic, Malawi) and three hospitals (Rahima Moosa Mother and Child Hospital, South Africa; Siriraj Hospital and Srinagarind Hospital, Thailand).

- Lighthouse Trust Clinic is a primary care facility in Kamuzu Central Hospital in Lilongwe, Malawi, which manages patients living with HIV from childhood through adolescence and into adulthood. As they transition from paediatric to adolescent to adult care, patients within this facility are seen in separate clinics (e.g., on different days of the week) using established guidelines for transition, making it highly feasible to identify the shift from paediatric to adolescent care in the data.
- The Empilweni Services and Research Unit within the Rahima Moosa Mother and Child Hospital in Johannesburg, South Africa offers routine maternity, neonatal and paediatric services. It is one of the largest paediatric HIV treatment clinics in Johannesburg, South Africa, managing infants and children with HIV or who are HV-exposed. Healthcare transition for AYLH involves them being transferred to a different facility with adult HIV care services. Transition is discussed with the adolescent during up to three visits before the planned transition, so they can discuss with family and decide which facility they would like to transition to. On the day of transition, adolescents are given a transfer letter that contains details of ART initiation, regimens and switches, blood results at initiation and transfer as well as other important clinical or psychosocial information.
- Siriraj Hospital, Mahidol University in Bangkok, Thailand is a paediatric and adult HIV referral centre, offering a dedicated sexually transmitted infections and HIV clinic. HIV paediatric to adult healthcare transition involves transfer of care to a different facility based on geographic proximity to the patient's home using established guidelines for preparing and implementing transition through a comprehensive youth program called the "Happy Teen Program," which has previously been described (184).
- Srinagarind Hospital in Khon Kaen, Thailand, is a tertiary hospital offering specialist paediatric and adult HIV services. Healthcare transition for AYLH involves transfer of care to a different facility based on geographic proximity to the patient's home (185).

AYLH within these facilities with the following criteria were eligible for enrolment into the pilot study: aged between ≥18 to ≤24 years of age (at the date of consent); have confirmed HIV; fully disclosed to

regarding their HIV status; with transition either scheduled to take place within the next year, or currently transitioning, or recently transitioned to adult HIV care within the previous one year. At all four facilities, routine electronic and paper-based medical records for enrolled participants were reviewed and anonymized data abstracted into the folder review form. In addition, study staff administered interview-based questionnaires to participating AYLH at Lighthouse Trust Clinic. Participants at Rahima Moosa Mother and Child Hospital completed self-administered questionnaires.

An online Research Electronic Data Capture (REDCap) data management platform was created using the REDCap tools hosted by the University of Cape Town. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources (186,187). All information obtained was anonymized and entered onto the online data management platform, with each site being able to view and having access only to their data, and the data centre having access to only anonymized data from all the sites.

Each site received ethics approval from their local Institutional Review Boards to conduct the pilot study and submit de-identified data for analysis, namely the National Health Sciences Research Committee of the Malawi Ministry of Health and Population, Rahima Moosa Mother and Child Hospital IRB, Siriraj IRB, and Khon Kaen University Ethics Committee for Human Research. CIDER at the University of Cape Town received ethics approval from the UCT-HREC to receive, merge and analyse the de-identified data. Written informed consent was required for all participants from Lighthouse Trust clinic and Rahima Moosa Mother and Child Hospital but was not for Siriraj and Srinagarind Hospitals, as their data used in the analysis were collected during routine care and their relevant IRBs waived consent for this research.

Statistical analysis

A descriptive analysis was done of the demographic, socio-economic, clinical, and laboratory characteristics of AYLH transitioning to adulthood across the sites and of transition-related processes and outcomes across settings. Key characteristics described and compared include sex, age at transition, duration in HIV care/on ART, likely route/timing of acquisition, regimen, adherence, disclosure, clinical, immunological and virologic status, education, housing, employment, incarceration, pregnancy, hospital admissions, mental health referrals and diagnosis, and preparedness for and attitude towards transition process. Covariates of interest were described, and bivariate associations explored, according to distributional patterns. The McNemar test was used to determine if there was a significant

difference in the proportion of participants with data available when using routine medical records compared to when using data obtained through questionnaires.

All data were analysed using Stata Version 15.0 (Stata Corporation, College Station, Texas).

7.5 Results

We identified 114 variables as essential to characterizing AYLH transitioning to adulthood within LMICs and capturing transition-related processes and outcomes. These include variables capturing socio-demographic characteristics, medication responsibilities, disclosure, adherence, substance and alcohol use, smoking, sexual history, laboratory findings, fractures, hospitalization, self-harm, mental health diagnosis, referral or treatment, transfers, and transition experiences (Table 7.1).

Table 7.1 Variables identified as key in capturing the characteristics of adolescents and young adults living with HIV transitioning to adulthood across LMICs, as well as the transition-related processes and outcomes

Theme	Variable
Socio-demographic	• Date of birth • Sex • Living arrangements • Type of dwelling currently live in • Longest duration of homelessness if any • Schooling including currently attending any formal school, attending secondary school • Current employment situation including any full-time or part-time work • Main source of income including any receipt of social grants • Episodes of incarceration (>1 day in prison) as an adolescent or young adult (ages 10-25 years), including age, number of separate incidents, and duration. • Vital status of biological mother and father • Current relationship status • Date of birth, HIV status, and HIV disclosure status of any biological children
Disclosure	• Disclosure status, process, and age, including self-disclosure to others
ART medication clinic visits	• Date of patient's visit • Type of clinic in terms of age group where patient is seen • Person responsible for making travel arrangements to get to clinic appointments and medicine collection. • Person responsible for patient taking ART medications.

Theme	Variable
ART adherence	• Time period over which ART adherence variables are asked. • Method of adherence measurement used and adherence (perfect vs imperfect)
Medical history	• Laboratory measures • Hospital admissions including date of admission and discharge, diagnosis, and any intensive care admissions • Mental health referrals, diagnoses, and treatment • History of fracture(s) including site and level of trauma that caused the fracture
Recorded outcome	• Dropping out of care and reasons • Patients' vital status
Alcohol intake	• Alcohol intake including age at which they first drank a whole unit of alcohol, frequency of drinking, and amount of alcohol units consumed on a typical day, binge drinking.
Smoking	• History of smoking, including age at which they first smoked a whole cigarette and frequency of smoking
Recreational drugs	• Use of non-injectable and injectable recreational drugs other than cigarettes and alcohol, including age at which they first started using and frequency of use
Sexual activity (only for children >12 years of age)	• Primary sexual preference • Sexual activity history including number of sexual partners, type of encounter (vagina, oral, anal), and frequency of condom use,
Self-harm	• Episodes of self-harm in the past 12 months including method(s) used
Transfer	• Date of transfer out • Did the patient attend a visit at the facility to which they were transferred? • Date of transfer in • Was this transfer referred by the transfer out facility or was it a self-referral/silent transfer that the transfer out facility was not aware of or did not initiate? • Primary (main) reason for transfer • Other reason for transfer (additional reasons for transfer e.g., patient moves to another area and commences antenatal care) • Program from which patient was transferred out
Transition experience (paediatric to adolescent or adolescent to adult transition, with or without a shared care clinic)	

Theme	Variable
Pre-transition	• How many weeks before last date at the transferring out clinic was the patient first told about transfer? • Number of clinic visits at which transfer was discussed prior to visit at which patient was transferred out? • Age of patient in years when first discussed transition to another clinic. • Did patient have a written transition/transfer plan before transfer (e.g., brochure, checklist, webpage, adolescent "passport") • Who brought the patient to the clinic visit immediately after transfer (i.e., the transfer in visit)?
Post-transition (6-12 months after the first visit to the new clinic/facility)	• Date on which post-transfer/transition questions are asked? • How prepared/unprepared did the patient feel for transfer/transition • How easy/difficult was the transfer/transition? • How satisfied/comfortable is patient with post-transfer clinic? • How satisfied/comfortable is patient with staff at post-transfer clinic

Of the 100 AYLH included in the pilot-study (52% female), 60 (53% female) were from the African sites (30 from Lighthouse Trust clinic and 30 from Rahima Moosa Mother and Child Hospital) and 40 (50% female) were from sites in Asia (20 from Siriraj Hospital and 20 from Srinagarind Hospital). Median age at enrolment (IQR) was 20.7 (19.2; 21.8) years. The youngest participant was aged 15 years and the eldest was 27 years (Table 7.2). All the participants with data available reported having been perinatally exposed to HIV and all were currently on ART. The median (IQR) age at which the participants became fully aware of their HIV status was 12 (11; 14) years with half (50.5%; 95% CI 40.2;60.8%) having been informed of their HIV status by a healthcare worker, 41% (95% CI 31.3;51.7%) by their caregiver and 6.2% (95% CI 2.3;13.0%) having worked it out themselves before being informed. One-third had been referred for a mental health diagnosis or treatment (32%; 95% CI 21.6;43.1) or had been hospitalized (38%; 95% CI 28.2;48.1%) during adolescence (Table 7.2).

Table 7.2 Description of 100 adolescents and young adults living with HIV included in the pilot study to evaluate the proportion of variables identified as key in describing the processes, predictors, and outcomes of transition available in routine medical records and examine the ease of obtaining these variables through questionnaires

Characteristic	African sites[#]	Asian sites[##]	Total
Number	60	40	100
Age (years), median (IQR)	20.2 (18.8; 21.9)	21.1 (19.8; 21.5)	20.7 (19.2; 21.8)
Females, n (%)	32 (53)	20 (50)	52 (52)

Characteristic	African sites[#]	Asian sites[##]	Total
Single or double orphaned, n/N (%)	50/60 (83)	27/38 (71)	77/98 (79)
Currently attending any formal schooling, n/N (%)	47/60 (78)	20/38 (53)	67/98 (68)
Currently employed, n/N (%)	9/60 (15)	12/21 (57)	21/81 (26)
Dependent on self as main source of income Self, n/N (%)	11/60 (18)	6/18 (33)	17/78 (22)
Has a biological child, n/N (%)	3/60 (5)	2/38 (5)	5/98 (5)
Perinatal HIV exposure (self-reported), n/N (%)	52/52 (100)	38/38 (100)	90/90 (100)
Age (years) at which became fully aware of HIV status, median (IQR)	13.0 (11.0; 15.0)	12.0 (11.0; 13.0)	12.0 (11.0; 14.0)
Told by caregiver, n/N (%)	36/60 (60)	4/37 (11)	40/97 (41)
Told by health care worker, n/N (%)	16/60 (27)	33/37 (89)	49/97 (51)
Worked out HIV status, n/N (%)	6/60 (10)	0	6/97 (6)
Has disclosed HIV status to others excluding family members, n/N (%)	29/59 (49)	15/20 (75)	44/79 (56)
Currently on ART, n/N (%)	60/60 (100)	39/40 (98)	99/100 (99)
Attended last clinic visit without any caregiver, n/N (%)	50/60 (83)	6/20 (30)	56/80 (70)
Responsible for making own travel arrangements to the clinic always, n/N (%)	35/60 (58)	19/20 (95)	54/80 (68)
Responsible for taking own ART medications always, n/N (%)	51/60 (85)	23/25 (92)	74/85 (87)
Ever been referred for a mental health diagnosis or treatment since the age of 10 years, n/N (%)	17/60 (28)	8/19 (42)	25/79 (32)
Episode of self-harm in the past 12 months, n (%)	3/59 (5.0)	0/40	3/67 (5)
Ever been hospitalized since the age of 10 years, n/N (%)	28/60 (47)	9/38 (24)	37/98 (38)
Ever had a bone fracture since the age of 10 years, n/N (%)	16/59 (27)	1/21 (5)	17/80 (21)
Ever smoked a whole cigarette, n/N (%)	13/59 (22)	6/16 (38)	19/75 (25)
Ever drunk a whole unit of alcohol, n/N (%)	35/60 (58)	6/15 (40)	41/75 (55)
Ever used injectable or non-injectable recreational drugs, n/N (%)	2/60 (3)	0/40	2/100 (2)
Ever engaged in vaginal, anal, or oral sex, n/N (%)	38/60 (63)	11/21 (52)	49/81 (61)
Transitioned to adult care[*], n (%)	32 (53)	39 (98)	71 (71)
Age at transition (years), median (IQR)	20.6 (20.2; 21.9)	19.7 (18.9; 20.5)	20.2 (19.4; 21.2)
Transferred care as part of transition, n/N (%)	2/32 (6)	39/39 (100)	41/71 (58)
Pre-transition discussion prior to transition, n/N (%)	32/32 (100)	35/39 (90)	67/71 (94)
Felt somewhat prepared or very prepared for the transition/transfer, n/N (%)	26/32 (81)	18/20 (90)	44/52 (85)
Feel the transition/transfer was somewhat easy or very easy, n/N (%)	20/32 (63)	N/A	20/32 (63)
Very or somewhat satisfied/comfortable with the post-transfer clinic, n/N (%)	20/29 (69)	N/A	20/29 (69)

Characteristic	African sites[#]	Asian sites[##]	Total
Very or somewhat satisfied/comfortable with the staff at the post-transfer clinic, n/N (%)	20/29 (69)	N/A	20/29 (69)

[#] Participants from Lighthouse Trust Clinic in Malawi (n=30) and Rahima Moosa Mother and Child Hospital in South Africa (n=30). Data obtained from routine medical records as well as from additional data collection through questionnaires.

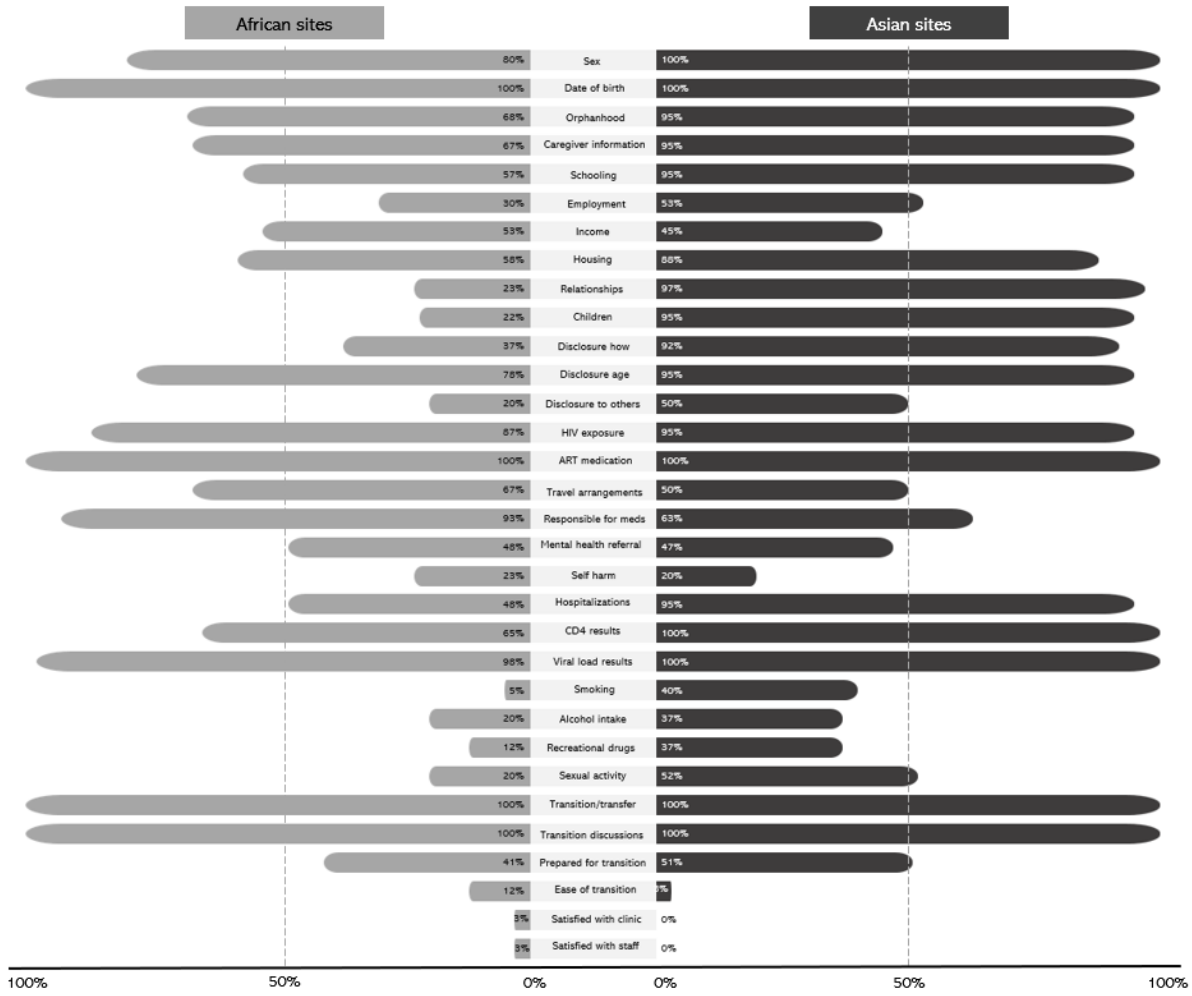
[##] Participants from Siriraj Hospital (n=20) and Srinagarind Hospital (n=20) in Thailand. Data obtained from routine medical records only.

[*] Definition of transition varies across the sites

In total, 71% (53% in African sites vs. 97.5% in Asian sites) had transitioned/transferred to adult care, as per the definition of each site. Of these, 30 (42%) of the participants transitioned from an adolescent-specific model of care within an integrated family clinic to having their clinic visits scheduled on a different day of the week while 41 (58%) transferred from a paediatric facility to a different facility offering adult HIV care. Median (IQR) age of transition/transfer was 20.6 (20.2; 21.9) years in African sites and 19.7 (18.9; 20.5) years in the Asian sites (Table 7.2). Ninety-four percent (95% CI 86;98%) of those who had transitioned/transferred to adult care had a transition-related discussion with their healthcare providers prior to the transition, 85% (95% CI 72%;93%) felt somewhat prepared or very prepared, 62.5% (95% CI 44;79%) felt that the transition/transfer was somewhat easy or very easy, and 69% (95% CI 49;85%) were somewhat or very satisfied/comfortable with the post-transfer clinic and the staff (Table 7.2).

Information on sociodemographic variables (sex and date of birth), ART medication history, viral load results, HIV exposure, and whether the adolescent had transitioned/transferred care and had prior discussions were available in ≥80% of routine medical records across both African and Asian sites (Figure 7.2). Information that varied greatly in availability across the sites, and with significantly less recording of this information within routine medical records for participants in the African sites, included that relating to recording of relationship status (African vs. Asian sites; 23% vs. 97%; difference -74%, p <0.01), biological children (22% vs. 95%; difference -73%; p <0.01), who had disclosed their HIV status to them (37% vs. 92%; difference -55%; p <0.01), history of hospitalizations (48% vs. 95%; difference -47%, p <0.01), smoking (5% vs. 40%), sexual activity (20% vs. 52%; difference; p <0.01).

Figure 7.2 Proportion of participants with data available within their routine medical records across the various themes.



For both African and Asian sites, there was incomplete recording in routine medical records of information relating to satisfaction with post-transition clinic (3% and 0%) and staff (3% and 0%), ease of transition (12% and 3%), self-harm (23% and 20%), smoking (5% and 40%), use of recreational drugs (12% and 37%), alcohol intake (20% and 37%), referral for mental health diagnosis or treatment (48% and 47%), sexual activity (20% and 52%), and level of preparedness for transition (41% and 51%), respectively (Figure 7.2).

Additional data collection through interviewer-based and self-conducted questionnaires was only conducted in the African sites. All participants within these sites completed the questionnaires. There was a significant increase across all variables in the data availability upon eliciting information through questionnaires (Table 7.3), with 100% availability noted across all variables included in the questionnaires. Most significant improvements could be noted for most transition-related variables such as feeling prepared for transition, ease of transition, and satisfaction with post-transition clinic and staff.

Table 7.3 Proportion of participants with data available within routine medical records compared to data that became available upon collecting additional data through questionnaire (N=60) among participants in African sites

Characteristic	Proportion with data available*, n/N (%)	Difference %	(95% CI) **	p-value
Sex	48/60 (80)	20.0%	(9.9 – 30)	<0.01
Orphanhood	41/60 (68.3%)	31.7%	(19.9 – 44)	<0.01
Caregiver information	40/60 (66.7%)	33.3%	(21.4 – 45.2%)	<0.01
Currently attending any schooling	34/60 (56.7%)	43.3%	(30.7 – 55.8%)	<0.01
Currently employed	18/60 (30.0%)	70.0%	(58.4 – 81.6%)	<0.01
Sources of income	32/60 (53.3%)	46.7%	(34.1 – 59.3%)	<0.01
Housing	35/60 (58.3%)	41.7%	(29.2 – 54.2%)	<0.01
Current relationship status	14/60 (23.3%)	76.7%	(66.0 – 87.4%)	<0.01
Biological children	13/60 (21.7%)	78.3%	(67.9 – 88.7%)	<0.01
How they became fully aware of HIV status (disclosure how)	22/60 (36.7%)	63.3%	(51.1 – 75.5%)	<0.01
Disclosure age	47/60 (78.3%)	21.7%	(11.3 – 32.1%)	<0.01
Disclosure of HIV status to others excluding family members	12/60 (20%)	80.0%	(69.9 – 90.1%)	<0.01
HIV exposure	52/60 (86.7%)	13.3%	(4.7 – 21.9%)	<0.01
Responsible for making own travel arrangements to the clinic always	40/60 (66.7%)	33.3%	(21.4 – 45.2%)	<0.01
Responsible for taking own ART medications always,	56/60 (93.3%)	6.7%	(0.4 – 13.0%)	0.04
Ever been referred for a mental health diagnoses or treatment during adolescence	29/60 (48.3%)	51.7%	(39.1 – 64.3%)	<0.01
Ever hurt themselves on purpose in the last 12 months (self-harm)	14/60 (23.3%)	76.7%	(66.0 – 87.4%)	<0.01
Hospitalizations since the age of 10 years	29/60 (48.3%)	51.7%	(39.1 – 64.3%)	<0.01
Smoking	3/60 (5.0%)	95.0%	(89.5 - 100%)	<0.01
Alcohol	12/60 (20%)	80.0%	(69.9 – 90.1%)	<0.01
Use of recreational drugs	7/60 (11.7%)	88.3%	(80.2 – 96.4%)	<0.01
Sexual activity	12/60 (20.0%)	80.0%	(69.9 – 90.1%)	<0.01
Feeling prepared for transition/transfer	13/32 (40.6%)	59.4%	(42.4 – 76.4%)	<0.01
Ease of transition/transfer	4/32 (12.5%)	87.5%	(76.0 – 99.0%)	<0.01
Satisfaction with post-transition clinic	1/32 (3.1%)	96.9%	(90.9 – 100%)	<0.01

Characteristic	Proportion with data available*, n/N (%)	Difference % (95% CI) **	p-value
Satisfaction with post-transition clinic staff	1/32 (3.1%)	96.9% (90.9 – 100%)	<0.01

* Data available only within routine medical records.

** Difference when comparing data available within routine medical records to that availability (100% across all variables) with additional data collection through questionnaires.

7.6 Discussion

We showed that it was feasible for a team of technical experts to agree on a set of variables and definitions that are key to measuring transition and transition-related outcome - despite managing AYLH across diverse geographic, economic, and social landscapes, and with varying definitions of adolescent to adult HIV care transition. Leveraging work already conducted by IeDEA, we were able to integrate the identified variables into the IeDEA DES to create a comprehensive set of data tables that can be used to extract information needed to describe and characterize AYLH transitioning to adult care, and to study transition-related processes and outcomes across LMICs more fully.

The GRADUATE project at least partly addressed the urgent need for the development and validation of robust and consistent measures of transition readiness, processes, and outcomes to allow interstudy comparison as well as to consistently report outcomes across varying settings (188–193). Using the additional data collection through the GRADUATE harmonized set of data tools, we were able to characterize the health and associated social determinants of AYLH transitioning to adulthood across our sites, and document key aspects of transition preparation, implementation, and outcomes more fully. We were able to gain insights into key domains known to be associated with transition readiness – disclosure, health navigation, self-advocacy, and health literacy (110,194,195). While the subject of healthcare transition is not new and has been noted for adolescents with other chronic diseases, there are still very few studies that examine transition measures and associated health conditions, which may be critical to achieving optimal disease specific outcomes. For example, there was very poor recording of information relating to referral for mental health diagnosis or treatment, self-harm, smoking, alcohol intake, use of recreational drugs, and sexual activity in routine health records, despite the fact that AYLH are known to be at risk of developing mental health complications, including depression, anxiety, substance use and post-traumatic stress disorder, which may all lead to self-reported non-adherence and missed ART doses as well as unsuppressed VL and poor treatment outcomes (34,196–200). Regular assessment, documentation and management of any conditions that may have a negative impact on adherence to medications is critical in AYLH, especially as they transition to adulthood when AYLH are known to have sub-optimal adherence (33)

The WHO emphasizes the importance of integrating HIV care with other relevant services, such as sexual and reproductive health, which has been found to be feasible across a variety of settings and integration models (201–203). This integration is also important to providing youth-friendly, "one-stop" health care delivery services to facilitate efficient uptake of key services (204). Therefore, the very poor recording of sexual health information observed in our study (e.g., sexual activity, consistency of condom use), suggests that true integration of services is limited. Also of concern was the poor recording of any biological children of ALYH among sites in Africa, with only one-fifth of participants having a record of this being documented at their HIV clinics.

In our study we included questions on when the process of disclosure started, age when HIV status was fully disclosed, who disclosed their HIV status, and non-family members to whom they had disclosed their status to. While age of disclosure was well documented within routine medical records, less than half of participants had information on disclosure practices documented in their routine medical records. Given that disclosure is known to be an important component of ART adherence and retention in care (113,205–207), as well as being a key prerequisite to transition, it is important for the disclosure process to be better documented by HIV care providers.

Inclusion of transition-related variables within local administrative and national HIV program databases would be valuable for conducting transition assessments, as it captures data from individuals who might otherwise not respond to surveys or participate in research, makes data easily accessible with limited additional costs, and facilitates linkage with other databases (192). Despite consistent recording of the pre-transition discussions, less than half of records across all the sites included any information on the transition and post-transition experience (e.g., individual perceptions of preparedness for the process, satisfaction with new clinics and providers). In our interviews, participants were forthcoming with this information once they were asked to do so.

Also of concern is that the interview responses showed that even though >80% felt prepared or somewhat prepared for transition, only two-thirds described their transition as easy or being satisfied with the post-transfer clinic and staff. Following up with ALYH after transition is still part of the overall process, and soliciting their feedback could be valuable to informing future improvements (188). Given that this is a critical phase of their lives, discussions around how AYLH are feeling are important to encourage them and understand barriers they are facing to continued care, and to guide the scope and depth of pre-transition discussions to make the process easier. Knowing whether AYLH are satisfied and comfortable with their new clinic and providers could assist with developing retention strategies to avoid clinic drop-out and improve outcomes, but very little data exist within routine medical records to fully describe this.

Central to assessing and comparing transition outcomes is knowing how to optimally measure this process and implementing data collection across different settings. There is growing recognition of the

need for data harmonization strategies. However, global programs currently set up to harness and improve large datasets have not focused on variables to capture transition preparation and implementation, and post-transition outcomes. Also, there are no mechanisms within current global surveillance data systems to distinguish what proportion of young people living with HIV have transitioned from paediatric to adult HIV care and when this is occurring (208). Unless the often-fragile healthcare systems delivering HIV care adapt to capture these outcomes, their data will be lost. If this population cannot be counted and reported, it may become less urgent for policy makers to support interventions to improve adolescent HIV outcomes. A model for gathering transition-related data in LMICs would also further global efforts to track adolescents moving out of paediatric care and promote age disaggregation in HIV surveillance (15).

Our study is especially relevant as it was conducted in public sector ART clinics in South Africa, Malawi, and Thailand, and most adolescents living with HIV reside in sub-Saharan Africa and receive care in similar healthcare settings. Furthermore, participants enrolled in our study received only routine services that were reflective of the local standard of care for adolescent ART patients. Evaluating availability of information both within the paper-based medical records as well as electronic-records is another study strength. Nonetheless, our results should be interpreted considering several limitations. The generalizability of our findings is limited as the pilot was conducted at only four sites, using a cross-sectional design with convenience sampling among mostly stable patients on ART. We were not able to conduct interviews in the Asian sites, and so our characterization and assessment of the utility of the questionnaires for this population were incomplete. The data obtained from interviews were based on self-report and may be subject to recall and desirability bias. Accuracy of self-reported medical history data was not confirmed with medical records.

7.7 Conclusion

We developed measures of transition readiness, processes, and outcomes that can be valuable resources across varying geographic areas and care delivery models. There is a need to improve the recording of transition-related variables within routine records and national HIV care databases to optimally measure transition preparation, implementation, and outcomes.

Chapter 8: Discussion

8.1 Overview of key findings

This thesis offers a comprehensive examination of the characteristics and outcomes of AYLH throughout the adolescent transition cascade in southern Africa. By utilizing routinely collected cohort data, it identifies the demographic and clinical characteristics of over 25,000 adolescents accessing HIV care, providing insights that could improve the classification of mode of HIV acquisition in data sets and the continuum of care. It evaluates the impact of aging into adulthood on continuity in care and virologic suppression within routine care settings, where physical transfer of healthcare to a different provider or facility may not be part of the transition process. Furthermore, it assesses the impact of a differentiated model of care for AYLH in southern Africa.

Recognizing the lack of standardized measurement tools for assessing transition-related processes and outcomes in resource-limited settings, the thesis contributes by developing a widely applicable and accessible data collection and management platform. This platform aims to facilitate the collection and measurement of transition processes and outcomes in routine adolescent HIV care, addressing a critical gap in current research and practice.

8.2 The importance of mode of HIV acquisition

AYLH have differing clinical and psychosocial needs which may be impacted by their mode of HIV acquisition. Accurate classification of HIV acquisition mode is important for targeting services effectively, tailoring interventions, and describing their epidemiology. Perinatally acquired HIV, typically managed in paediatric services, is associated with dependence on caregivers, multiple comorbid conditions including chronic lung disease, stunting, and physical and neurocognitive deficits which may be due to chronic exposure to HIV from an age at which the immune system is immature and extensive treatment history. By the time of transition to adulthood, AYLH with vertically acquired HIV would have been in care for longer and are likely to have switched ART due to drug resistance or changing guidelines (4,5,209–211). On the other hand, those with non-perinatally acquired HIV, often seen in adult HIV services from diagnosis, would have been on treatment for a shorter period (85,116,212) and may not experience a transition in care provision. They may exhibit normal physical and cognitive development.

Transition processes vary for these two groups due to differences in entry points into care, social support availability, and familiarity with the healthcare system (116,212). Recognizing and addressing differences in care needs and experiences among AYLH based on HIV acquisition mode is critical for optimizing HIV care and treatment outcomes. However, in resource-limited settings, distinguishing HIV acquisition modes is challenging due to limited documentation within routine medical records

(15,213). Our study to determine algorithmic approaches to infer mode of HIV acquisition found that only 20% of routine health records documented mode of acquisition. Therefore, we developed a low-cost method using data, such as height and sex, routinely available within medical records to infer HIV acquisition mode among AYLH. Perinatal HIV acquisition was associated with younger age at presentation, while including height and being female improved the predictive accuracy of the model compared to using age alone.

Though the natural progression of HIV varies among individuals (214), it generally follows a well-defined trajectory in the absence of ART. Historically, few children with perinatally acquired HIV were expected to survive beyond the age of five years in the absence of ART (215). Studies have shown that slow progressors who do survive constitute a distinct subset, effectively controlling inflammation and immune activation despite ongoing viral replication (216). The timing of HIV acquisition influences the anti-HIV immune response and disease trajectory, with children acquiring HIV postnatally through breast feeding more likely to be slow progressors (217,218).

We found that while most children with perinatally acquired HIV enter HIV care before the age of 10 years, approximately a third access HIV care during early adolescence. This is in keeping with the finding that up to 30% of untreated children with perinatally acquired HIV do survive to adolescence in the absence of ART, reported from studies including a population-based survey conducted in five countries across southern Africa (219), other pooled cohort analyses (120,132,220–225), and a risk algorithm classifying mode of HIV acquisition based on age of HIV diagnosis or entry into care, sexual history, and maternal HIV status (219). Furthermore, a logic decision-making algorithm including questions about the adolescent's sexual, family, clinical, and ART initiation history showed that an age cut-off at 14 and 15 years had the highest positive predictive value in determining non-perinatal HIV acquisition, compared to an age cut off of 10, 11, or 12 years (218). Missed opportunities for earlier diagnosis and treatment for these children may be due to the lack of scaled early infant diagnosis services and limited availability of testing strategies such as index testing of family members when these adolescents were infants (227,228).

Based on our finding from the analysis to infer mode of HIV acquisition, we assumed perinatal transmission for AYLH entering care aged less than 13 years in our analysis describing the characteristics and outcomes of adolescents living with perinatally acquired HIV within Southern Africa. This was based on observations of gender proportions and growth patterns consistent with perinatal HIV acquisition. There were no differences in the proportion of males and females between those entering care before the age of 10 years and those aged 10-13 years. Had those presenting for care aged 10-13 years acquired HIV non-perinatally, a higher proportion of females would be anticipated, based on previous research showing the heightened risk of HIV acquisition among young girls explained by earlier puberty and sexual debut, greater likelihood of older sexual partners and additional sociological issues such as gender-power imbalances. In addition, females are more likely to seek

healthcare services for sexual and reproductive health and receive HIV testing (38,138). Also, both groups showed poor linear growth, one of the hallmarks for longstanding HIV in childhood due to perinatal HIV acquisition (5,133,140).

In the same analysis, nearly half of the AYLH presented for care severely immunosuppressed, with no differences observed between those who presented as children and those presenting in early adolescence. This supports our assumption that those presenting in early adolescence before the age of 13 years are likely to be slow progressors rather than have acquired HIV non-perinatally. Nearly half presented for care stunted and wasted, in keeping with other studies showing that adolescents with vertically acquired HIV frequently present with physical and cognitive developmental challenges, including stunting, pubertal delay, and neurocognitive deficits (4,134).

It is evident that a subset of children with perinatally acquired HIV can sustain high immunologic function and low viral loads over protracted periods without necessitating ART or experiencing notable HIV-related symptoms. Using a logic decision-making algorithm, we validated age cut-off allocations, recommending an age cut-off of 13 years for vertical HIV acquisition. Therefore, analyses utilizing age cut-offs of less than 10 years to determine mode of HIV acquisition when undocumented (229) may misclassify up to a third of adolescents with perinatally acquired HIV. This misclassification could lead to suboptimal management, considering the likelihood of complex treatment regimens requiring specialist care, along with advanced psychosocial support needs as these adolescents become sexually active and require sexual and reproductive health services.

8.3 Characteristics of AYLH across key stages

Since 2000, WHO guidelines for HIV treatment have evolved to reflect advancements in knowledge and antiretroviral medication availability. Initially, emphasis was placed on administering ART to individuals with advanced HIV disease, defined firstly by a CD4 count below 200 cells/mm³ or a WHO stage 3 or 4 diagnosis of AIDS. However, evidence demonstrating improved clinical outcomes, reduced mortality rates, and decreased transmission risks with earlier treatment initiation led to expansions of recommended thresholds. The CD4 cell count threshold was raised to a CD4 count of ≤ 350 cells/mm³ in 2006 and ≤ 500 cells/mm³ in 2010 (18,19,141). A pivotal moment occurred in 2015 when WHO introduced guidelines advocating for ART initiation for all individuals living with HIV, regardless of their CD4 count - a strategy known as "treat all" or "universal treatment" (202). This paradigm shift aimed to provide immediate treatment upon diagnosis, improving individual health outcomes and curbing transmission rates.

Recommended first-line regimens for children living with HIV have also evolved over time, reflecting emerging evidence, drug availability, and considerations of tolerability, adherence, and long-term outcomes. Initially, regimens included drugs such as zidovudine, stavudine, nevirapine, and efavirenz

(141). However, stavudine-related toxicity concerns led to its replacement with tenofovir and abacavir in 2010 (19). A significant shift occurred in 2013 with the recommendation of boosted protease inhibitors (PIs) for children previously exposed to non-nucleoside reverse transcriptase inhibitors due to observed better virologic outcomes (202). By 2018, dolutegravir-based regimens were endorsed as the preferred first-line treatment for children, marking a notable advancement in paediatric HIV care. However, this drug was only made available to younger children recently, and rollout across age groups slowed down during the COVID-19 epidemic. Additionally, long-acting injectable ART as an alternative to daily oral therapy for certain individuals was introduced in 2020 but is not yet available in Africa.

These changes highlight the dynamic nature of paediatric HIV treatment guidelines, driven by ongoing research and efforts to optimize therapy for children living with HIV. These changes also reflect the journey of HIV management for AYLH in the earlier stages of ART treatment programs when initiation criteria were more stringent and paediatric antiretroviral options were less than optimal

In our analyses describing the characteristics of over 25,000 adolescents living with HIV across southern Africa, who initiated ART at an average of 9 years of age, we demonstrate that the majority of AYLH currently transitioning to adulthood entered HIV care and initiated ART between 2005 and 2011, before the “treat all” era. Consequently, many AYLH endured prolonged exposure to untreated HIV, resulting in persistent viral replication, chronic inflammation, and subsequent complications stemming from either HIV or the adverse effects of less optimal antiretroviral regimens.

The vast majority of AYLH initiated ART at a median age of 9 years, with this age ranging between 6 to 11 years. Nearly two-thirds initiated ART at an advanced clinical disease stage, severely immunosuppressed, stunted, and wasted, which is unsurprising due to the restrictive ART initiation criteria at the time when they would have started ART, requiring immunologic and clinical deterioration before ART start. Our findings are in keeping with those from a population-based survey conducted in five countries within southern Africa as well as other research, showing severe immunodeficiency, underweight, and stunting among this population at ART start (30,219,229). The ART coverage observed in our analysis (>90%) is higher than the current reported ART coverage rates of 64% (149). This discrepancy is likely due to the cohorts in our study being mainly ART cohorts which would preferentially include adolescents who had been diagnosed and started ART, compared to the population level coverage which is much lower likely due to limited scale of early infant diagnosis and HIV testing among children then, with children often only presenting to care and being diagnosed when they have progressed to severe illness.

Adolescence presents an opportunity for catch-up growth to mitigate the effects of early life growth faltering (230). While height-for-age scores typically improved during adolescence, our analysis revealed a pattern of poor linear growth with no significant catch up observed over several years of

follow-up. This corroborates findings from previous studies indicating growth faltering among children with HIV in early childhood (142,143). Height growth was severely impaired among AYLH with perinatal HIV acquisition, with those in upper-middle-income countries experiencing the most improvements in linear growth. This suggests that AYLH in LMICs with perinatally acquired HIV may never reach their full height potential (144,145,229,231). Growth faltering, including impaired childhood linear growth and pubertal delay, is a common co-morbidity among adolescents with perinatally acquired HIV (232). HIV is known to disrupt the adolescent growth spurt, delaying its onset and reducing linear growth velocity (233). Despite receiving ART, these children remain at risk of multisystem comorbidities that may further impair growth and overall health. This could result in self-stigma as one transitions to adulthood. Addressing these challenges requires comprehensive care strategies that encompass both medical treatment and psychosocial support to optimize health outcomes for AYLH as they transition to adulthood. The benefit of universal ART on these characteristics will be realised in the next decade, when children with perinatally acquired HIV who initiated ART in infancy reach adolescence and beyond.

8.4 Retention in care as AYLH transition to adulthood

Retention in HIV care is essential for AYLH, ensuring they receive continuous monitoring and support from healthcare providers. It plays a critical role in managing HIV effectively, facilitates timely adjustments to treatment regimens, optimizing health outcomes and reducing transmission risks within communities. When AYLH remain engaged in care, they are more likely to adhere to ART, achieve viral suppression, and prevent the progression of HIV-related diseases.

Moreover, retention in care addresses broader psychosocial needs, providing ongoing support to AYLH to manage emotional, social, and practical challenges associated with living with HIV. It facilitates access to supportive services such as mental health counselling, substance abuse treatment, and assistance with medication adherence. Therefore, addressing and reducing loss to follow-up is crucial for successful HIV management and control.

Our analysis on the outcomes of adolescents living with HIV across southern Africa revealed substantial rates of disengagement from care among AYLH, with less than 60% retained in care by the end of follow-up. Mortality was low, at 3% however, this could be an underestimate as rates of disengagement from care included all with no outcome ascertained. These findings are consistent with previous literature noting that retention in care is problematic in AYLH (84,234).

Slow progressors exhibit a concerning trend, as they are twice as likely to be lost to care and approximately five times more likely to die compared to those who initiate care before adolescence. These findings align with those from a multi-regional analysis (30). Despite their slower decline in CD4 cell count in our study, slow progressors still have compromised immune systems, leaving them

vulnerable to opportunistic infections and other HIV-related complications. Prolonged periods without treatment allow HIV to replicate unchecked, causing further damage to the immune system and escalating the risk of disease progression and mortality. Timely diagnosis, prompt initiation of treatment, and comprehensive healthcare management are imperative for improving outcomes and mitigating mortality risk in slow progressors with HIV.

Transitioning from adolescence to adulthood presents unique challenges for AYLH, particularly in regions like southern Africa, where physical transfer to adult HIV clinics may not occur (104). Our findings showed a decline in retention in care after reaching assumed transition age thresholds, highlighting the need for targeted interventions as AYLH age. Our results align with studies from other cohorts indicating sub-optimal engagement in care as adolescents transition to adulthood. Studies from South Africa and Zimbabwe examining outcomes as children age to young adulthood without transferring to different clinics revealed an increased risk of disengaging from care as adolescents moved from young (10-14 years) to older adolescence (15-19 years), and further into young adulthood (20-24 years). As with our study, consistent prior engagement in HIV care emerged as the strongest predictor of retention in care after reaching ages where individuals assume greater responsibilities (84,165). AYLH with previous disengagements from care were more likely to not be retained in care as they grew older. This highlights the importance of interventions to support continuity and consistency of HIV care throughout the transition to adulthood.

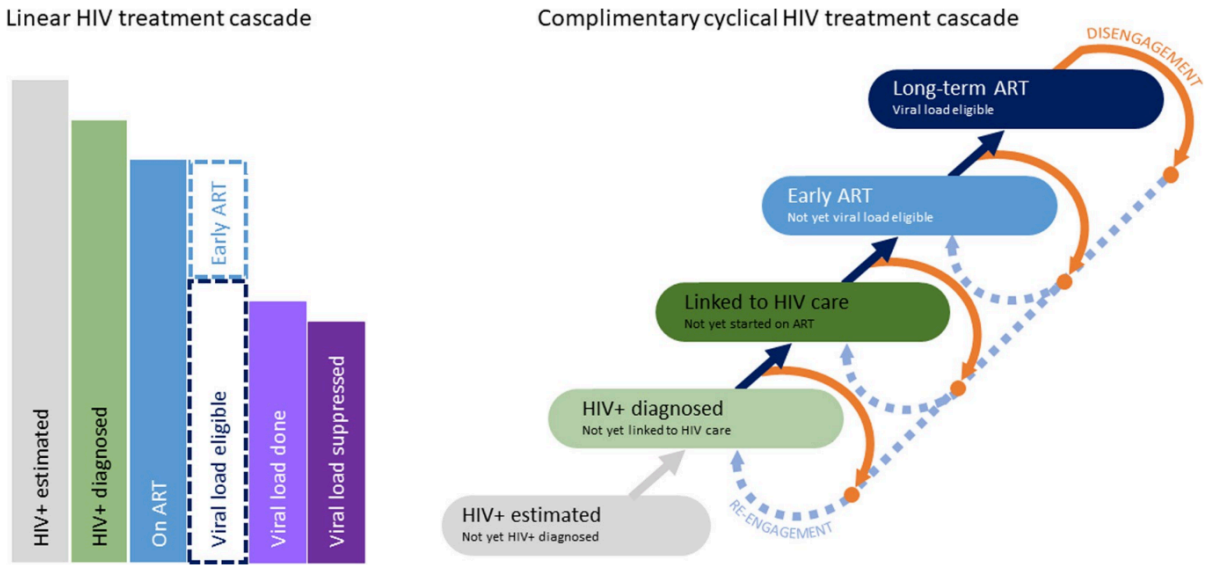
One reason for this could be that adolescents engaged in HIV care are more likely to have established healthcare habits and routines and familiar with the healthcare system, contributing to their continued engagement in care as they transition to adulthood. Trusting relationships with healthcare providers and support staff fostered through prior engagement are pivotal for promoting retention in care. This trust motivates adolescents to continue seeking care, knowing they have a supportive network to rely on.

Moreover, engagement in care equips AYLH with the knowledge and skills needed to manage their HIV condition, enhancing their health literacy and self-efficacy. This empowerment enables adolescents to take ownership of their health and navigate the challenges of transitioning to adulthood with confidence. Recognizing the importance of continuity and consistency in healthcare utilization, healthcare providers and policymakers can develop targeted interventions and support services to promote retention in care among adolescents living with HIV as they transition to adulthood. These interventions should address not only AYLH transitioning care but also those still in younger age groups to limit rates of disengagement prior to the transition to adulthood.

The concept of a cyclical continuum of engagement and disengagement in care, with individuals re-engaging in care after periods of disengagement, is gaining recognition (Figure 8.1) (235,236). This differs from the previously described linear, unidirectional cascade, and may be an especially important approach for assessing adolescent transition which may well include temporary periods of

disengagement. Further research using linked health information systems is needed to explore how this cyclical cascade of care applies to AYLH transitioning to adulthood, from period of "down-referrals when transferred out of specialist paediatric care to primary health care facilities to adult care services.

Figure 8.1 A comparison between the linear and cyclical HIV treatment cascades



ART - antiretroviral therapy

Adapted from: The cyclical cascade of HIV care: Temporal care engagement trends within a population-wide cohort (236).

8.5 Virologic outcomes as AYLH transition to adulthood

The integration of HIV viral load testing into public health facilities across southern Africa has been driven by technological advancements, policy changes, and efforts to enhance HIV treatment outcomes through enhanced monitoring and management of patients on ART. Initially limited to research settings due to complexity and cost, viral load testing gained prominence following the WHO's 2013 recommendation, highlighting its superiority over CD4 cell count monitoring in guiding ART management (202). This prompted countries in southern Africa to prioritize its integration into national HIV programs, albeit with varied timelines influenced by resources, capacity, policy frameworks, and funding availability.

South Africa implemented routine viral load monitoring as part of the HIV program from inception, strengthening data management systems and tracking viral load results. Therefore, virologic outcomes across our analyses focused solely on South African AYLH. Our analysis describing outcomes of adolescents living with HIV found that During adolescence, viral load completion rates ranged from 68% to 82%, with older adolescents exhibiting higher completion rates. However, viral load suppression

rates were generally low across all ages, with older adolescents experiencing poorer suppression compared to younger ones. Eleven-year-olds had the highest suppression rates (77%), which gradually declined 66% among 16-year-olds and 67% among 18-year-olds.

These findings align with a regional survey across five southern African countries, indicating suboptimal viral suppression rates among AYLH, with better outcomes experienced among younger adolescents (219). Similarly, AYLH were significantly less likely to achieve viral suppression compared to adults across nine African countries, highlighting the heightened risk of viral rebound (38). These findings may be exacerbated by the use of non-nucleoside reverse transcriptase inhibitors, known for lower barrier to resistance and higher rates of virologic failure. Further analysis among the cohort of AYLH that has been transitioned to dolutegravir-based regimens will indicate if viral suppression outcomes have improved among this population.

The analysis comparing the HIV cascade before and after pre-defined transition age thresholds found that after reaching assumed transition age thresholds, virologic suppression rates remained low, mirroring pre-transition rates. Notably, poor treatment adherence in paediatric care often predicts adherence in adult care, with virologic suppression rates in adult clinics not differing substantially from those in the paediatric setting (53,171). Maintaining viral suppression is crucial as AYLH age and face increased risks associated with sexual activity and pregnancy.

8.6 Enhancing healthcare transition for AYLH: differentiated models of care

DSD models based on individual needs and preferences offer the opportunity to address the retention and virologic suppression gaps described in chapters 4 and 6. DSD improves the client experience by adapting HIV service provision according to the heterogenous needs, preferences and expectations of different groups of people living with HIV, while facilitating service scale-up by reducing the burden on health systems and increasing efficiency.

In addition to the rapidly evolving changes that characterise the adolescent period, including rapid physical, psychological and emotional changes, AYLH face particular challenges in accessing and adhering to HIV treatment. This impacts how adolescents view their health, make decisions, perceive risk and interact with health and related services (237). However, delivering DSD to adolescents and youth can be challenging as they are a heterogeneous group, with different expectations and experiences.

In parallel with DSD models, adolescent- and youth-friendly services have the potential to facilitate smoother transitions between as AYLH transition to adulthood. By providing age-appropriate services which are made further patient-centred through DSD, these models can encourage adolescents to actively participate in their healthcare and adhere to treatment regimens. Structuring the models in such

a way that transitions occur in groups rather than as individuals ensures continuity and uninterrupted access to healthcare services as they transition to adulthood.

We showed that a differentiated model of care dedicated for AYLH and integrating psychosocial support, sexual and reproductive health services, and peer support groups showed remarkably higher rates of transition to adult HIV care, lower rates of attrition, and higher completion of viral load assessments and suppression rates compared to those accessing routine care. This is in keeping with other studies. In South Africa, retention and viral suppression among adolescents with perinatally acquired HIV were better in a Saturday "Teen Clinic" vs. standard clinic and lower LTFU among adolescents initiating ART at clinics with sexual and reproductive health services and adolescent support groups (36,153). Of note, Teen Clinic studies have involved substantial extra resources including having clinics on Saturdays and providing food and other supportive activities. This may not be scalable. The DSD in our analysis was implemented without the majority of the extra resources often made available in dedicated adolescent clinics in research studies.

Peer support strategies are critical to improve health services for AYLH (238). Differentiated models of care have a unique opportunity to foster peer support and need to consider development stage, cognitive abilities, emotional health, and overall capacity for independent self-care management. In our DSD model, the majority entered HIV care and initiated ART in late adolescence and early adulthood. Based on our algorithm prediction that those presenting at older ages more likely have non-perinatally-acquired HIV, this could indicate the difference in the preference of accessing care in this model for those with more recently acquired HIV compared to those who likely acquired HIV perinatally. A growing body of evidence suggests improved retention and viral load outcomes among adolescents in differentiated models of care (158,159,162,163).

Youth clubs, the DSD model evaluated in our analysis, provided an effective approach for the transition from youth to adult care as they provide an opportunity to organize group transfers to the adult clubs offered by the adult clinic. These group transfers provide a supportive approach preferred by young people, potentially contributing to the observed success in the transition process. Organisation of group transfers prepares youth for DSD in adult care as well.

Our study provides valuable insights into the effectiveness of youth clubs as part of routine healthcare services for youth living with HIV. The positive outcomes observed in youth clubs, such as lower attrition rates and higher viral load completion, suggest the potential benefits of differentiated care models. In addition, the study shows the importance of differentiated care models like youth clubs in supporting the transition from youth to adult care and for providing integrated sexual and reproductive health services. The tracking of patient outcomes beyond the primary facility provides a more nuanced understanding of care patterns. Youth clubs appear to offer an effective option for long-term chronic care for young people living with HIV in this setting.

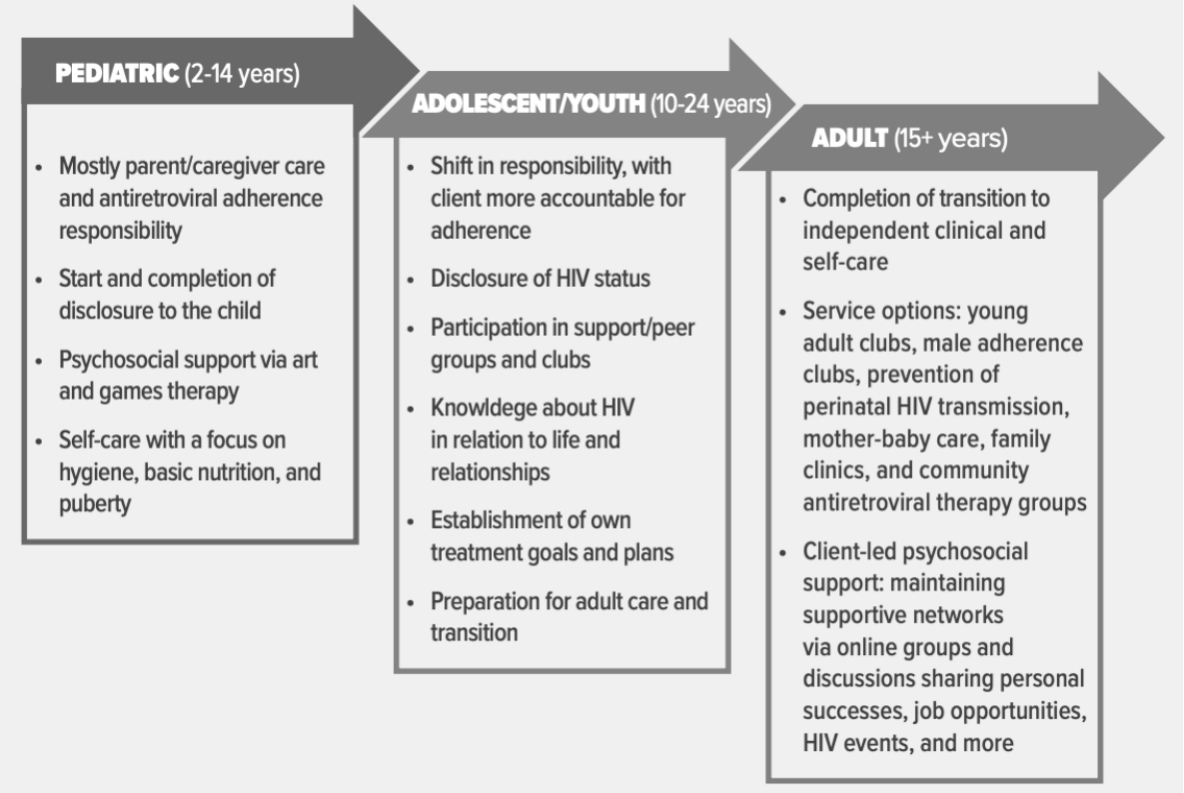
8.7 Enhancing measurement of transition processes and outcomes in adolescent HIV care

The measurement of transition processes and outcomes in adolescent HIV care is crucial for optimizing healthcare delivery, improving continuity of care, enhancing health outcomes, empowering adolescents, and informing policy and practice (169). By tracking this process, healthcare systems can better support AYLH as they navigate the transition and tailor interventions and services to meet their unique needs, ensuring patient-centred and effective care throughout this period. By identifying gaps and challenges in the continuum of care, healthcare systems can implement strategies that promote seamless transitions, maintain treatment adherence, and prevent disease progression. By tracking transition outcomes such as retention in care, viral suppression, and adherence to treatment, healthcare providers can identify areas for improvement and implement targeted interventions to enhance health outcomes among AYLH. Involving AYLH in discussions about their transition plan promotes their self-efficacy and autonomy, empowering them to take an active role in managing their HIV care. Additionally, data on transition processes and outcomes inform the development of evidence-based policies and guidelines for adolescent HIV care, providing policymakers with valuable insights into the effectiveness of existing transition programs and helping them to allocate resources effectively.

The analyses in chapters 4 to 6 of this thesis were based on existing routinely collected data and are all limited by the lack of routine collection of variables to track the transition process and key related health exposures and outcomes. For example, in chapter 4 we had to infer likely mode of HIV acquisition and in chapter 5 and 6 use age thresholds or place of clinic attendance to infer when transition occurred. For the measurement of transition processes and outcomes to be truly effective, it must comprehensively cover all the relevant components of the HIV transition process across the continuum of paediatric, adolescent, and adult HIV care, as illustrated in Table 7.1 and Figure 8.2.

This entails capturing key milestones and aspects of care at each stage of the transition journey, from initial diagnosis and entry into paediatric HIV care, through the adolescent years, and into adulthood. It should include measures related to socio-demographic characteristics, medication responsibilities, disclosure, healthcare utilization, treatment adherence, substance and alcohol use, smoking, sexual history, laboratory findings, hospitalization, self-harm, mental health diagnosis, referral or treatment, transfers, transition experiences, and clinical outcomes. Additionally, the measurement should consider contextual factors such as psychosocial support, socioeconomic status, access to healthcare services, and cultural considerations that may influence the transition experience.

Figure 8.2 Components of HIV care transition process throughout the continuum of paediatric, adolescent, and adult HIV care



Adapted from the Adolescent and youth transition of care toolkit. Available here: https://www.newhorizonshiv.com/assets/pdf/new_horizons_adolecent_toolkit_interactive.pdf

In addition, the needs of each AYLH need to be individualized, and the evolving HIV service delivery models that AYLH will experience should be captured. The multi-disciplinary teams involved in the planning and implementation during the transition process need to have access to relevant information throughout the transition process (99,239). Several factors and determinants of health outcomes before, during, or following transition, and tracking of progress throughout the transition phase need to be captured.

We developed measures of transition readiness, processes, and outcome across diverse geographic, economic, and social landscapes. Scales evaluating transition readiness (92) and toolkits with transition checklists that summarize transition tasks (240) have been developed. While this is commendable, unfortunately, without proper documentation of the required variables within medical records, measurement of transition processes and outcomes in adolescent HIV care will remain suboptimal.

Dedicated cohorts within wealthy countries (e.g. UK, Canada, USA) enable the measurement and tracking of key variables over prolonged periods of time. However, within southern Africa, this is hindered by reliance on resource-intensive tracing or record reviews, often conducted as research.

Within routine care records, we identified lack of documentation of essential variables crucial in the measurement of transition processes and outcomes as well as factors known to have an impact on the treatment outcomes, such as mental health diagnosis and treatment, episodes of self-harm, smoking, alcohol intake, use of recreational drugs, and sexual activity in routine health records (34,196–200). The poor recording of sexual health information (e.g., sexual activity, consistency of condom use, biological children), limits the feasibility of integrating HIV care with sexual and reproductive health services, as emphasized by the WHO (201–203). Furthermore, disclosure information, an important component of ART adherence and retention in care (113,205–207), is often missing., along with transition-related experiences (e.g., individual perceptions of preparedness for the process, satisfaction with new clinics and providers) which may be essential determinants of continuity in care before, during, or after transition.

While the importance of collecting this information is recognized, requiring healthcare providers to document these variables meticulously and consistently within paper-based medical records may not be achievable in southern Africa due to high volumes of data collection, overworked healthcare providers, and patient movement.

8.8 Limitations

The analyses presented in this thesis primarily relied on routinely collected healthcare data. While invaluable for real-world insights, routine healthcare data present several methodological limitations that must be acknowledged. Routine health data are collected for clinical monitoring and programmatic reporting purposes rather than research. Nonetheless, they offer significant strengths for observational epidemiology using secondary data analysis: large sample sizes, repeated measures over time, and coverage across multiple populations and geographic and programmatic contexts.

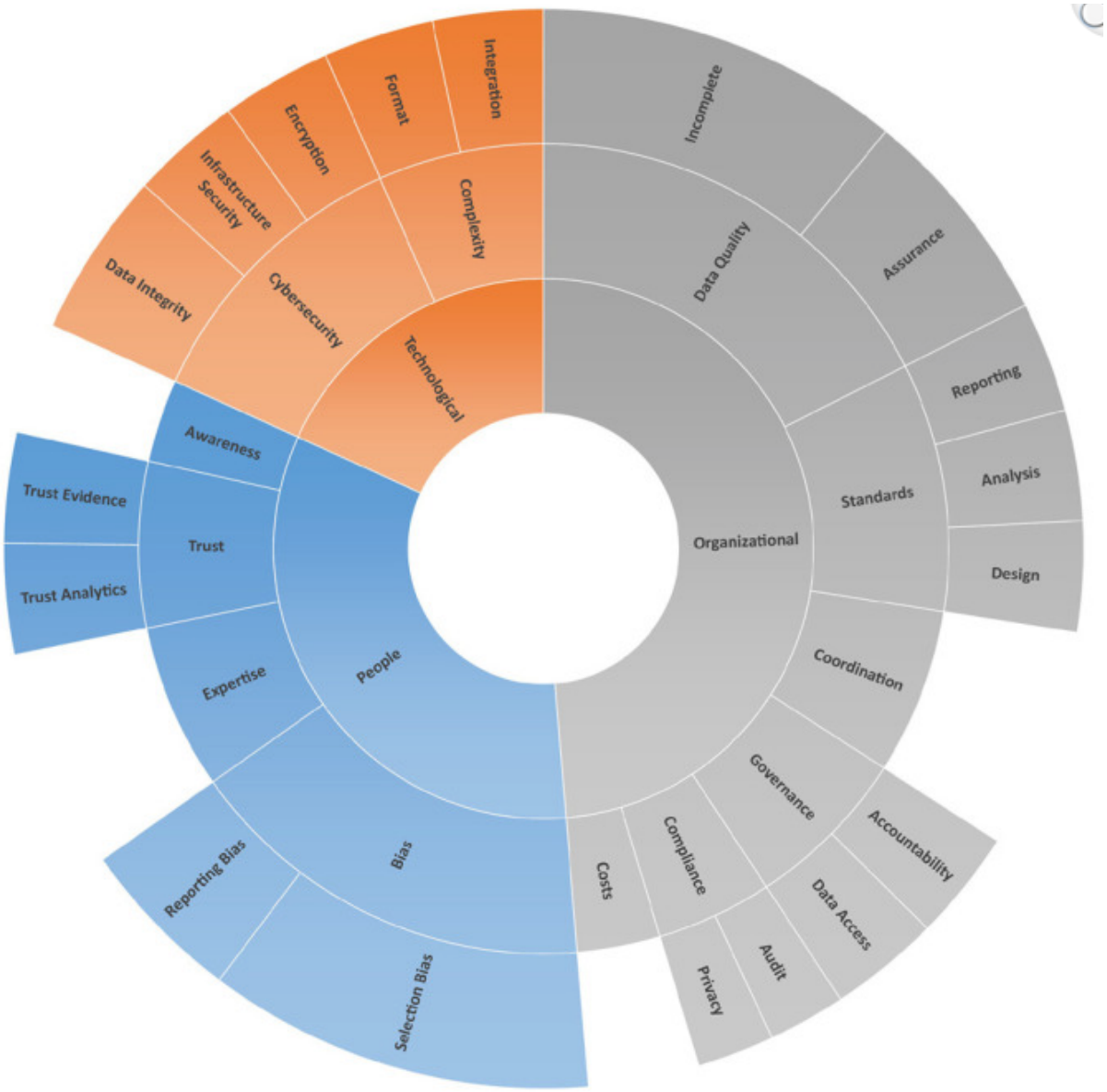
Several epidemiological concerns arise when using routine data. Firstly, data quality can be inconsistent due to variability in data collection practices and clinical documentation standards across sites and over time. Key variables, such as HIV viral load, CD4 cell count, WHO staging, or ART regimens, may be incomplete, inaccurate, or missing entirely, and certain data (e.g., adherence, disclosure, mental health, and social support) are often not captured. These issues can introduce measurement error and information bias, limiting the accuracy and interpretability of the findings (241,242).

Second, outcome ascertainment is a particular challenge. Mortality, transfers, and LTFU may be misclassified due to incomplete documentation or weak linkage with vital registration systems. In addition, the observational nature of routine data analyses increases susceptibility to confounding, selection bias, and unmeasured heterogeneity. Non-random error can be introduced through factors like data entry mistakes and misclassification of variables. Without randomization, residual confounding

remains a persistent limitation despite statistical adjustment. Lastly, routine data may lack standardization, harmonization, interoperability and systematic data quality checks (241,242).

These, and additional, data limitations shown in Figure 8.3 (241), can bias estimates and limit the generalizability of findings. However, despite these challenges, routine data offer invaluable insights into real-world program performance and patient outcomes at scale.

Figure 8.3 Challenges with real-world data across the three categories: Organisational, Technological and People



** Each category consists of various subcategories, with the size of the respective subcategories proportional to the relevance or scope; the larger the field, the more important the topic is.*
Adapted from: The real-world data challenges radar: A review on the challenges and risks regarding the use of real-world data (241).

In these analyses, critical data elements were missing, which may have biased the results. The mode of HIV acquisition was assumed based on the age of entry into HIV care and limited to perinatal and non-perinatal, with missing data on more detail about modes of acquisition. Our predictive models of mode of HIV acquisition were also limited by missing data. Critical measures such as CD4 count, HIV viral load, WHO clinical staging, and anthropometric measures were also missing, particularly among older adolescents. Laboratory testing and anthropometric evaluations could have been obtained more frequently among those at higher risk of poor outcomes. Viral load outcomes were assessed only in cohorts offering routine (annual) viral load measurements. Mortality may have been underestimated due to limited ascertainment in those lost to follow-up. We had no additional data from tracing or death registry linkage on outcomes of those "lost to follow-up" which included all patients with an unknown outcome, including under-ascertained mortality, which might affect the accuracy of the findings.

This analysis was conducted from 2015 to 2019, at the start of the "Treat All" era hence the results may not be generalizable to the current treatment context where “treat all” has been widely established. In addition, dolutegravir was not yet available during the period, limiting our analysis on viral suppression rates.

The interpretation of the study comparing the cascade of care before and after transition to adulthood was limited by the use of age as a proxy for transition to autonomy in clinical care, without knowing when individuals actually became responsible for their own health management. The study did not include a comparison with those transferred out of care for other reasons such as due to relocations, silently transferred, or lost to follow-up before each respective age threshold. Also, the data were obtained from facilities participating in the IeDEA collaboration, affecting generalizability to all adolescents within the region. The definition of "retention" defined as pragmatic but relatively crude, potentially misclassifying patients with temporary gaps in care. Despite these limitations, the analysis using routinely collected longitudinal data provides insights into engagement in care and viral suppression before and after transition, characterizing youth care experiences as a continuum and showing how care-related behaviours earlier in life impact those later in life.

8.9 Beyond adolescent transition

There is a need for a paradigm shift in understanding transition for AYLH. Historically, transition research has concentrated on growth, continuity of care, viral suppression and mortality outcomes, often neglecting the broader spectrum of general health outcomes. Transition to adulthood or adult HIV care is not a singular event but a continuous, cyclical process that involves multiple life transitions, each with its own healthcare implications. Viewing adolescent transition as a one-time event oversimplifies the reality; adolescents, regardless of their HIV status, continuously undergo transitions that impact

their health and well-being. For instance, an AYLH might transition to adult HIV care through pregnancy, antenatal care, postpartum care and then routine HIV care, while another might transition through transferring from a paediatric to an adult HIV care facility. Also, transition is not a uniquely adolescent thing. People may also transition at different stages across the life course e.g., for education and employment opportunities or when they experience traumatic life events or a comorbidity. Each of these represents healthcare transition and might even include requiring access to services that are not typically integrated within HIV care and provided by different healthcare providers or facilities.

To adequately capture and track outcomes across all transitions without overburdening the patient or the health facility to explicitly record that a transition has occurred there is a need for routine health records to be strengthened. Electronic medical records could play a key role in tracking individuals over time and across the various facilities or community-based programs they may utilize. The digitization of health data and the implementation of linked electronic medical records would greatly facilitate fully capturing these multiple transition episodes. Linked electronic medical records offer numerous advantages, including real-time access to patient information such as laboratory investigations during clinical consultations which can improve patient care, improved continuity of care across different health services, ability to incorporate other health episodes and their outcomes like pregnancy and comorbidities, ability to link parents and children, streamlined administrative tasks, population-level case-based surveillance, and enhanced reporting and data analytics capabilities. The WHO recommends strengthening patient-level monitoring systems and progressively transitioning from paper-based to electronic patient information systems (243) which improves quality of care and supports data linkages.

The PHDC serves as a prototype for health data systems that are digitized, integrated, and longitudinal in nature. It brings together data from various points of care, across different facilities, levels of service, and health domains, into a unified platform. This enables comprehensive tracking of individual and population health data over the life course, supporting continuity of care, more accurate health surveillance, and data-driven decision-making. The PHDC demonstrates how health information systems can move beyond fragmented, siloed data to a cohesive structure that improves not only service delivery but also monitoring and health outcomes.

For AYLH that have been engaged in HIV care for extended periods, access to historical health records enables comprehensive and appropriate management as healthcare providers can quickly review the various healthcare transitions that the AYLH has gone through. Implementing a cyclical cascade framework to support program management requires robust data collection at the routine, programmatic level. Individual-level data that captures the entire transition cycle is essential for designing and targeting interventions that minimize care interruptions and facilitate re-engagement in care. These various transitions necessitate comprehensive documentation and tracing within healthcare records to ensure continuity of care.

8.10 Conclusion

This thesis uses routinely collected health data to characterise AYLH in the periods before and after transitioning to adulthood, including developing an approach to improve determination of likely mode of HIV acquisition, ascertaining determinants that influence continuum of care during these periods and comparing engagement in care and virologic outcomes among between AYLH accessing care through a DSD model to those in routine care. This thesis also developed data tables and tools to facilitate capturing of transition-related processes and outcomes of AYLH. Rather than future research continuing to focus solely on research related to transitioning to adult care for AYLH, it is time to invest in strengthening routine electronic monitoring systems. Data systems that monitor transitions over the life course and across different settings are the only practical means of ensuring high-quality clinical care and effective programmatic responses at scale. It is time for research cohorts to strengthen collection of routine data to make it available to health workers to improve service delivery instead of separately collecting routine data. Leveraging individual patient data from multiple systems can create a comprehensive record of an individual's HIV care as they go through various transitions, which offer the opportunity for enhancement with research data in consented cohorts to answer specific research questions. Such platforms will facilitate both research and improved service delivery not only for adolescents and youth with HIV, but across health care domains and throughout the life course.

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Supplementary Information

Supplementary Table 6.1: Outcomes of adolescents and young adults living with HIV at transition age threshold 15 years

Outcomes	"Transition" at 15 years (N=7836)	"Transition" at 15 years – restricted to patients still in care at end of follow-up (N=5028)
No gap in care 12 months *before* age of transition	87%	88%
No gap in care 12 months *after* age of transition	80%	87%
Difference (95% CI)	7.0 (6.0 – 8.0)	1.5 (0.4 – 2.6)
HIV-RNA viral load done[†]	**(N=2872)**	**(N=1878)**
18 months before age of transition	83%	80%
18 months after age of transition	83%	82%
Difference (95% CI)	-0.08 (-2.5 – 0.9)	-2.2 (-4.5 – 0.1)
HIV-RNA <400 copies/mL[§]	**(N=2076)**	**(N=1288)**
18 months before age of transition	70%	67%
18 months after age of transition	63%	61%
Difference (95% CI)	6.3 (4.3 – 8.4)	6.0 (3.3 – 8.7)

CI: confidence interval

[‡] limited to patients within facilities with annual routine viral load monitoring

[§] limited to patients with viral load measurements done before and after the respective age threshold

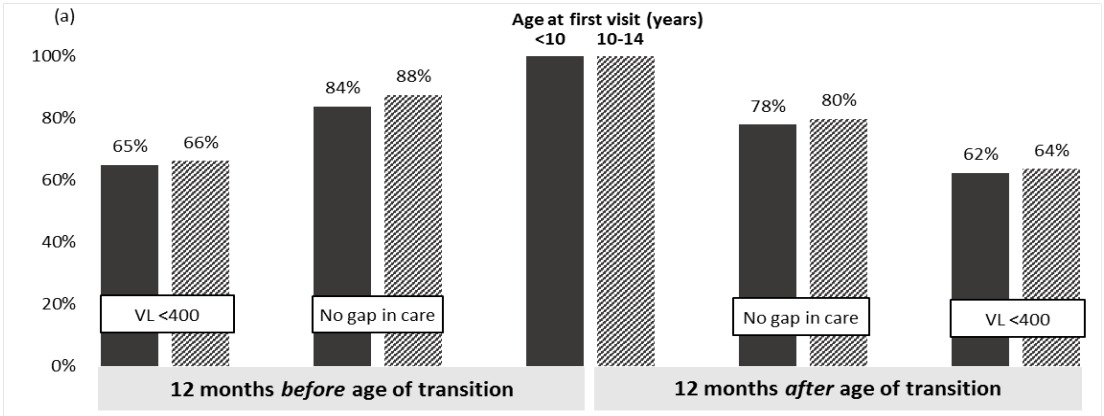
Supplementary Table 6.2. Outcomes of adolescents and young adults living with HIV at different transition age thresholds by age of enrolment into HIV care

	Transition at 16 years (N=5516)		*Transition at 18 years (N=3864)*			*Transition at 20 years (N=1463)*		
	Age at enrolment into HIV care		**Age at enrolment into HIV care**			**Age at enrolment into HIV care**		
Outcomes	**<10 years (n=1884)**	**10-14 years (n=3632)**	**<10 years (n=543)**	**10-14 years (n=2489)**	**15-16 years (n=832)**	**<10 years (n=67)**	**10-14 years (n=993)**	**15-16 years (n=403)**
No gap in care 12 months *before* age of transition	84%	88%	86%	83%	81%	85%	79%	79%
No gap in care 12 months after *age* of transition	78%	80%	76%	74%	72%	67%	69%	73%
Difference (95% CI)	5.9 (3.9-8.0)	7.9 (6.4-9.3)	9.9 (6.1-13.8)	9.0 (7.1-11.0)	9.7 (6.3-13.2)	17.9 (5.5-30.3)	9.4 (6.0-12.7)	5.7 (0.8-10.6)
HIV viral load done[†]	**(n=886)**	**(n=1066)**	**(n=284)**	**(n=608)**	**(n=148)**	**(n=37)**	**(n=177)**	**(n=66)**
18 months *before* age of transition	87%	82%	91%	81%	66%	92%	81%	62%
18 months *after* age of transition	87%	82%	88%	80%	70%	68%	77%	71%
Difference (95% CI)	-0.6 (-3.4-2.3)	0.4 (-2.5-3.2)	2.8 (-2.1-7.7)	1.6 (-2.3-5.6)	-4.1 (-13.9-5.8)	24.3 (5.9-42.8)	4.5 (-4.3-13.3)	-9.1 (-25.0-6.8)
HIV-RNA<400 copies/mL[§]	**(n=693)**	**(n=766)**	**(n=232)**	**(n=422)**	**(n=76)**	**(n=24)**	**(n=112)**	**(n=32)**
18 months *before* age of transition	65%	66%	63%	66%	68%	71%	57%	66%
18 months *after* age of transition	62%	64%	58%	64%	66%	54%	54%	81%
Difference (95% CI)	2.4 (-1.2-6.1)	2.6 (-0.9-6.1)	4.7 (-2.3-11.7)	1.7 (-3.4-6.7)	2.6 (-9.0-14.2)	16.7 (-6.4-39.7)	2.7 (-7.3-12.7)	-15.6 (-34.0-2.8)

[†] limited to patients within facilities with annual routine viral load monitoring

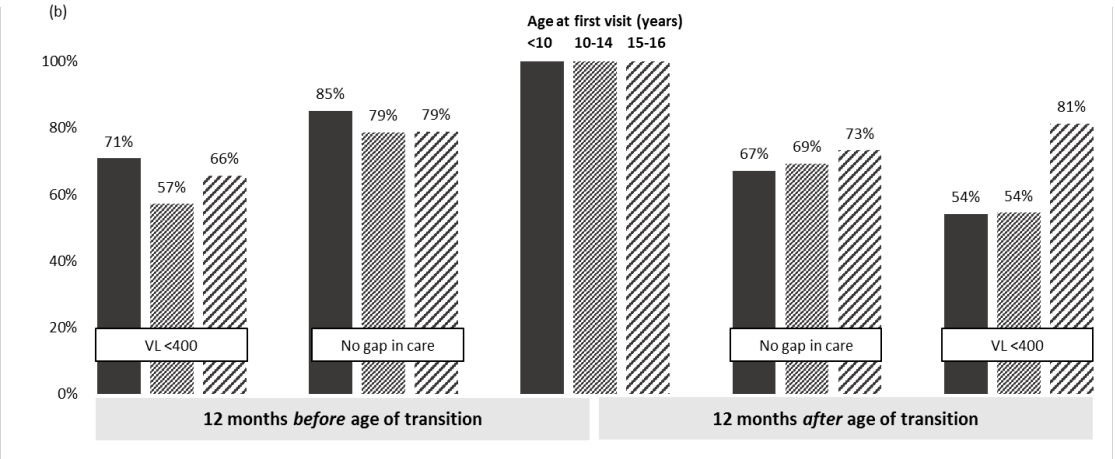
[§] limited to patients with viral load measurements done before and after the respective age threshold

Supplementary Figure 6.1. Outcomes of adolescents and young adults living with HIV at different transition age thresholds by age of enrolment into HIV care: at transition age thresholds a) 16 years b) 20 years



Number of patients with outcome	449	507		1580	3180		1884	3632		1468	2894		432	487
Total number of patients in whom outcome assessed	693	766		1884	3632		1884	3632		1884	3632		693	766

Age at first visit <10 years Age at first visit 10-14 years



Number of patients with outcome	17	64	21		57	781	318		67	993	403		45	688	295		13	61	26
Total number of patients in whom outcome assessed	24	112	32		67	993	403		67	993	403		67	993	403		24	112	32

Age at first visit <10 years Age at first visit 10-14 years Age at first visit 15-16 years

Supplementary Information 7.1 The Global fRAmework of Data collection Used for Adolescent HIV Transition Evaluation (GRADUATE) Data exchange standard

GRADUATE Data Exchange Standard

Draft Modifications to include Adolescent Transition to Adulthood/Adult Care

Note: Colour coding:

Turquoise: New tables and variables essential to capture transition information
Pink: Existing variables that are key to studying transition but don't directly capture transition information
Lime green: Existing variables that are "nice to have" but not essential to study transition and not directly related to transition.

Designations based on HICDEP version 1.100

Table Name	Description	Not Yet Designated	HICDEP	HICDEP +	Non-HICDEP
tblADOL	Key adolescent events				X
tblART	antiretroviral drugs			X	
tblART_MUM	antiretroviral medication of mother				X
tblBAS	basic Information			X	
tblCANC	cancer diagnoses		X		
tblCENTER	site-specific information			X	
tblCEP	clinical events including serious non-AIDS conditions	X			
tblCHILD	Information about the number and date of birth of biological children (born alive) for both male and female patients				X
tblDELIVERY_CHILD	delivery information related to child			X	
tblDELIVERY_MUM	delivery information related to mother			X	
tblDIS	diseases (CDC-C & WHO stage diseases)			X	
tblDIS_FRAC	Fractures (?only during adolescence)				X
tblDIS_MH	Mental health diagnoses/referral/treatment				X
tblDISCL_CHILD	Disclosure of child's HIV status to him/herself				X
tblHOSP	Admissions to hospital				
tblLAB	laboratory tests			X	
tblLAB_BP	blood pressure		X		
tblLAB_CD4	CD4 measurements		X		
tblLAB_RES	resistance testing information			X	
tblLAB_RES_LVL_1	nucleoside sequence for PRO and RT	X			
tblLAB_RES_LVL_2	mutations and positions of PRO and RT sequences		X		
tblLAB_RES_LVL_3	resistance result			X	
tblLAB_RNA	viral assay		X		
tblLAB_VIRO	viro-/serological Tests			X	
tblLTFU	death and drop-out			X	
tblMED	other medications			X	
tblNEWBORN	information related to newborns			X	
tblNEWBORN_ABNORM	information related to abnormalities of newborn			X	
tblOVERLAP	participation in other cohorts		X		
tblPREG	general pregnancy-related information			X	
tblPREG_OBS	obstetrical problems	X			
tblPREG_OUT	pregnancy outcome			X	
tblPROGRAM	linking sites to programs		X		
tblREFILL	prescription refills	X			
tblSAMPLES	biological sample storage	X			
tblTRANSFER	Information about transfers				X
tblTRANS_EXP	Pediatric to Adult transition experiences				X
tblVIS	visit-related information			X	

tblADOL (Information about key adolescent experiences)

Relation to HICDEP: non-HICDEP

This table would be filled in for any HIV-infected patient who has a visit between the ages of 10 and 25. It can be completed multiple times.

Field	Format	Description
PATIENT	Character (or numeric if possible)	Code to identify patient (Cohort Patient ID)
ADOL_D(_A)	yyyy-mm-dd	Date of completion of tblADOL
DISCL_ST_Y	Numeric with codes: 0=No 1=Yes 8=Not applicable 9=Unknown	Has the process of informing the child/adolescent of his/her HIV diagnosis (disclosure process) been initiated? Enter 8 if adolescent was personally informed of their diagnosis by a HCW when HIV was first diagnosed.
DISCL_ST_D(_A)	yyyy-mm-dd	Date of start of disclosure process. Leave blank if DISCL_ST_Y = 0 or 8 or 9
DISCL_Y	Numeric with codes: 0=No 1=Yes 9=Unknown	Does the patient fully know and can name his/her HIV status using the name "HIV" (or local language equivalent)?
DISCL_AGE	Numeric (integer)	Age in years at which patient was fully disclosed to or became fully aware of HIV status (i.e. knows and can name HIV status using the name "HIV"?) Enter 8888 if not applicable (patient not yet disclosed to or disclosure unknown or patient was personally informed of HIV diagnosis by HCW on date of first diagnosis or i.e. DISCL_Y = 0 or 8 or 9) Enter 9999 if unknown
DISCL_HOW	Numeric with codes: 1=Told by caregiver 2=Told by healthcare worker/counsellor 3=Told by Other (someone who is not a caregiver or health care worker/ counsellor) 4=Worked out their HIV status before being told 88=Not applicable 99=Unknown	How did the patient become fully aware of HIV status (i.e. fully disclosed)? Note that this refers to the time the patient became fully aware that they were HIV infected. Enter 8888 if not applicable (patient not yet disclosed to or disclosure unknown or patient was personally informed of HIV diagnosis by HCW on date of first diagnosis or i.e. DISCL_Y = 0 or 8 or 9) For example, if the patient was told but had already figured out their HIV status by some other means then this should be entered as 4. If the patient was told by a caregiver or health care worker but had previously heard about their HIV status from someone else (e.g. another patient, sibling who is not a caregiver etc) then this should be entered as 3.
SEC_SCHOOL_Y	Numeric with codes: 0=No 1=Yes 9=Unknown	Has the patient started secondary school?
SEC_SCHOOL_D(_A)	yyyy-mm-dd	Date patient started secondary school
SMOKE_Y	Numeric with codes: 0 = No 1 = Yes 9 = Unknown	Has the patient ever smoked a whole cigarette?
SMOKE_AGE	Numeric (integer)	Age in years at which patient first smoked a whole cigarette. Enter 8888 if SMOKE_Y = 0 or 9 Enter 9999 if age is unknown
ALC_Y	Numeric with codes: 0 = No 1 = Yes 9 = Unknown	Has the patient ever drunk a whole unit of alcohol? (This excludes taking a few sips)

Field	Format	Description
ALC_AGE	Numeric (integer)	Age in years at which patient first drank a whole unit of alcohol. Enter 8888 if ALC_Y = 0 or 9 Enter 9999 if age is unknown
REC_DRUGS _Y	Numeric with codes: 0 = No 1 = Yes 9 = Unknown	Has the patient ever used any **non-injectable** recreational drugs (not prescribed by a doctor) other than cigarettes and alcohol? This includes inhalation, smoking or ingestion of drugs including cocaine, amphetamines, methamphetamine, sedatives, ecstasy, cannabis, amyl nitrates, heroin, hallucinogens, inhalants (glue, thinners).
REC_DRUGS_AGE	Numeric (integer)	Age in years at which patient first used non-injectable recreational drugs. Enter 8888 if REC_DRUGS_Y = 0 or 9 Enter 9999 if age is unknown
REC_DRUG_INJECT_Y	Numeric with codes: 0 = No 1 = Yes 9 = Unknown	Has the patient ever **injected** recreational drugs (not prescribed by a doctor)?
REC_DRUG_INJECT_AGE	Numeric (integer)	Age in years at which patient first injected recreational drugs? Enter 8888 if REC_DRUGS_INJECT_Y = 0 or 9 Enter 9999 if age is unknown
HOMELESS_ADO_Y	Numeric with codes: 0 = No 1 = Yes 9 = Unknown	Has the patient ever been homeless as an adolescent or young adult (ages 10-25 years)?
HOMELESS_ADO_DUR	Numeric with codes: 1 = <1 month 3 = 1 to 3 months 6 = 4 to 6 months 7 = longer than 6 months	Duration in months of the longest period of homelessness as an adolescent or young adult between ages 10-25 years. Enter 8888 if patient is not known to have been homeless as an adolescent or young adult (i.e. HOMELESS_ADO Y= 0 or 9) Enter 9999 if duration of homelessness is unknown
INCARC_ADO_Y	Numeric 0 = No 1 = Yes 9 = Unknown	Has the patient ever been incarcerated or imprisoned (spent >1 day in jail or prison) as an adolescent or young adult (ages 10-25 years)
INCARC_ADO_AGE	Numeric (integer)	Age in years at first incident of incarceration or imprisonment as an adolescent or young adult (ages 10-25 years). Enter 8888 if INCARC_ADO_Y = 0 or 9 Enter 9999 if age is unknown
INCARC_ADO_FREQ	Numeric with codes 0 = 0 incidents 1 = 1 incident 2 = 2 incidents 3 = 3 incidents 4 = 4 or more incidents 9 = Unknown	Number of separate incidents of incarceration or imprisonment as an adolescent or young adult (ages 10-25 years) Enter 0 if patient has never been incarcerated (spent >1 day in jail or prison) as an adolescent or young adult (ages 10-25 years)
INCARC_ADO_DUR	Numeric with codes: 1 = <1 month 3 = 1 to 3 months 6 = 4 to 6 months 7 = longer than 6 months	Duration in months of the longest period of incarceration/imprisonment as an adolescent or young adult between ages 10-25 years. Enter 8888 if patient is not known to have been incarcerated as an adolescent or young adult (i.e. INCARC_ADO Y= 0 or 9) Enter 9999 if duration of incarceration is unknown
SEX_VAGINAL_Y	Numeric with codes: 0 = No 1 = Yes 9 = Unknown	Has the patient ever had vaginal sex? Question should only be asked in children >12 years of age

Field	Format	Description
SEX_ VAGINAL _AGE	Numeric (integer)	Age in years at which patient first had vaginal sex. Question should only be asked in children >12 years of age Enter 8888 if SEX_VAGINAL_Y = 0 or 9 Enter 9999 if age is unknown
SEX_ORAL_Y	Numeric with codes: 0 = No 1 = Yes 9 = Unknown	Has the patient ever had oral sex? Question should only be asked in children >12 years of age
SEX_ ORAL _AGE	Numeric (integer)	Age in years at which patient first had oral sex. Question should only be asked in children >12 years of age Enter 8888 if SEX_ORAL_Y = 0 or 9 Enter 9999 if age is unknown
SEX_ANAL_Y	Numeric with codes: 0 = No 1 = Yes 9 = Unknown	Has the patient ever had anal sex? Question should only be asked in children >12 years of age
SEX_ ANAL _AGE	Numeric (integer)	Age in years at which patient first had anal sex. Question should only be asked in children >12 years of age Enter 8888 if SEX_ORAL_Y = 0 or 9 Enter 9999 if age is unknown

tblCHILD (Information about the number and date of birth of biological children (born alive) for both male and female patients)

Relation to HICDEP: HICDEP+

Field	Format	Description
PATIENT	Character (or numeric if possible)	Code to identify patient (Cohort Patient ID)
CHILD_ID	Character (or numeric if possible)	Patient ID of the child OR Dummy ID (If child has never been enrolled into care at an IeDEA site, enter parent's ID with dashed numeric suffix such as [PATIENT]-1, [PATIENT]-2, etc. here)
CHILD_ENROL	Numeric with codes: 0=No 1=Yes 9=Unknown	Has child ever been enrolled into care at an IeDEA site?
CHILD_BIRTH_D (_A)	yyyy-mm-dd	Date of birth of child

tblDELIVERY_CHILD (Delivery information related to child)

Relation to HICDEP: HICDEP+

Field	Format	Description
MOTHER_ID	Character (or numeric if possible)	Patient ID of pregnant woman (mother of the child) OR Dummy ID (If mother is not enrolled into care at an IeDEA site, enter child's ID with "_mum" suffix, i.e., [CHILD_ID]_mum)
MOTHER_ENROL_Y	Numeric with codes: 0=No 1=Yes 9=Unknown	Is mother enrolled into care at an IeDEA site?
CHILD_ENROL_Y	Numeric with codes: 0=No 1=Yes 9=Unknown	Is child enrolled into care at an IeDEA site?
CHILD_ID	Character (or numeric if possible)	Patient ID of the child OR Dummy ID (If child is not enrolled into care at an IeDEA site, enter mother's ID with dashed numeric suffix such as [MOTHER_ID]-1, [MOTHER_ID]-2, etc. here)
PREG_ID	numeric	Unique identifier for this pregnancy
DELIV_D (_A)	yyyy-mm-dd	Date of delivery/birth
DELIV_M	Numeric with codes: 1=Vaginally, spontaneous 2=Vaginally, forceps 3=Vaginally, vacuum 4=Vaginally, assisted (not further specified) 5=Vaginally, unknown 9=Unknown 10= Cesarean section, primary/elective (before onset of labour and rupture of membrane) 11=Cesarean section, Secondary 12=Cesarean section (not further specified)	Mode of delivery
BREECH_Y	Numeric with codes: 0=No 1=Yes 9=Unknown	Was the child born from a breech presentation?

tblDELIVERY_MUM (Delivery information related to mother)

Relation to HICDEP: HICDEP+

Field	Format	Description
MOTHER_ID	Character (or numeric if possible)	Patient ID of pregnant woman (mother of the child) OR Dummy ID (If mother is not enrolled into care at an IeDEA site, enter child's ID with "_mum" suffix, i.e., [CHILD_ID]_mum)
PREG_ID	Numeric	Unique identifier for this pregnancy
ROM_DUR	Numeric (metric: hours) , 999=unknown	Duration of rupture of membranes
ROM_DUR_A	Character '<' = less than value specified '>' = greater than value specified '=' = value specified	Qualifier for duration of rupture of membranes (relates to value specified for ROM_DUR)
DELIV_LOCATION	Numeric with codes: 1=health facility 2=home 3=other 9=unknown	Location of Delivery
PLANNED_HOME	Numeric with codes: 0=No 1=Yes 9=Unknown	If patient delivered at home, was it planned in advance?
DELIV_ASSIST	Numeric with codes: 1=Doctor /Nurse/Midwife 2=Traditional Birth Attendant 3=Relative/Friend 4=No one 9=Unknown	Who assisted with the delivery? (If multiple, select response with the lowest associated numeric code)
TEAR_Y	Numeric with codes: 0=No 1=Yes 9=Unknown	Episiotomy/tear

tblFRAC (Fractures)

Relation to HICDEP: non HICDEP but attempts to have similar format to DIS table

Field	Format	Description
PATIENT	Character (or numeric if possible)	Code to identify patient (Cohort Patient ID)
FRAC_D (_A)	yyyy-mm-dd	Date of fracture The patient will have no records in this table if he/she has never had a fracture
FRAC_SITE	Numeric with codes: 1 = head, skull, jaw or face 2 = ribs or sternum 3 = spine 4 = upper limb (shoulder, clavicle, upper or lower arm and hand) 5 = lower limb (pelvis, hip, thigh, lower leg, foot) 8 = Other 9 = Unknown	Site of fracture – use combinations of codes if sustained fractures at more than one site on the same date. e.g 14 = head and upper limb
FRAC_TRAUMA	Numeric with codes 1 = Minimal / No trauma (e.g. a fall from standing height or less during normal activities) 2 = Trauma (Intentional or Unintentional) 9 = Unknown	Level of trauma that caused the fracture

tblDIS_MH (Referrals for mental health and diagnoses and treatment)

Relation to HICDEP: non HICDEP but attempts to have similar format to DIS table

Field	Format	Description
PATIENT	Character (or numeric if possible)	Code to identify patient (Cohort Patient ID)
MH_D (_A)	yyyy-mm-dd	Date of mental health referral or diagnosis or treatment (mental health event) The patient will have no records in this table if he/she has never had a mental health referral or diagnosis or treatment
MH_ED (_A)	yyyy-mm-dd	End date of mental health event
MH_REF	Numeric with codes: 0 = No 1 = Yes 9 = Unknown	Was the patient referred to a mental health service?
MH_DX	Character - CODED	Mental Health Diagnosis Code according to the MH_DX_VOCAB below. For ICD codes, enter at least the letter plus the first digit of the ICD code. Enter 88 if no diagnosis was made Enter 99 if unknown
MH_DX_VOCAB	1 = ICD-9 2 = ICD-9-CM 3 = ICD-10 4 = ICD-10-CM 5 = ICD-11 6 = ICD-11-CM 7 = SNOMED-CT 8 = GRADUATE MH CODES 99 = OTHER	Source vocabulary for diagnosis code
MH_RX	Numeric with codes: 0 = No treatment 1 = Medication 2 = Counselling/outpatient sessions 3 = Inpatient treatment (including ECT) 4 = Other 9 = Unknown	Modalities used to treat the patient Use combinations of codes if more than one treatment modality was used e.g. 123 if medication, counselling and inpatient treatment was used. If medication was used, please enter details as far as possible in tblMED If patient was admitted to hospital, please enter details as far as possible in tblHOSP

Codes	Description
ANXD	Anxiety disorder
EATD	Eating disorder
MOOD	Mood disorder
COGD	Cognitive disorder
PERSD	Personality disorder
PSYD	Schizophrenia or other psychotic disorder
SUBD	Substance-related disorder
ICD	Diagnosis entered as an ICD 10 code
NODG	No diagnosis made
OTHD	Other disorder not specified above
UNKD	Diagnosis unknown

tblHOSP (Hospital Admissions)

Relation to HICDEP: Modified single variable from the HICDEP tblCEP

Name	Format	Description
PATIENT	Character (or numeric if possible)	Code to identify patient (Cohort Patient ID)
ADMIT_D(_A)	yyyy-mm-dd	Date of admission to hospital
DISCHARGE_D(_A)	yyyy-mm-dd	Date of discharge from hospital
ADMIT_DX	Character (coded)	Admission diagnosis (coded)
DISCHARGE_DX	Character (coded)	Discharge diagnosis (coded)
HDX_VOCAB	Numeric (coded) 1 = ICD-9 2 = ICD-9-CM 3 = ICD-10 4 = ICD-10-CM 5 = ICD-11 6 = ICD-11-CM 7 = SNOMED-CT 99 = OTHER	
HDX_VOCAB_OTH	Character	Other source vocabulary (describe and provide weblink)
FACILITY_TYPE		
DISCHARGE_TO_LOC		
ADMIT_THROUGH		
ICU	Numeric with codes: 0 = No 1 = Yes 9= Unknown	Was the patient admitted into the intensive care unit (ITU/ICU) during stay in the hospital
ICU_DAYS	Numeric (e.g. 2)	Number of days spent in the intensive care unit during this admission Enter 0 if patient not in ITU/ICU Enter 9999 if number of days is unknown or if not known whether patient was admitted to ICU or not

tblLAB (Laboratory values)

Relation to HICDEP: HICDEP+

Field	Format	Description
PATIENT	Character (or numeric if possible)	Code to identify patient (Cohort Patient ID)
LAB_ID	character, see coding table for valid codings	Code representing the measurement
LAB_D (_A)	yyyy-mm-dd	Date of measurement/sample
LAB_R	Numeric with codes: 1 = Positive (including trace, 1+, 2+, etc.) 0 = Negative 9 = Unknown/borderline	Measurement result
LAB_V	Numeric: -1 = undetectable or detection limit as negative value	Value of measurement
LAB_U	Character or numeric, see coding table for valid codings	Unit of measurement
LAB_FA	Numeric with codes: 0=No 1=Yes 9=Unknown	Was the sample taken while fasting?
LAB_ST	Character, see coding table for valid codings	Specimen type

Code	Measurement
A1C	Haemoglobin A1C
ACRA	Albumin Creatinine Ratio
ALB	Albumin
AFP	Alfa Fetoprotein
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMY	Amylase
AST	Aspartate aminotransferase
BIL	Total Bilirubin
BUN	Blood Urea Nitrogen
CD3	CD3
CD3P	% CD3 of leukocytes
CD8	CD8
CD8P	% CD8 of leukocytes
CHOL	Total Cholesterol
CL-	Cl-
CRE	Creatinine
DIPB	Dipstick result for blood in Urine
DIPG	Dipstick result for glucose in Urine
DIPK	Dipstick result for ketones in Urine
DIPLE	Dipstick result for leucocyte esterase in Urine
DIPP	Dipstick result for protein in Urine
GGT	Gamma-glutamyl transferase
GLUC	Glucose
HAEM	Haemoglobin
HDL	Serum HDL
HEMA	Hematocrit
IGRA	Interferon-Gamma Release Assay
INR	Quick/INR
LACT	Lactate
LDL	Serum LDL
LEUK	Leukocytes
LYM	Lymphocytes
LYMP	% Lymphocytes of leukocytes
MCV	MCV
NA+	Na+
NEU	Neutrophils
PCRA	Protein Creatinine Ratio
PHA	PH arterial
PHV	PH venous
PP	PP factor (II, VII, X)
PROT	Protein
PSA	Prostate-specific antigen
PTH	Parathyroid Hormone
PTR	Prothrombin rate
TBC	TB culture
TBM	TB smear/microscopy
TBHIST	TB histology
TBGX	TB GeneXpert
TBNAAT	TB NAAT/LPA (non-GeneXpert)
THR	Thrombocytes/platelets
TRIG	Serum Triglyceride
URA	Uric acid
UREA	Urea/Blood Urea Nitrogen

Code	Unit String
1	mmol/L
2	g/L
3	g/dL
4	mg/dL
5	IU/L (u/L)

6	µmol/L
7	INR
8	1E+9/L
9	1E+6/L
10	cells/µL
11	µkat/L
12	%
13	µg/L = ng/mL
14	mg/24h
15	mg/mmol
16	fl (Femtoliter)
17	µg/mL = mg/L
99	no units (e.g. for Dipstick results)

It is recommended to use the string codes from the above table since this makes the data human readable.

Code	Specimen Type
WB	Whole blood
P	Plasma
S	Serum
U24	24-hour urine
U	Urine
CSF	Cerebrospinal fluid
SP	Sputum
SA	Saliva
UNK	Unknown
OTH	Other

tblLTFU (death and dropout)

Relation to HICDEP: HICDEP+

Field	Format	Description
PATIENT	Character or numeric	Code to identify patient (Cohort Patient ID)
DROP_Y	Numeric with codes: 0 = No 1 = Yes	Has the patient dropped out?
DROP_D (_A)	yyyy-mm-dd	If patient has dropped out, Date of last visit
DROP_RS	numeric, see coding table below	Reason for Drop
DEATH_Y	Numeric with codes: 0 = No 1 = Yes	Has the patient died?
DEATH_D (_A)	yyyy-mm-dd	Date of Death
L_ALIVE_D (_A)	yyyy-mm-dd	Last date of information for patient
MOTHERDEATH_Y	Numeric with codes: 0 = No 1 = Yes 9 = Unknown	Has the patient's biological mother died?
MOTHERDEATH_D (_A)	yyyy-mm-dd	Date of death of the patient's biological mother
FATHERDEATH_Y	Numeric with codes: 0 = No 1 = Yes 9 = Unknown	Has the patient's biological father died?
FATHERDEATH_D (_A)	yyyy-mm-dd	Date of death of the patient's biological father

Code	Reason for Drop Out
0	Patient was not infected (mainly for children)
1	Patient lost to follow-up / not known to be dead
2	Patient has not had visit within required amount of time
2.1	Patient did not respond to several invitations

3	Patient moved away
3.1	Patient moved to another country
4	Patient is followed by another centre
4.1	Paediatric patient transferred to adult care
5	Patient's decision
5.1	Patient's caretaker wanted to discontinue (for children)
6	Consent withdrawn
7	Incarceration/jail
8	Institutionalisation (drug treatment, psychological …etc.)
9	Other

tblVIS (Visit-related Information)

Relation to HICDEP: HICDEP+

Field	Format	Description
PATIENT	Character (or numeric if possible)	Code to identify patient (Cohort Patient ID)
CENTER	Character	Code for Clinic/Centre/Hospital where patient is seen.
VIS_D (_A)	yyyy-mm-dd	Date of patient visit
CLINIC_TYPE (Modified from HICDEP Codes which are related to transition only)	Numeric with codes (see list CLINIC_TYPE)	Type of clinic in terms of age group where patient is seen Note – this is different from describing the age group for the center/facility as a whole (which is already captured in tblCENTER) e.g. children may move from a pediatric to an adolescent to an adult clinic all within the same facility.
WEIGH	Numeric: 999 = Unknown	Weight of patient at visit in kilograms (kg)
HEIGH	Numeric: 999 = Unknown	Height/length of patient at visit in meters (m)
CDC_STAGE	N, A, A1, A2, A3 B, B1, B2, B3 C, C1, C2, C3 9= Unknown	Clinical CDC stage at visit
WHO_STAGE	Numeric with codes: 1 = WHO Stage I 2 = WHO Stage II 3 = WHO Stage III 4 = WHO Stage IV 9 = Unknown	Clinical WHO stage at visit
SMOKING_Y	Numeric with codes: 0=No 1=Yes 9=Unknown	Is the patient currently a smoker?
PREG_Y	Numeric with codes: 0=No 1=Yes 9=Unknown	Is the patient currently pregnant? If possible, provide additional details in tblPREG.
BREASTF_Y	Numeric with codes: 0=No 1=Yes 9=Unknown	{*For infants and children only*} Is the patient currently breastfeeding?
FEEDOTH_Y	Numeric with codes: 0=No 1=Yes 9=Unknown	{*For infants and children only*} Is the patient currently receiving foods or liquids other than breast milk?
CAREGIVER	Numeric with codes: 1=Mother 2=Father 3=Sibling	{*For infants and children only*} Who is the patient's primary caregiver?

Field	Format	Description
	4=Grandparent 5=Aunt or uncle 6=Self 7=Other family member 8=Other non-family member 9=Unknown 10=Other non-coded	
BROUGHT_PATIENT	Numeric with codes: 1=Mother 2=Father 3=Sibling 4=Grandparent 5=Aunt or uncle 6=Self 7=Other family member 8=Other non-family member 9=Unknown 10=Other non-coded	{*For infants and children only*} Who brought the patient to this clinic visit?
HIV_STATUS	Numeric with codes: 1=HIV status indeterminate 2=HIV infected 3=HIV uninfected	Current HIV status
STATUS_KNOWN	Numeric with codes: 0=No 1=Yes 2=Disclosure ongoing 9=Unknown	{*For HIV-infected children and adolescents only*} Does the patient know his/her HIV status?
SCHOOL_Y	Numeric with codes: 0=No 1=Yes 9=Unknown	{*Optional for adult patients*} Is the patient currently attending school or on break for customary school holidays?
SCHOOL_LVL	Numeric (see coding table SCHOOL_LVL)	{*Optional for adult patients*} Current level of education (ISCED97 refers to the 1997 International Standard Classification of Education)
GENDER_ID	Numeric with codes: 1=Male 2=Female 3=Transgender male 4=Transgender female 5=Other 9=Unknown	Current gender identification
EMPLOY (HICDEP CODES)	Numeric with codes: 0 = Unemployed and not actively seeking work 1 = Employed as employee 2 = Self-employed / Family worker 3 = Apprentice/trainee 4 = Unemployed and actively seeking work 6 = Retired/pre-retired 7 = Engaged in family/household duties 8 = Unable to work due to ill health 9 = Other situation 99 = Unknown	What is the patient's current employment situation?
EMPLOY_HRS (own codes)	Numeric with codes: 1 = Full-time (30 hours or more/week) 2 = Part-time (less than 30 hours/week) 3 = Other 8 = Not applicable 9 = Unknown	If the patient is working, does the patient work full-time or part-time? Enter 8 if patient is not working i.e. if EMPLOY=0 or EMPLOY > 3.
INCOME	Numeric with codes:	What is the patient's **main** source of income?

Field	Format	Description
	1 = Self (This includes money earned as employee, money earned from self-employment, interest/dividends, loans or bursaries or welfare payments/grants) 2= Dependent on someone else's income (this could be parents, caregiver, partner, other relative or any other person) 9 = Unknown	
SOCIAL_GRANT_Y	Numeric with codes: 0 = No 1 = Yes 1.1 = Yes – Grant to self 1.2 = Yes – Grant to parent/caregiver 1.3 = Yes – Grant to someone else 9 = Unknown	Is the patient in any way currently dependent on a social grant being received by themselves or someone else?
CURR_REL (modified from STAY codes)	Numeric with codes: 1 = Single (no formal partnership) 2 = Married / Civil partnership 3 = Separated 4.= Divorced 5 = Widowed 9 = Unknown	Current relationship status of patient
LIVE_WITH (Modified HICDEP codes)	Numeric with codes: 1 = Mother 2 = Father 12 = Mother and Father 3 = Foster family 4 = Institution 5 = Other adult caregiver (e.g older sibling, aunt/uncle/grandparent) 6 = Does not live with caregiver (e.g. lives with partner, friend etc) 7 = Lives alone 9 = Other 10=Unknown	*{For infants children, adolescents and youth up to 25 years of age only}* With whom does the patient currently live?
HOUSE_TYPE	Numeric with codes: 1 = Community (House/Apartment/Flat/Informal dwelling/shack) 2 = Dormitory/Student Accommodation/Boarding School 3 = Children's Home/Care home/shelter 4 = Homeless 5 = Incarcerated/ in prison 90 = Other 99 = Unknown/prefer not to answer	*{For infants children, adolescents and youth up to 25 years of age only}* What type of dwelling does the patient currently live in?
DISCL_OTH	Numeric with codes: 0 = No 1 = Yes 9 = Unascertained/Unknown	Has the patient disclosed his/her HIV status to other people – (excluding health care workers and family members)?
DISCL_NUM	Numeric with codes: 0 = None 1 = 1 to 2 people 3 = 3 to 5 people 5 = more than 5 people 99 = Unascertained/Unknown	How many people (excluding family members and health care workers) has the patient disclosed their HIV status to? Enter 0 if DISCL_OTH=0

Field	Format	Description
TRAVEL_RESP	Numeric with codes: 1 = No/never 2 = Yes / always 3 = Sometimes 8 = Not applicable – patients is >25 years of age 9 = Unknown	*{For infants, children, adolescents and youth up to 25 years of age only}* Does the patient make his or her own travel arrangements to get to clinic appointments and medicine collection?
ART_RESP	Numeric with codes 1 = No/never 2 = Yes /always 3 = Sometimes 8 = Not applicable – patients is >25 years of age 9 = Unknown	*{For infants children, adolescents and youth up to 25 years of age only}* Is the patient responsible for taking his or her own ART medications?
ART_ADHERE_DUR_1	Numeric (Integer) Enter 8888 if not applicable e.g. patient is not on ART or is >25 years Enter 9999 if adherence questions not asked or unknown	Time period in DAYS over which ART_ADHERE_XXX variables are asked. This is purposefully left flexible as different cohorts will ask over different periods. It is expected that common time periods would be 3 days, 7 days, 30 days, 90 days. There is an option to report adherence over 2 different durations for example if patients are asked about adherence in the last 3 days and the last 30 days. (ART_ADHERE_DUR_1 and ART_ADHERE_DUR_2)
ART_ADHERE_SOURCE_1	Numeric with codes 1 = Patient self-report 2 = Caregiver report 3 = Pill count 4 = Medication Event Monitoring System (MEMS) caps 5 = Other 9 = Unknown	What method of adherence measurement was used during ART_ADHERE_DUR_1? Enter 9 if unknown or adherence questions not asked
ART_ADHERE_PERF_1	Numeric with codes 0 = Perfect (no missed doses) 1 = Imperfect (≥1 missed dose) 9 = Unknown or adherence questions not asked	Was adherence perfect (no missed doses) or imperfect (≥1 missed dose) during ART_ADHERE_DUR_1 Enter 9 if unknown or adherence questions not asked
ART_ADHERE_DUR_2	Numeric (Integer) Enter 8888 if not applicable e.g. patient is not on ART or is >25 years Enter 9999 if adherence questions not asked or unknown	Time period in DAYS over which ART_ADHERE_XXX variables are asked (second period). This is purposefully left flexible as different cohorts will ask over different periods. It is expected that common time periods would be 3 days, 7 days, 30 days, 90 days. There is an option to report adherence over 2 different durations for example if patients are asked about adherence in the last 3 days and the last 30 days. (ART_ADHERE_DUR_1 and ART_ADHERE_DUR_2)
ART_ADHERE_SOURCE_2	Numeric with codes 1 = Patient self-report 2 = Caregiver report 3 = Pill count 4 = Medication Event Monitoring System (MEMS) caps 5 = Other 9 = Unknown	What method of adherence measurement was used during ART_ADHERE_DUR_2? Enter 9 if unknown or adherence questions not asked
ART_ADHERE_PERF_2	Numeric with codes 0 = Perfect (no missed doses) 1 = Imperfect (≥1 missed dose) 9 = Unknown or adherence questions not asked	Was adherence perfect (no missed doses) or imperfect (≥1 missed dose) during ART_ADHERE_DUR_2 Enter 9 if unknown or adherence questions not asked

Field	Format	Description
ALC_FREQ	Numeric with codes 0 = Never 1 = Once a month or less 2 = 2 to 4 times a month 3 = 2 to 3 times a week 4 = 4 times or more a week 5 = Do not remember 9 = Not recorded	How often has patient had a drink containing alcohol in the past 3 months? Enter 9 if patient doesn't report or if no ALCOHOL questions asked
ALC_NUM	Numeric with codes 0 = 1 or 2 1 = 3 or 4 2 = 5 or 6 3 = 7 to 9 4 = 10 or more 88 = Not applicable 99 = Not recorded	In the past 3 months, how many drinks (units) of alcohol did patient have on a typical day when drinking? Enter 88 if patient has never had a drink during the recording period (i.e. if ALC_FREQ=0) Enter 99 if patient doesn't report or no ALCOHOL questions asked (i.e. if ALC_DUR =99)
ALC_BINGE	Numeric with codes 0 = Never 1 = Less than once a month 2 = monthly 3 = weekly 4 = daily or almost daily 8 = not applicable 9 = not recorded	How often did the patient have 6 or more drinks (units) of alcohol on one occasion during the last 3 months? Enter 8 if patient has never had a drink during the recording period Enter 9 if patient doesn't report or no ALCOHOL questions asked.
SMOK_FREQ	Numeric with codes 0 = Never 1 = Once a month or less 2 = 2 to 4 times a month 3 = 2 to 3 times a week 4 = 4 times or more a week 5 = Do not remember 9 = Not recorded	How often has patient smoked cigarettes during the last 3 months? Enter 9 if patient doesn't report or if no SMOK questions asked.
NON_INJ_FREQ	Numeric with codes 0 = Never 1 = Once a month or less 2 = 2 to 4 times a month 3 = 2 to 3 times a week 4 = 4 times or more a week 5 = Do not remember 9 = Not recorded	In the past 3 months, how often has patient used any non-injectable recreational drugs (not prescribed by a doctor) – this includes cocaine, amphetamines, methamphetamine, sedatives, ecstasy, cannabis, amyl nitrates, heroin (not injected), hallucinogens, inhalants (glue, thinners) Enter 9 if patient doesn't report or if no NON_INJ questions asked.
INJ_FREQ	Numeric with codes 0 = Never 1 = Once a month or less 2 = 2 to 4 times a month 3 = 2 to 3 times a week 4 = 4 times or more a week 5 = Almost every day 6 = Do not remember 9 = Not recorded	In the past 3 months, how often has patient used recreational injectable drugs (not for medical purposes) – this includes injection into skin, vein or muscle? Enter 9 if patient doesn't report or if no INJ questions asked.
SEX_PREF (New Codes – nothing in the adolescent surveys)	Numeric with codes: 1 = same-sex partner 2 = opposite-sex partner 3 = both same- and opposite-sex partners 8 = Not applicable 9 = Unknown	*{For patients age >15 years only}* What is the patient's current (last 3 months) PRIMARY sexual preference? For patients who are not sexually active, can ask to which sex is the patient mostly attracted?
SEX _NUM	Numeric with codes 0 = 0 1 = 1 2 = 2 to 3	Number of partners with whom patient has had sex during the last 3 months? (This includes vaginal, anal and/or oral sex)

Field	Format	Description
	4 = 4 to 5 5 = more than 5 9 = Unknown	Enter 0 if no episodes of sex in the past 3 months. Enter 9 if patient doesn't report or if no SEX questions asked
SEX_COND	Numeric with codes 0 = Never 1 = Sometimes 2 = Usually 3 = Always 8 = Not applicable 9 = Not reported	Frequency of condom use during sex in the last 3 months. Enter 8 if patient has not had sex during the last 3 months. Enter 9 if patient doesn't report or no SEX questions asked.
SELF_HARM_FREQ (Based on AALPHI quality of life codes)	Numeric with codes: 0 = None 1 = Once 2 = 2 to 5 times 5 = 5 to 10 times 10 = more than times 99 = Not reported	How many times have you hurt yourself on purpose in the past 12 months? Enter 0 if patient has not hurt him/herself at all. Enter 99 if patient doesn't report or self-harm questions not asked.
SELF_HARM_ACT	Numeric with codes: 1 = Swallowed pills or poison 2 = Cut him/herself 3 = Burnt him/herself (e.g. with cigarette) 4 = Other 8 = Not applicable 9 = Unknown	How did the patient harm him/herself the last time he / she harmed him/herself in the last 12 months? Use combinations of codes if patient has harmed themselves in more than one way e.g. 13 if both swallowed pills and burnt him/herself. Enter 8 if patient has not hurt him/herself at all. Enter 9 if patient doesn't report how he/she hurt him or herself or self-harm questions not asked.

Code	CLINIC-TYPE
1	Paediatric only clinic (This could be a facility that provides only pediatric care or a dedicated pediatric service/day within a facility that provides care for other ages as well)
2	Adolescent within paediatric care (An adolescent service (e.g. a dedicated section of the clinic or a dedicated day) within a pediatric service i.e. care for adolescents)
3	Adolescent within adult care (An adolescent service (e.g. a dedicated section of the clinic or a dedicated day) within an adult service i.e. care for adolescents)
4	Adolescent stand-alone/youth (This could be a facility that provides only adolescent care or a dedicated adolescent service/day within a facility that provides care for other ages as well)
5	Adult (This is a facility/service that provides only services for adults or services for adults that are separate from those of children or adolescents)
6	Integrated paediatrics, adolescents and adults / Family clinic (This is a facility where children, adolescents and adults are all seen together in the same service)
7	Antenatal or Maternal and Child Health clinic (This is a facility/service that provides services only to pregnant girls and women and/or services to women post-delivery and to their newborn babies)
8	Other
9	Unknown

Code	SCHOOL_LVL
0	none
1	primary education (ISCED97-1)
2	lower secondary (ISCED97-2) OR end of basic education
3	upper secondary or post-secondary non-tertiary (ISCED97 3 and 4)
4	university or post-graduate (ISCED97 5A and 5B)
8	other, only if none of the codes 0 to 4 applies
9	unknown

tblTRANSFERS (Transfers table)

Relation to HICDEP: not in HICDEP at all

This table captures information about patients moving from one facility to another or from one clinic to another within the same facility. The table may be filled in:

- From the perspective of the transferring out site (for patients transferring out of a facility – i.e. variable TFRS_CAPTURE=1)
  OR
- From the perspective of the transferring in site (for patients transferring in to a facility – i.e. variable TFRS_CAPTURE=2)
  OR
- From the perspective of BOTH the transferring out and transferring in site (for patients transferring to a different clinic in the same facility - i.e. variable TFRS_CAPTURE=3 OR where patients have transferred out and a study is being conducted on post-transfer outcomes - i.e. variable TFRS_CAPTURE=1.1.)

There will be one record per transfer which should include as much information as possible about what is known both about a transfer out and a transfer in event even if the exact dates and exact facility are unknown for one or both aspects of the event.

For example – if the patient transfers out of your facility and you don't know anything about whether they successfully transferred in or not then TFRS_TO_VIS_Y = 0 or 9 and TFRS_TO_D will be left blank. Alternatively, if your facility is the transferring in facility one can assume that there was a previous transfer out even if one has very little information about the transfer out e.g. TFRS_OUT_PROG = NIP (non-IeDEA program) and TFRS_OUT_CENT = NIC (non-IEDEA Centre) and TFRS_OUT_D = 1911-11-11.

Name	Format and codes	Description
PATIENT	Character (or numeric if possible)	Code to identify patient (Cohort Patient ID)
TFRS_ID	Numeric	Unique identifier for each transfer event
	Numeric with codes: 1 = Facility that is transferring out 1.1 = Facility that is transferring out with a study on post-transfer outcomes 2 = Facility that is receiving the patient 3 = Both: Patient is transferred to a different clinic within the same facility (includes transfer to a club /community adherence group linked to the facility) 9 = Unknown	Which facility is capturing the transfer information: Is it the facility transferring the patient out or the facility receiving the patient?
TFRS_OUT_D (_A)	yyyy-mm-dd	Date of transfer out. Estimate if exact date unknown per IeDEA date conventions Enter 1911-11-11 if completely unknown per IeDEA date conventions.
TFRS_TO_VIS_Y	Numeric with codes: 0 = No 1 = Yes 9 = Unknown	Did the patient attend a visit at the facility to which they were transferred?

Name	Format and codes	Description
TFRS_TO_D (_A)	yyyy-mm-dd	Date of transfer in. Estimate if exact date unknown per IeDEA date conventions Enter 1911-11-11 if completely unknown per IeDEA date conventions. Leave blank if the patient did not ever visit the facility to which s/he was transferred or if it is unknown whether the patient ever visited the facility to which s/he was transferred. (i.e. TFRS_TO_VIS_Y=0 or 9)
TFRS_REF	Numeric with codes 1 = Referred by transfer out facility 2 = Not referred by transfer out facility 8 = Not applicable 9 = Unknown whether patient was referred by the transfer out facility or not	If TRFRS_CAPTURE=2, Was this transfer referred by the transfer out facility or was it a self-referral/silent transfer that the transfer out facility was not aware of or did not initiate? Enter 8 if TFRS_CAPTURE is not 2.
TFRS_RS	Numeric with codes (See coding table TRANSFER_RS)	Primary (main) reason for transfer Note that it TFRS_RS = 4 or 4.1/4.2/4.3 then complete tblTRANS_EXP
TFRS_RS_OTHER_1	Numeric with codes (See coding table TRANSFER_RS)	Other reason for transfer 1– Additional reasons for transfer as there may be additional reasons for transfer e.g. patient moves to another area and commences antenatal care and moves from a community group to a club. For each reason provide the most detailed amount of information possible Note that it TFRS_RS_OTHER_1 = 4 or 4.1/4.2/4.3 then complete tblTRANS_EXP
TFRS_RS_OTHER_2	Numeric with codes (See coding table TRANSFER_RS)	Other reason for transfer 2– See above Note that it TFRS_RS_OTHER_2 = 4 or 4.1/4.2/4.3 then complete tblTRANS_EXP
TFRS_RS_OTHER_3	Numeric with codes (See coding table TRANSFER_RS)	Other reason for transfer 3– See above Note that it TFRS_RS_OTHER_3 = 4 or 4.1/4.2/4.3 then complete tblTRANS_EXP
TFRS_OUT_PROG	Character	Program from which patient was transferred out. Use IeDEA program name if transferred out of IeDEA program Enter NIP if transferred out of a program that is not part of IeDEA or is unknown.
TFRS_OUT_CENT	Character	Code for Clinic/Centre/Hospital where patient is transferred out from. Must match with code for CENTER in tblCENTER if patient transfers out of an IeDEA Center Enter NIC if transferred out of a program that is not part of IeDEA or in unknown
TFRS_TO_PROG	Character	Program to which patient was transferred or intended to tranfer into. Note that the TFRS_TO_XXX variables should be completed if the intended transfer program and center is known, even if the patient does not successfully transfer. Use IeDEA program name if transferred into an IeDEA program. Enter NIP if transferred to a program that is not part of IeDEA or is unknown.

Name	Format and codes	Description
TFRS_TO_CENT	Character	Code for Clinic/Centre/Hospital to which patient is transferred or intended to tranfer into. Must match with code for CENTER in tblCENTER if patient transfers to an IeDEA Center. Enter NIC if transferred to a program that is not part of IeDEA or in unknown

Code	Transfer reason (TRANS_RS)
1	Moved
2	Change in level of care
2.1	Moved to lower level of care
2.2	Moved to higher level of care
3	New clinic available
4	Paediatric to adult clinic (transition)
4.1	Child to adolescent/youth care
4.2	Adolescent/Youth to adult clinic
4.3	Child to adult clinic
5	Adult to paediatric clinic (These are “back-transitions”)
5.1	Adult to adolescent/youth care
5.2	Adolescent/youth care to child care
5.3	Adult to child clinic
6	Antenatal/Pregnancy
6.1	Pregnancy started – to antenatal facility
6.2	Pregnancy / breastfeeding ended – out of antenatal facility
7	Club / Community Group
7.1	Transferred into club/community group
7.2	Transferred from club/community group to facility care
8	Partaking in a trial
8.1	Trial started
8.2	Trial ended
90	Other
95	Unknown/not ascertained

tblTRANS_EXP (Transition Experience table)

Relation to HICDEP: not in HICDEP at all

This table captures information about patients undergoing paediatric to adult transition. This can include

paediatric to adolescent or adolescent to adult transition, with or without a shared care clinic – i.e. only for TFRS_RS=4 or 4.1/4.2/4.3 or TFRS_RS_OTHER_1/2=4 or 4.1/4.2/4.3 There should be no entries in this table if none of the variables TFRS_RS or TFRS_RS_OTHER_1/2 are coded as 4 or any of the 4 subcodes.

Name	Format and codes	Description
PATIENT	Character (or numeric if possible)	Code to identify patient (Cohort Patient ID)
TFRS_ID	Numeric	Unique identifier to identify each transfer event and link record to tblTRANSFERS
TRANS_PREP_WKS	Numeric (integer) Enter 0 if transfer was discussed for the first time at patient’s last date at the transferring out clinic or transfer was never discussed Enter 9999 if unknown	How many weeks before last date at the transferring out clinic was the patient first told about transfer?

Name	Format and codes	Description
TRANS_PREP_VIS	Numeric (integer) Enter 0 if transfer was discussed for the first time at patient's last date at the transferring out clinic or transfer was never discussed Enter 9999 if unknown	Number of clinic visits at which transfer whas discussed prior to visit at which patient was transferred out?
TRANS_PREP_AGE	Numeric (integer) Enter patient's age at last visit if transition was discussed for the first time at patient's last date at the transferring out clinic or transition was never discussed Enter 9999 if unknown Enter 8888 if not applicable (Patients >25 years)	Age of patient in years when first discussed transition to another clinic?
TRANS_PLAN_Y	Numeric with codes 0 = No 1 = Yes 9 = Unknown	{*For infants children, adolescents and youth up to 25 years of age only*} Did patient have a written transition/transfer plan before transfer (e.g. brochure, checklist, webpage, adolescent "passport")
BROUGHT_PAT_POST_TRANS	Numeric with codes 1 = Mother 2 = Father 3 = Both mother and father 4 = Sibling 5 = Grandparent 6 = Aunt or uncle 7 = Self 8 = Other family member 10 = Other non-family member 11 = Other non-coded 9 = Unknown 90 = not applicable (no clinic visit after transfer)	Who brought the patient to the clinic visit immediately after transfer (i.e. the transfer in visit)?
We strongly recommend that the following transition experience questions are asked 6-12 months after the first visit to the new clinic/facility. They should not be asked at the first transfer-in visit as it is too early to assess the transition experience. They should ideally be asked within 12 months after transition so the patient still accurately recalls the experience.		
POST_TRANS_D(_A)	yyyy-mm-dd	Date on which post-transfer/transition questions are asked? This should not be the same as the date of transfer as patient will have had to have experienced the new clinic to answer these questions. **We recommend transition experience questions are asked 6-12 months after the patient has transferred in.**
TRANS_PREP	Numeric with codes 1 = Very prepared 2 = Somewhat prepared 3 = Neither prepared nor unprepared 4 = Somewhat unprepared 5 = Very unprepared 9 = Unknown Enter 8 if not applicable – patient never attends for post-transfer visit	How prepared/unprepared did the patient feel for transfer/transition? **We recommend transition experience questions are asked 6-12 months after the patient has transferred in.**

Name	Format and codes	Description
TRANS_EASE	Numeric with codes 1 = Very easy 2 = Somewhat easy 3 = Neither easy nor difficult 4 = Somewhat difficult 5 = Very difficult 9 = Unknown Enter 8 if not applicable – patient never attends for post-transfer visit	How easy/difficult was the transfer/transition? **We recommend transition experience questions are asked 6-12 months after the patient has transferred in.**
CLIN_SAT	Numeric with codes 1 = Very satisfied/comfortable 2 = Somewhat satisfied/comfortable 3 = Neither satisfied/comfortable nor dissatisfied/uncomfortable 4 = Somewhat dissatisfied/uncomfortable 5 = Very dissatisfied/uncomfortable 9 = Unknown Enter 8 if not applicable – patient never attends for post-transfer visit	How satisfied/comfortable is patient with post-transfer clinic? **We recommend transition experience questions are asked 6-12 months after the patient has transferred in.**
STAFF_SAT	Numeric with codes 1 = Very satisfied/comfortable 2 = Somewhat satisfied/comfortable 3 = Neither satisfied/comfortable nor dissatisfied/uncomfortable 4 = Somewhat dissatisfied/uncomfortable 5 = Very dissatisfied/uncomfortable 9 = Unknown Enter 8 if not applicable – patient never attends for post-transfer visit	How satisfied/comfortable is patient with staff at post-transfer clinic **We recommend transition experience questions are asked 6-12 months after the patient has transferred in.**

Appendices

Appendix 1.1 PhD thesis ethics approval – original and latest approvals

Appendix 1.2 Ethics approvals from sites participating in the GRADUATE study

Appendix 1.3 Ethics approval for CIDER to receive and analyse data related to the GRADUATE study

Appendix 1.4 Permission by the University of Cape Town's Doctoral Degrees Board to include publications in PhD thesis

Appendix 1.4 Letters from co-authors giving permission to include publications in PhD thesis

Appendix 1.5 GRADUATE study data collection forms