Characteristics and outcomes of children, adolescents and young adults on antiretroviral therapy in Southern Africa, incorporating additional outcome ascertainment through linkage and tracing studies

By

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ABSTRACT

Despite significant progress in pediatric HIV care and treatment, children, adolescents, and young adults living with HIV (CAYHIV) continue to face challenges in achieving optimal outcomes compared to adults due to challenges like virologic non-suppression (VNS) among those in care and loss to follow-up (LTFU). Adolescents, in particular, face psychosocial and structural barriers that hinder their adherence to antiretroviral therapy (ART), leading to VNS and associated negative consequences, such as increased morbidity, drug resistance, mortality and a higher risk of HIV transmission to sexual partners and, for those who are pregnant, to their infants. LTFU is concerning as CAYHIV who are not in care are also likely not to be on ART resulting in faster disease progression, VNS, and increased morbidity and mortality. LTFU also poses a challenge to accurately measuring programme outcomes as the true outcomes of those LTFU are unknown. Accurate estimation of mortality rates among CAYHIV requires ascertaining outcomes in those LTFU and is important for the effective management of HIV care programmes. The thesis therefore aimed to describe the characteristics and outcomes of CAYHIV in Southern Africa, including additional outcomes ascertained from linkage and tracing studies among those who had been reported as LTFU at the original sites of ART initiation.

The thesis consists of five papers (three published, two submitted) reporting the results from observational HIV cohorts of the International epidemiology Database to Evaluate AIDS -Southern Africa (IeDEA-SA) in six Southern African countries of Lesotho, Malawi, Mozambique, South Africa, Zambia and Zimbabwe. Chapter 1 (Introduction) lays the foundation for key issues and concepts. This is followed by the literature review (Chapter 2) which gives a comprehensive discussion on virologic outcomes among adolescents, LTFU, ascertaining outcomes among CAYHIV reported as LTFU and correction of programme-level mortality estimates for LTFU among all CAYHIV using outcomes ascertained through tracing or linkage studies. Chapters 3 and 4 examine virologic outcomes and early LTFU among younger adolescents (10-14 years, Chapter 3) and older adolescents (15-19 years, Chapter 4), with a sub-analysis among those initiating treatment during pregnancy. Chapter 3 reports increasing 75th quantile viral load values with a three-fold increase at age 14

vs age 10 years, but no specific age at which this increase is more marked, and no differences observed by sex. Chapter 4 reports a relatively low rate of virologic non-suppression (15%), but a high proportion of early LTFU following ART initiation (around 30%) irrespective of pregnancy status. Chapters 5 and 6 provide results on outcomes of CAYHIV previously reported as LTFU and either traced (Chapter 5) or linked to a health information exchange (Chapter 6). We defined tracing as the physical tracking of patients reported as LTFU using text messages, phone calls and home visits while linkage was defined as the process of linking patient unique identifiers to different healthcare data platforms like pharmacy records, laboratory records, hospital admissions to identify if they have had any interaction with the healthcare system within the province outside of their original facility or ART registration. The tracing approach reveals a high proportion of unreported mortality (9%) and a low proportion of self-transfers (21%) among CAYHIV while the linkage approach reveals a low proportion of mortality (3%), and a high proportion of self-transfers (47%). Chapter 7 consolidates the results in Chapters 5 and 6 alongside routinely collected data to correct mortality estimates comparing three uncorrected and three corrected methods. There is a two-fold increase in estimated mortality after incorporating deaths among successfully traced CAYHIV due to the high mortality in traced patients. In contrast, incorporating linkage data has minimal impact on mortality estimates as there were few deaths but a high number of self-transfers. Tracing and linkage-informed studies both show substantial variability in mortality among retained children and those LTFU across countries and sites, respectively.

The thesis concludes that virologic response among CAYHIV, particularly adolescents, has greatly improved in more recent years with improved ART regimens and is expected to continue improving with the introduction of dolutegravir-based therapies. However, this can easily be jeopardized by the persistent high proportion of CAYHIV reported as LTFU across the entire continuum of HIV care. Mortality estimates can also be substantially impacted if no additional outcome ascertainment is conducted among those reported as LTFU. Tracing and linkage-informed studies are, therefore, important for accurate estimation of mortality and retention estimates.

DEDICATION

I dedicate this thesis to my late mother, Ms. Hope Turyasingura. Continue resting in heavenly peace. Until we meet again.

DECLARATION

I, Patience Nyakato hereby declare that the work included in this thesis 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 unless otherwise stated in acknowledgements or in the case of published papers with multiple co-authors. The role of the candidate in published papers with multiple co-authors is outlined at the start of each results chapter.

DECLARATION ON THE INCLUSION OF PUBLICATIONS IN A PHD THESIS

"I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publication(s) in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publication(s)."

1. **Nyakato, P**., Schomaker, M., Sipambo, N., Technau, K. G., Fatti, G., Rabie, H., ... & Davies, M. A. (2021). Virologic response of adolescents living with perinatally acquired HIV receiving antiretroviral therapy in the period of early adolescence (10-14 years) in South Africa. AIDS, 35(6), 971.

2. **Nyakato, P**., Schomaker, M., Fatti, G., Tanser, F., Euvrard, J., Sipambo, N., ... & Cornell, M. (2022). Virologic non-suppression and early loss to follow up among pregnant and non-pregnant adolescents aged 15–19 years initiating antiretroviral therapy in South Africa: a retrospective cohort study. Journal of the International AIDS Society, 25(1), e25870.

3. **Nyakato, P**., Christ, B., Anderegg, N., Muhairwe, J., Jefferys, L., van Dijk, J., ... & Cornell, M. (2022). High unreported mortality in children and youth (< 25 Years) living with HIV who were lost to care from Antiretroviral Therapy programmes in Southern Africa: Results from a multi-country tracing Study. Journal of Acquired Immune Deficiency Syndromes, 91(5), 429.

4. **Nyakato P.**, Boulle, A., Wood, R., Eley, B., Rabie, H., Egger, M., Yiannoutsos, CT., Davies, M. A., …& Cornell, M. Self-transfers, hospital

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5. **Nyakato, P**., Schomaker, M., Boulle, A., Wood, R., Eley, B., Rabie, H.,... & Davies, M. A. Correcting mortality estimates among children and youth on antiretroviral therapy in Southern Africa, a comparative analysis between a multi-country tracing study and linkage to a health information exchange. Submitted to Tropical Medicine and International Health in October 2023.

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ABBREVIATIONS

AIDS: Acquired Immune Deficiency Syndrome
ART: Antiretroviral therapy
AGYW: Adolescent girls and young women
AHIV: Adolescents living with HIV
APHIV: Adolescents living with perinatally acquired HIV
AnPHIV: Adolescents living with non-perinatally acquired HIV
AYHIV: Adolescents and young adults living with HIV
AYPHIV: Adolescents and young adults living with perinatally acquired HIV
AYnPHIV: Adolescents and young adults living with non-perinatally acquired HIV
CAHIV: Children and adolescents living with HIV
CAYHIV: Children, adolescents and young adults living with HIV /Children and Youth living with HIV
CC: Complete case
CHIV: Children living with HIV
DTG: Dolutegravir
F&R: Frangakis & Rubin
HIV: Human immunodeficiency virus
IeDEA-SA: International epidemiology Databases to Evaluate AIDS- Southern Africa
IPW: Inverse probability weighting
IQR: Interquartile range
LTFU: Loss to follow-up
MAR: Missing at random
MI: Multiple imputation
NIC: Non-Informative Censoring
PLWH: People living with HIV
SSA: Sub-Saharan Africa
UNAIDS: Joint United Nations Programme on HIV/AIDS
VL: Viral load
VS: Virologic suppression
VNS: Virologic non-suppression
WHO: World Health Organization
WCPHDC: Western Cape Provincial Health Data Centre

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CHAPTER 1 Introduction

1.1 Background

Global HIV epidemiology among children, adolescents and young adults living with HIV

In 2022, 39 million people were estimated to be living with HIV (PLWH) globally, among whom 2.7 million were children and adolescents aged 0-19 years [1, 2]. Among these, 1.0 million were children aged 0-9 years, and 1.7 million were adolescents aged 10-19 years. UNAIDS also estimated that there were 3.2 million youth aged 15-24 years living with HIV globally in the same year [3].

In the same year, there were an estimated 130,000 new HIV infections among children aged 0-14 years, 140,000 among adolescents aged 10-19 years and 350,000 among young people aged 15-24 years. New infections in 15-24-year-olds accounted for 30% of new infections globally in 2022, with 18% of these being in young women [4, 5]. Adolescent girls and young women (AGYW), aged 15-24 years bear a higher HIV burden compared to their male counterparts, being eight times more likely to acquire HIV infection and generally acquiring HIV at an earlier age [6].

In 2022 there were approximately 630,000 AIDS-related deaths, of which 84,000 were among children aged 0-14 years, 27,000 among adolescents aged 10-19 years, while 42,000 young people aged 15-24 years experienced AIDS-related death [3].

HIV epidemiology among children, adolescents and young adults living with HIV in sub-Saharan Africa

Sub-Saharan Africa (SSA) continues to bear a disproportionate share of the global HIV burden, particularly among children and adolescents [5]. In 2021, SSA accounted for approximately 67% of all PLWH worldwide, with 88% of them being children and adolescents. Eastern and Southern Africa have the highest global burden of paediatric HIV, with 930,000 children aged 0-14 years, 1.1 million adolescents aged 10-19 years and 1.9 million youth aged 15-24 years living with HIV

in 2022 [3-5]. Notably, South Africa has the world's largest paediatric ART programme, with approximately 130,000 children aged 0-9 years and 320,000 adolescents aged 10-19 years estimated to be living with HIV in 2021 [7, 8]. The impact of HIV/AIDS on SSA's healthcare systems has strained resources, healthcare personnel and infrastructure.

Despite a decline in new HIV infections, SSA still faces a substantial number of new infections, primarily through heterosexual transmission, with the majority occurring among females. In 2022, women and girls of all ages in Eastern and Southern Africa accounted for 63% of all new HIV infections [5, 9]. Although progress has been made in reducing vertical transmission, many mothers living with HIV and children born to mothers living with HIV still lack access to prevention of vertical transmission services, leading to children acquiring HIV [9]. In 2022 alone, there were 58,000 children aged 0-14 years, 77,000 adolescents aged 10-19 years and 170,000 young adults aged 15-24 years who acquired HIV in Eastern and Southern Africa [3]. In the same year, there were estimated to be 8,746 children aged 0-14 years, and 59,324 young adults aged 15-24 years who acquired HIV in South Africa [10].

In comparison to adolescents and young adults, children had fewer new HIV infections but the greatest proportion of AIDS-related deaths in Eastern and Southern Africa [3]. AIDS-related deaths in this region amounted to 35,000 among children aged 0-14 years, 16,000 among adolescents aged 10-19 years and 26,000 among young adults aged 15-24 years. In South Africa, there were 2,200 and 2,700 AIDS-related deaths among children aged 0-9 years and adolescents aged 10-19 years respectively in 2021 [7].

1.2 The fast track 95: 95: 95 testing and treatment cascade among children, adolescents and young adults living with HIV

Progress made in the fight against HIV among children, adolescents and young adults living with HIV

Notwithstanding these challenges, considerable progress has been made in expanding pediatric HIV care and treatment globally, with a remarkable 38% reduction in new HIV infections and a 51% reduction in AIDS-related deaths since

2010 [3]. The percentage of pregnant persons living with HIV and accessing treatment increased from 48% in 2010 to 82% globally in 2022, accompanied by a 58% reduction in new child HIV infections within the same time span. ART coverage among pregnant persons is even higher in Eastern and Southern Africa, reaching 93%, with Botswana achieving a milestone of eliminating vertical transmission [3]. Furthermore, the integration of HIV testing and treatment with maternal and childcare services has resulted in a notable reduction in global AIDS-related deaths among children from 360,000 deaths in 2004 to 84,000 in 2022 [9]. There have also been improvements in the survival of children living with perinatally acquired HIV from infancy (≤2 years) to adolescence and adulthood [11]. Consequently, there has been a shift in the epidemic to older children (2-9 years old), adolescents (10-19 years old), and young adults (20-24 years old) living with HIV.

In 2020, the Joint United Nations Programme on HIV/AIDS (UNAIDS) introduced ambitious targets aiming for 95% of PLWH to be aware of their HIV status, 95% of those aware to receive life-saving antiretroviral therapy (ART) and 95% of those on ART to achieve virologic suppression (VS) <1000 copies/ml by 2025. These targets were set after eight countries achieved the 90-90-90 targets for the same goals introduced in 2014, five of which are in SSA (Eswatini, Rwanda, Botswana, Uganda and Malawi) [12-14]. By 2023, Botswana, Eswatini, Rwanda, the United Republic of Tanzania and Zimbabwe, all within SSA, had achieved the 95-95-95 targets. Additionally, 16 other countries, eight of which are in SSA, are on the verge of attaining them [9].

Even with these achievements, CAYHIV lag behind older adults in reaching the 95-95-95 targets. CAYHIV encounter several challenges along the HIV testing and treatment cascade which set them apart from older adults. These challenges include lower rates of testing and linkage to care, inadequate treatment coverage, lower rates of VS, increased mortality rates and higher rates of loss to follow-up (LTFU) from care [9, 15, 16].

First 95: Testing and linkage to care

While some progress has been made in expanding access to HIV testing services, testing rates remain low, resulting in delayed diagnoses for many children including

during their adolescent years [17, 18]. In 2021, around 59% (48-73%) of infants exposed to HIV were tested within the recommended two months of birth globally [7], meaning that four in ten infants born to mothers living with HIV, who are at high risk of vertical transmission, missed out on a timely diagnosis, a pivotal step in accessing treatment for those with HIV. Adolescents and young adults aged 15-24 years face the highest risk of HIV infection, with the majority who get infected remaining undiagnosed [1]. Globally, in 2021, this age group accounted for 31% of new HIV infections among adults aged 15 years and older [19], with approximately 61% being among adolescent girls and young women [5, 20, 21].

Second 95: Treatment coverage

Despite recommendations for universal ART, many CAYHIV initiate treatment with advanced disease, which increases their mortality risk. Globally, the ART coverage of children living with HIV (CHIV) aged 0-14 years was only 57% in 2022. Among adolescents, 54% received ART in 2020, with similar proportions of girls and boys [22]. In South Africa, in 2017 only 40% of adolescents and young adults living with HIV aged 15-24 years were exposed to ART with a 10% lower coverage among males compared to females and approximately 48% of all those living with HIV in this age group achieved VS [23].

Third 95: Virologic suppression

Adherence to ART is important for achieving VS and improving health outcomes for PLWH. However, adherence rates are low among CAYHIV, resulting in high rates of virologic non-suppression (VNS) [24, 25]. VNS is associated with increased morbidity and mortality and raises the risk of HIV transmission to sexual partners and, for pregnant and breastfeeding individuals, to their infants [26]. The rates of VS in CHIV still fall well below the desired target of 95% and lag behind those observed in adults [4, 5, 9, 23]. In 2022, approximately 81% of CHIV achieved viral suppression compared to 93% of adults. Reasons for this include suboptimal HIV pediatric medicines and the challenges of retaining children in care [9].

Virologic non-suppression among adolescents living with HIV

Even among those enrolled into care and on treatment, adolescents with HIV continue to experience higher rates of VNS compared to younger children or adults.

In SSA, many studies have reported worse VS, failure and adherence among adolescents than any other age group [18, 27, 28]. Many of these individuals initiate treatment late, often with advanced disease and severe immune-suppression, thereby increasing their risk of virologic failure and drug resistance. Notably, adolescents with perinatally acquired HIV (APHIV) who enter adolescence with suppressed viral loads (VLs) may experience a decline in VS compared to those who acquire HIV and initiate ART during adolescence [29].

Adolescence is a challenging phase characterised by physical, physiological, and emotional changes, along with increased autonomy, financial responsibilities, exploration of sexuality and exposure to gender norms [30, 31]. Adolescents are also at a heightened risk of several health problems, including HIV, substance use, injuries, poor mental health, and violence, and require multifaceted interventions [30]. For those growing up with HIV, there is an additional burden of dealing with a potentially stigmatising chronic illness [32, 33]. They must navigate keeping clinic appointments while being in school, adhering to treatment and deciding whether to disclose their HIV status to peers and potential sexual partners [34-36]. While the normal developmental changes of adolescence may make adherence especially challenging, other risk factors for poor adherence to treatment and, subsequently, VNS, include poverty, stigma, fear of HIV disclosure and mental health problems [31]. Additionally, adolescent girls and young women may become pregnant which adds to the complexities of managing chronic illness alongside the physical and emotional changes of pregnancy and adolescence [6, 37].

1.3 Longitudinal ART programme outcomes among children, adolescents and young adults living with HIV

The 95-95-95 targets collectively form a comprehensive framework to focus on PLWH being aware of their HIV status and accessing life-saving treatment and care, leading to VS and improved health. Achieving these targets is instrumental in controlling the spread of HIV, improving the quality of life for PLWH and ultimately ending the AIDS epidemic [9]. While the 95-95-95 targets offer a snapshot of the current state of HIV management, they do not provide insights into the trajectories patients follow across the care continuum or their long-term outcomes. These

outcomes (being alive and in care, transfers, mortality, and reported LTFU) are important indicators of programme effectiveness and are discussed below, and are addressed by some of the analyses in the thesis.

Being alive and in care (retained in care)

CAYHIV who are alive and taking ART should have VS, with improved health and reduced or zero transmission risk for those involved in sexual relationships. With a growing number of CHIV reaching adolescence and adulthood, CAYHIV will undergo longer periods of ART compared to adults who acquire HIV during adulthood [11, 38]. Ensuring their continued engagement in care is necessary for achieving VS, which is essential to their well-being and for curbing HIV spread [38].

Mortality

Despite major progress in reducing AIDS-related mortality, CAYHIV continue to face a disproportionate burden of AIDS-related deaths. In 2022, although CHIV constituted only 4% of PLWH, they accounted for 13% of AIDS-related deaths globally [4, 5, 9]. Similarly, although AIDS-related deaths have declined considerably in all age groups, adolescents and young adults living with HIV (AYHIV) still experience unacceptably high numbers of AIDS-related deaths [39-41]. HIV/AIDS remains one of the leading causes of death in adolescents aged 10-19 years globally [5, 42].

Mortality rates among CAYHIV vary by region, with higher risks reported in West African programmes compared to programmes in Eastern Africa, Southern Africa or Asia [5]. These deaths are largely preventable and generally occur in children who are yet to be diagnosed and are thus not on treatment, or within the first 24 months among those who have started ART [43, 44]. Among AYHIV, mortality further varies between those with perinatally acquired HIV and those with non-perinatally acquired HIV (AnPHIV) [24, 45]. For example, in a global cohort analysis of mortality among 61,000 adolescents from 34 countries, Kariminia et al. found a lower four-year cumulative incidence of mortality in APHIV than AnPHIV on ART: 3.9% vs 5.4% respectively [46]. Additionally, there are variations in mortality between younger adolescents aged 10-14 years and older adolescents/young adults aged 15-24 years, with higher mortality rates in the older adolescents [46].

Transfers

Transfers between healthcare providers are expected for CAYHIV as they advance through HIV care programmes, transitioning from pediatric specialists to adolescent specialists in some settings and eventually to adult healthcare providers [47-49]. Another transition route among these patients occurs when severely ill CAYHIV initiate ART at tertiary care facilities and are later transferred to primary care facilities nearer to their residences or communities upon stabilisation [50]. Additionally, adolescence and young adulthood can be a period of high mobility as people move for educational or employment opportunities or as they become independent from their caregivers [51]. Understanding these transfers is necessary for supporting CAYHIV during transition between sites or caregivers [49]. However, challenges emerge when these transfers are not properly documented at the transferring site due to administrative errors, with some transfers not being captured and patients still recorded as in care or as LTFU [52]. Further challenges may occur when the transferred patient fails to reach the designated transfer site as they may have self-transferred to another facility of their preference without notifying the original site, or may have genuinely become LTFU, with the facility unaware of their true outcomes [47, 48].

Loss to follow-up (LTFU)

LTFU remains one of the biggest challenges in the scaling up of pediatric HIV care programmes. When programmes report patients as “lost to follow-up”, this may reflect 1) that the programme may not know the true outcome of that patient (“reported LTFU”) but there may be a clear alternate explanation of where the patient is or 2) may include patients who are actually not in care anywhere (“true LTFU”).

Reported LTFU

Reported LTFU can be complex to interpret, as it masks a range of true outcomes. Some patients who appear LTFU may have died, while others may have self-transferred to a different site and remained in care [53-56]. Apparent high rates of reported LTFU may also reflect data errors and weak administrative systems, as some people considered LTFU are still in care at the same facility, with some visits not being captured. Therefore, not accounting for the true outcomes of those reported as LTFU (as is generally the case in national programme reporting) may

result in outcome misclassification and possible under-ascertainment of mortality and retention estimates [57-59]. These may impact policy decisions using such estimates, leading to the misallocation of scarce resources. For example, UNAIDS SPECTRUM models that utilize these estimates may underestimate mortality in this population if mortality among those LTFU is not accounted for. Consequently, decisions made by UNAIDS regarding global HIV/AIDS targets could be misinformed.

True LTFU

True LTFU can occur at any stage in the 95-95-95 cascade of care, with some individuals being lost before their HIV status is even diagnosed, some lost before linkage to treatment or on treatment, and others lost before or after achieving VS [60]. AYHIV have higher rates of reported LTFU before ART initiation and linkage to care than children or older adults [61]. Moreover, AYHIV who are lost from care before initiating ART and only return due to HIV-related illnesses usually present with advanced HIV disease [11]. Being LTFU while on treatment may affect adherence, resulting in VNS and increasing mortality risk. Most CAYHIV are LTFU in the early period after ART initiation which is also the time with the highest mortality risk [18, 62].

1.4 Approaches for ascertaining outcomes among those who are reported LTFU

Existing studies generally estimate mortality at the site level from patient files or electronic databases. However, these sources often have incomplete and inaccurate data, especially regarding the true outcomes among those reported as LTFU. Studies conducted in low- and middle-income countries (LMIC) with adult populations have shown considerable under-ascertainment of retention and mortality, with up to 50% of undocumented deaths and transfers misreported as LTFU [53, 54, 58, 63]. However, limited data are available on outcomes among CAYHIV who are reported as LTFU, making it difficult to estimate mortality accurately in this population. The extent of undocumented mortality among CAYHIV remains unclear, particularly in the period following ART initiation, when high mortality rates are observed [55].

To generate unbiased mortality estimates, we need additional data on true outcomes in at least a sample of those reported as LTFU. These can be obtained through tracing or linkage to comprehensive health registers that record all health service encounters, not just HIV-related ones, and the outcomes can be compared with the outcomes of those retained in care [53, 54, 64, 65].

Tracing

Tracing of patients who are reported as LTFU can be done using text messages, phone calls, or home visits [66]. Outcomes from those who are traced and found can be used to represent those who were not traced or those who were traced and not found, using appropriate statistical methods to correct mortality estimates for the entire cohort. However, the number of tracing studies among CAYHIV is limited despite the high rates of LTFU and mortality [67]. This means age-aggregated data for the outcomes of all CAYHIV who are LTFU are also limited.

Linkage to health registries or health information exchange

While physical tracing of patients reported as LTFU is valuable for accurately ascertaining programme outcomes, it is labour-intensive, expensive and time-consuming. Unique patient identifiers, tracking systems for CAYHIV and digital information systems can enhance programme effectiveness by accurately documenting patient movements and outcomes within the healthcare system. The Western Cape Provincial Health Data Centre (WCPHDC) in South Africa, is one example of a system that combines various data sources including hospital visits, laboratory and pharmacy data, and electronic HIV and TB registers [68]. Linking patient data to the WCPHDC offers an efficient means of estimating HIV programme outcomes. Furthermore, such a system allows ongoing assessment of outcomes among those LTFU, which is not feasible in a once-off tracing exercise. Having an accurate measurement of the “true” outcomes of CAYHIV and the factors associated with these outcomes allows programmes to be modified or developed to optimise outcomes.

1.5 Methods of incorporating ascertained outcomes of successfully traced/linked patients in programme-level estimates

Incorporating outcomes obtained from tracing or linkage studies for those who are LTFU has resulted in a substantial increase in estimated mortality compared to site-reported data alone [69-71]. Extensive research has been done on methods for correcting mortality and retention estimates in adults living with HIV to account for the ascertained outcomes in those reported as LTFU and traced or linked. These methods include a nomogram using correction factors, inverse probability weighting (IPW), and multiple imputation (MI) [58, 63, 65, 70]. The choice of method depends on factors such as the proportion reported as LTFU, the technique used in ascertaining their outcomes (tracing or linkage to health registers) and variables that predict the likelihood of outcome ascertainment, for example, distance from a patient's home to a health facility, or having correct contact details. While these analyses have been extensively carried out in adult populations, there is a dearth of research in this area among CAYHIV.

1.6 Rationale

The unique characteristics of CAYHIV necessitate tailored approaches to their diagnosis, treatment and care throughout their healthcare journey. For example, different criteria are needed to maintain optimal treatment regimens for CAYHIV as they may require ongoing adjustment as they grow and develop. Models of care must also be designed to ensure virologic suppression and retention of CAYHIV on treatment, taking into account the specific opportunities and challenges faced at each stage of their lives. However, the lack of age-disaggregated data in these age groups hampers the ability of programmes to identify gaps, tailor services towards CAYHIV of different ages and monitor progress.

To address the gaps in outcome ascertainment among CAYHIV and assess risk factors for VNS in adolescents, this thesis used data from the International epidemiology Databases to Evaluate AIDS Southern Africa (IeDEA-SA) collaboration. IeDEA-SA is a large HIV/AIDS observational cohort collaboration spanning six countries in Southern Africa, providing valuable insight from diverse

ART programmes and settings in the region. It is one of seven regional collaborations established in 2006 by the US National Institutes of Health to provide a rich resource for globally diverse HIV data [72]. Therefore, IeDEA-SA pediatric data are a valuable asset for examining outcomes among CAYHIV. This thesis explores virologic outcomes among adolescents who remain in care and outcomes from tracing and linkage studies among CAYHIV initially reported as LTFU, and updates programme-level mortality by incorporating the ascertained outcomes from linkage and tracing studies in Southern Africa.

1.7 Aim and Objectives

This thesis aims to describe the characteristics and outcomes after starting ART (HIV virologic response, mortality and retention) of CAYHIV in Southern Africa with additional outcome ascertainment from linkage and tracing studies among those reported as LTFU at the original site of ART initiation.

The specific objectives of this research are: -

- To describe the virologic responses among adolescents living with HIV in South Africa through two main analyses:
    - describe virologic outcomes among APHIV in early adolescence (10-14 years) in South Africa.
    - describe VNS and early reported LTFU among adolescents initiating ART between 15-19 years of age in South Africa, and separately among pregnant adolescents.

- To determine the “true” outcomes of CAYHIV on ART reported as LTFU at the original sites of ART initiation and to identify factors associated with these outcomes through two analyses:
    - multi-country physical tracing studies.
    - linkage to the WCPHDC.

- To correct programme-level mortality estimates among CAYHIV after incorporating outcomes from tracing and linkage studies separately; and to assess factors associated with these outcomes.

1.8 Data sources, data management, ethics review and funding

Data sources

International epidemiology Databases to Evaluate AIDS-Southern Africa (IeDEA-SA) collaboration

Data in this thesis were obtained from sites within the IeDEA-SA collaboration [72, 73]. These sites collect routine clinical data on PLWH in Southern Africa, from countries which are some of those most affected by HIV globally. The sites are predominantly primary healthcare facilities or public hospitals offering ART in six countries across Southern Africa (Lesotho, Mozambique, Zimbabwe, Malawi, Zambia, and South Africa).

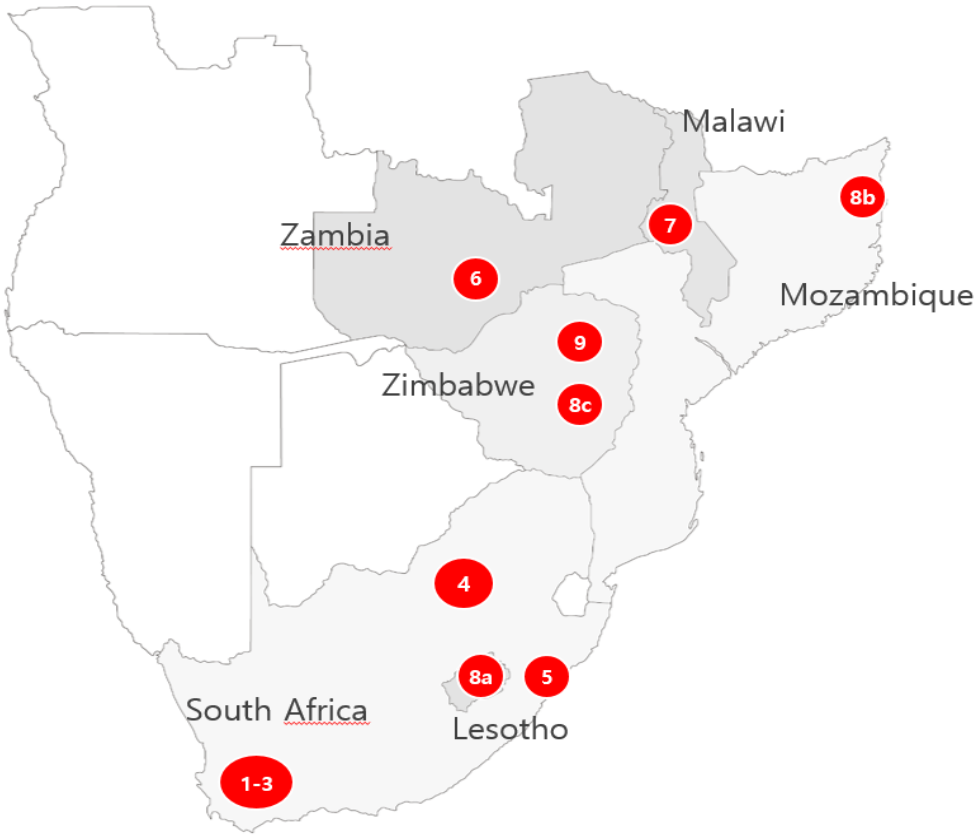

Figure 1-1 : IeDEA-SA collaboration sites [72]

Key:

1)Western Cape Provincial Health Data Center (WCPHDC), South Africa

1a) WCPHDC – Gugulethu (Desmond Tutu HIV Centre), South Africa

1b) WCPHDC – Khayelitsha ART Programme, South Africa

1c) WCPHDC – Red Cross War Memorial Children's Hospital, South

Africa

1d) WCPHDC – Tygerberg Hospital, South Africa

2) Aid for AIDS, South Africa

3) Kheth'Impilo AIDS Free Living, South Africa

4) WITS Health Consortium (WHC), South Africa

4a) WHC – Harriet Shezi Children's Clinic, South Africa

4b) WHC – National Cancer Registry (NCR) – SAM study, South Africa

4c) WHC – Rahima Moosa Mother and Child Hospital, South Africa

4d) WHC – Themba Lethu Clinic, South Africa

5) Hlabisa – Africa Health Research Institute, South Africa

6) Centre for Infectious Disease Research in Zambia (CIDRZ), Zambia

7) Lighthouse Trust, Malawi

8a) SolidarMed, Lesotho

8b) SolidarMed, Mozambique

8c) SolidarMed, Zimbabwe

9) Newlands Clinic (Ruedi Luethy Foundation), Zimbabwe

The Western Cape Provincial Health Data Centre (WCPHDC)

The WCPHDC consolidates patient-level data across government services in the Western Cape using unique identifiers, investments in patient registration systems, and the development of administrative and clinical digital health systems [68]. Data sources include hospital information systems providing records of any visits to hospitals or primary care facilities, laboratory and pharmacy data and electronic registers for HIV and tuberculosis (TB).

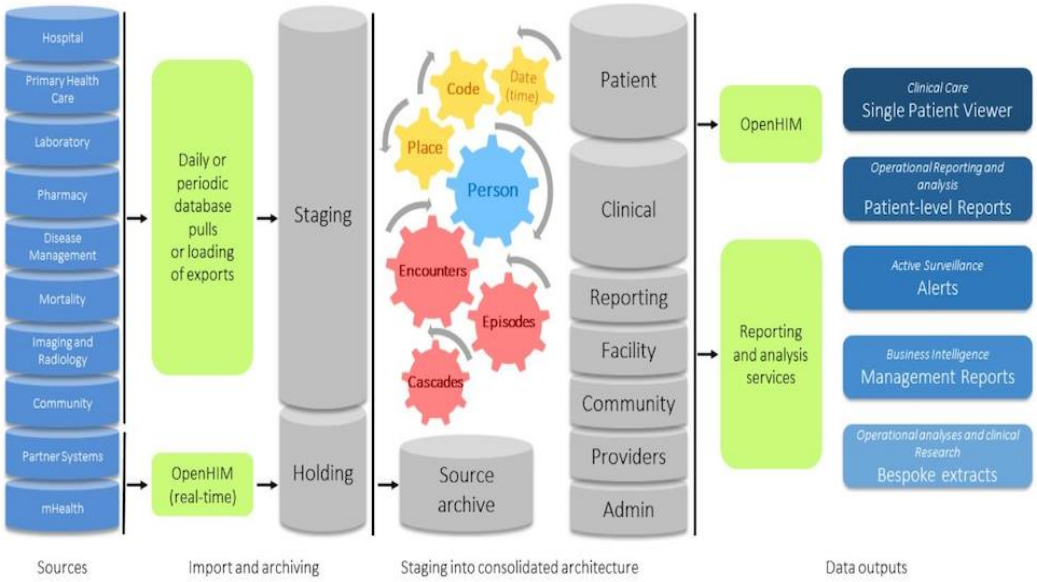

Figure 1-2: Architecture of the Western Cape Provincial Health Data Centre (WCPHDC)

Data management

Data submitted to IeDEA-SA are managed at data centres at the University of Cape Town (UCT), South Africa, for sites within South Africa, and the University of Bern, Switzerland, for sites outside South Africa. Anonymised, routinely collected patient data are periodically received in a standardised data transfer protocol agreed upon with the different sites. The data are then merged into one database by the data managers at the data centres. All analyses are subject to a concept proposal and approval process that ensures that data are only used for approved concepts. All individuals working with IeDEA data are required to do human subjects protection training before accessing patient data. Within the global IeDEA consortium, the IeDEA data harmonisation working group has standard operating procedures and a system for data protection and sharing to prevent confidentiality breaches.

Ethics review

The IeDEA-SA collaboration has approval from the University of Cape Town Faculty of Health Sciences Research Ethics Committee (HREC) for analyses utilising data from IeDEA-SA (HREC Ref Number: 084/2006) sites. Additional ethics amendments were sought for tracing and linkage data that are not routinely collected and for use of the data for the PhD (HREC Ref Number: 059/2021).

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1.9 Thesis overview, context and structure

The thesis consists of chapters including an introduction, a literature review, five results chapters and a discussion chapter. The introduction chapter provides a broad context of the challenges and negative HIV treatment outcomes experienced by CAYHIV. It outlines the objectives and rationale of the thesis, along with the data sources used. The literature review summarises the existing literature relating to outcomes of CAYHIV along the HIV testing and treatment continuum. The subsequent results chapters focus on different objectives of the thesis in three papers that have been published, one has been accepted for publication and one paper is under review at separate accredited peer review journals. They present results from routinely collected data and tracing data among CAYHIV in Southern Africa who initiated ART between 2004-2019.

Objective 1 is explored in Chapters 3 and 4. Chapter 3 examines the virologic response of younger adolescents aged 10-14 years living with perinatally acquired HIV as they progress through early adolescence. Chapter 4 explores VNS and early reported LTFU among older adolescents aged 15-19 years, with a sub-analysis among pregnant adolescents. Objective 2 is addressed in Chapters 5 and 6. Using results from the tracing study, Chapter 5 examines outcomes among CAYHIV reported as LTFU at their ART initiation sites. Through linking their unique health records to the WCPHDC, Chapter 6 explores outcomes among CAHIV reported as

LTFU in the WC. Objective 3 is addressed in Chapter 7 which compares mortality among CAYHIV obtained from tracing and linkage studies and then corrects programme-level estimates using additional mortality data ascertained from tracing and linkage. Finally, the discussion (Chapter 8) synthesises key findings and offers strategies and alternative approaches to improve outcomes of VS, survival and retention among CAYHIV.

CHAPTER 2 Literature Review and Research gaps

2.1 Overview

This literature review aims to provide context for this thesis with a focus on virologic outcomes among adolescents, LTFU, outcomes among CAYHIV reported as LTFU, correction of mortality estimates in all CAYHIV on ART after incorporation of true outcomes in those reported as LTFU, and factors associated with mortality and both reported and true LTFU among CAYHIV.

Definitions

To ensure clarity, the following definitions are used throughout this review:

- Children: Ages <10 years or 0-14 years (term used interchangeably as both these definitions are widely used in the literature reviewed).
- Adolescents: Ages 10-19 years.
- Younger adolescents: Ages 10-14 years.
- Older adolescents: Ages 15-19 years.
- Young adults/youth: Ages between 20-24 years or 15-24 years (terms used interchangeably, specifying age range when necessary).
- ART: Regimen of at least three drugs from two different classes.

The review aims to report on the following items and identify the research gaps.

- Virologic outcomes among adolescents living with HIV and factors associated with these outcomes.
- Reported LTFU and true outcomes (death, transfer, true LTFU) among CAYHIV reported as LTFU and subsequently traced or linked.
- Updating mortality estimates by incorporating outcomes in those reported as LTFU from tracing or linkage studies.
- Factors associated with mortality and true and reported LTFU among CAYHIV.

The literature review reports findings from key studies in SSA on virologic suppression among adolescents and challenges of LTFU in the scaling up of CAYHIV programmes, outcomes among CAYHIV on ART who are reported as

LTFU, correcting of mortality estimates for true outcomes among CAYHIV who are reported as LTFU, and factors associated with mortality and reported LTFU. Some studies are among adult cohorts due to limited studies that disaggregate children and youth age categories. Some studies from countries outside SSA will also be included for a contextual comparison. This review is not a systematic review of all available studies but rather a summary of the necessary studies that give context to the objectives of this thesis.

Search strategy

A search in PubMed was conducted for literature on outcomes of virologic response among adolescents, LTFU, outcomes among those who are reported as LTFU, mortality at the facility level, and mortality after correcting for outcomes in those reported as LTFU. The search was restricted to articles published in English between 2013-2023. Other relevant articles were obtained either from article reference lists or Google Scholar. Reports from UNAIDS, UNICEF and WHO are also included. The first search (Table 1) was about virologic outcomes among adolescents, and the following terms were used: HIV, adolescents, adolescents living with HIV, viral load outcomes, virologic outcomes, viral suppression, viral non-suppression, virologic response, treatment response, virologic failure, treatment adherence. The second search (Table 2) was about LTFU, retention in care and mortality among CAYHIV, and the following terms were used: loss to follow-up, antiretroviral therapy, children, adolescents, young adults, HIV, retention in care, attrition, patient drop out, mortality, death(s), and treatment outcomes.

2.2 Virologic outcomes among all adolescents living with HIV

Adolescents living with HIV can be categorised into those who acquire HIV perinatally or non-perinatally, and each group faces unique challenges along the continuum of care [11, 74-76]. Within these categories, there are further disparities based on the age of the adolescents (younger (10-14 years) vs. older (15-19 years)), with younger adolescents mainly comprising individuals with perinatally acquired HIV [74, 77]. Younger adolescents face challenges related to orphanhood, delayed puberty, chronic illness, medication fatigue, and transitioning from pediatric to adult services and autonomous care [32, 76, 78, 79]. Older adolescents may face similar

challenges as the younger adolescents but these are compounded by additional issues such as negotiating safe sexual practices, adherence, disclosing their HIV status to sexual partners or peers, and the added concern of pregnancy [76, 79]. Additionally, gender disparities exist, with similar proportions of males and females among younger adolescents and a higher proportion of females among older adolescents [5, 22, 77].

Virologic outcomes are key indicators of treatment success and are associated with long-term health outcomes among PLWH [5]. High treatment adherence is necessary for virologic suppression [79, 80]. Individuals with fully suppressed VLs have a lower risk of virologic failure, morbidity, and mortality [26, 81, 82]. Moreover, having a suppressed VL reduces the risk of sexual and vertical HIV transmission. VS may also imply that these individuals are retained on ART, which has both individual and public health benefits. However, adolescents living with HIV have consistently shown poorer virologic outcomes than children or adults despite the scale-up of pediatric HIV treatment and care programmes [16, 83, 84]. A global systematic review on VS among adolescents aged 10-19 years on ART from Africa, North America, Europe, Asia, and Latin America reported varying proportions of VS at 12 months (among six studies that reported this proportion) after ART initiation, ranging from 27% in South Africa to 89% in Uganda [84]. Another systematic review of studies conducted in South Africa, which has the highest number of adolescents living with HIV globally, reported that adolescents consistently had lower rates of virologic suppression than other age groups [8]. As highlighted in this review, a contributing factor to the low rate of VS among adolescents is the limited number of adolescents receiving ART. According to the review, only 14% of adolescents were reportedly on ART in South Africa in 2013. Furthermore, prior to the implementation of Universal Test and Treat ((UTT), a policy that promotes initiation of ART for all people testing positive for HIV, regardless of their CD4 count), the review estimated that only 10% of youth living with HIV achieved VS in 2013 (encompassing ages 9-29 years, extending beyond the adolescence phase).

Virologic suppression among adolescents living with HIV and on ART

A recent large-scale study across the seven IeDEA regional cohorts analysing data from children, adolescents and adults starting ART between 2010 and 2019 found that adults with HIV were close to achieving the global target of 95% VS [85]. However, progress in achieving VS among children and adolescents has been much slower, with only 59% of children and adolescents on ART having achieved VS three years after ART initiation in 22 countries.

A study in South Africa examining the HIV care cascade among 1,080 adolescents aged 10-19 years who initiated ART between 2000-2017 in the Eastern Cape found that only 48% of the entire cohort were fully suppressed at their most recent VL (VL<50 copies/mL) [86]. Only 51% of the cohort had a VL done in the last 12 months, hence only 23% of the total cohort could be considered confirmed suppressed in the year preceding study closure [86]. Similarly, a study in Cameroon conducted between October 2016 and August 2017 comparing VS during the era of UTT among children, adolescents and adults reported that only 53% of adolescents aged 10-19 years achieved VS compared to 81% of adults and 76% of children [87]. On the other hand, a cross-sectional study in the same country, among 280 adolescents aged 10-19 years who initiated ART in the same period (2009-2019), found a VS rate of 88% [88]. The high VS rate in this study may be attributed to the intervention of enhanced adherence counselling and the fact that these adolescents were actively recruited at a clinic visit; hence, only retained adherent adolescents were included. In Uganda, the VS rate among 567 adolescents aged 13-19 years who initiated ART between 2009-2019 was 69%, comparable to the national age-specific rate among adolescents in 2017/2018 of 72% [89].

Even with adherence counselling, adolescents still have lower VS rates than adults. For example, a study done in Swaziland [90] among adolescents aged 10-19 years reported that adolescents had the highest adjusted odds of having a detectable VL with three-fold higher odds than adults (adjusted odds ratio (OR): 3.2 (95% confidence interval (CI): 2.2, 4.8)) after enhanced adherence counselling, with only 65% achieving VS.

Table 2.1: Literature on virologic suppression among adolescents in antiretroviral therapy (ART)

Author, year	Country	Study /ART initiation period	Sample size of adolescents in the study	Adolescent age group in years	Perinatally acquired vs. not	Study design	Routinely available VL or measured by study	Definition of virologic suppression (copies/ml)	Proportion suppressed at varying periods
Ferrand et al., 2016 [84]	Systematic review (20 articles)	2004-2014	4794	10-19	Mixed	50% cohorts, 50% Cross-sectional	Both	Several	27-89% at 12 months
Han et al., 2021 [85]	Global (148 sites)	2010-2019	7050	10-17	Not specified	Cohorts	Routine	VL<1000	Adjusted: 64% (including children) at 1 year, 59% at 3 years
Zanoni et al., 2016 [8]	Systematic review of South Africa articles	2005-2015	867283	15-19 (full group: 15-24)	Not specified	>50% cohorts	Routine		10% (15-24)
Haghighat et al., 2021 [86]	South Africa	2014-2015	1080	10-19		Cohort	Routine	VL<1000	23%
Evans et al., 2013 [18]	South Africa	2004-2010	652	10-19		Cohort	Routine	VL<400	10-14: 70% 15-19: 83%
Anderson et al., 2019 [91]	South Africa	2002-2005	127	≥10	Perinatal	Cohort	Routine	VL<400	80%
Jobanputra et al., 2015 [90]	Swaziland	2012-2013	588	10-19	Not specified	Cross-sectional	Routine	VL<100	65%
Makadzange et al., 2015 [92]	Zimbabwe	2004-2011	418	10-19		Cross-sectional	Routine	VL<1000	10-14: 60% 15-19 65%
Djiyou et al., 2023 [88]	Cameroon	2009-2019	280	10-19	Mixed	Cross-sectional	Measured	VL<1000	88%
Fokam et al., 2017 [93]	Cameroon	2016	145	10-19	Perinatal	Cross-sectional	Routine	VL<50	71%
Fokam et al., 2019 [87]	Cameroon	2009-2019	105	10-19	Not specified	Cross-sectional	Routine	VL<1000	53%
Salou et al., 2016 [94]	Togo	2014	136	11-19	Perinatal	Cohort	Measured	VL<1000	11-14: 52% 15-19: 39%
Maena et al., 2021 [89]	Uganda	2009-2019	567	13-19		Cross-sectional	Routine		69%
Mwangi et al., 2021 [95]	Kenya	2009-2019	908	10-19	Not specified	Cross-sectional	Routine	VL<1000	80%
Desta et al., 2020 [96]	Ethiopia	2009-2019	420	15-19	Not specified	Cross-sectional	Routine	VL<1000	49%

ART: Antiretroviral therapy, VL: Viral load

Virologic outcomes among adolescents on ART by age (younger vs. older)

Older adolescents living with HIV on ART have been reported to have poorer virologic outcomes than younger adolescents, often with poorer adherence [83]. A Ugandan study found that older adolescents aged 16-19 years were nearly twice as likely to experience VNS compared to those aged 13-15 years [89]. Similarly, a study in Ethiopia among nearly 20,000 PLWH found that older adolescents aged 15-19 years were almost five times more likely to experience VNS than adults aged ≥50 years [96]. However, a study done in Kenya found similar rates of VS between older (81%) and younger (79%) adolescents [95]. In South Africa, a study conducted in five urban and two rural HIV clinics revealed that older adolescents had nearly twice the risk of VNS compared to older adults and three times the risk of virologic failure [18]. These findings may be attributed to various factors. Older adolescents have often been on treatment for longer periods, which can lead to treatment fatigue and poorer adherence [96]. Additionally, older adolescents are transitioning from pediatric to adult services, gaining increased autonomy over their health, experiencing higher peer pressure, and being more sensitive to stigma. These factors and substance use may contribute to poorer virologic outcomes among this age group [92].

Virologic outcomes among adolescents on ART by mode of HIV transmission (perinatal vs. non-perinatal)

The evidence is conflicting regarding virologic outcomes among APHIV and AnPHIV [97]. A study done in the Netherlands among adolescents and young adults who entered care before the age of 25 years, reported higher rates of virologic failure among individuals with perinatally acquired compared to the individuals with non-perinatally acquired HIV (19% vs 7%) in 2020 [97].

In contrast, a study done in South Africa among children with perinatally acquired HIV who had been on treatment for at least ten years (median time on treatment: 12.2 years) found that 80% of them had attained VS (defined as VL <400 copies/ml) at the last assessment [91]. Another study in Togo reported that 52% of children and adolescents with perinatally acquired HIV in the study experienced virologic failure (defined as VL>1000 copies/ml) [94]. APHIV who enter adolescence with suppressed VLs may experience deteriorating outcomes compared to AnPHIV and

adolescents who only initiate ART during adolescence [98]. Among APHIV in Cameroon, only 36% self-reported adhering to their medications in the previous 14 days, 71% achieved VS, and 52% achieved sustained VS (defined as maintaining a history of VS=VL<50 copies/ml) [93]. Poor VS among adolescents is not unique to SSA. A study in the United States among youth living with non-perinatally acquired HIV reported high rates of virologic failure (29%) at a median time of 12 months from achieving VS [99].

Effects of dolutegravir on virologic outcomes among adolescents living with HIV

Dolutegravir (DTG) has recently been recommended as the primary third drug in ART regimens for all populations, including children and women of childbearing age [81, 100], due to characteristics such as high genetic resistance barrier, cost-effectiveness, tolerability, fewer side effects and rapid VS [101-103]. South Africa has also recently adopted DTG for all PLWH, irrespective of treatment experience [104]. However, with the increasing use of DTG among adolescents, it is important to consider the potential risks associated with this transition in pediatric populations. Non-adherence has been identified as the main reason for treatment failure in individuals taking DTG, and given the unique adherence challenges faced by adolescents, there is a risk of treatment failure even with DTG [105, 106].

A study done in the Democratic Republic of Congo found that one in four patients on a DTG-based regimen did not attain VS within six to 12 months [107]. Factors associated with this lack of VS included advanced disease stage, adolescence and young adulthood. On the other hand, a study conducted in Malawi reported a high proportion (>95%) of participants achieving VS one year after transitioning to DTG [108]. However, they also observed persistent VL failure among individuals with high pre-transition VL, ongoing adherence challenges, and possible pre-existing resistance from nucleoside reverse transcriptase inhibitors. Therefore, monitoring VL among treatment-experienced or naïve adolescents is important to ensure early detection of suboptimal adherence and/or resistance that could lead to treatment failure with DTG.

Factors associated with virologic suppression among adolescents living with HIV

Many factors associated with VS overlap with factors related to treatment adherence, as ART aims to suppress viral replication in the body [109]. A cross-sectional study conducted in South Africa among 9,386 adolescents living with HIV across 136 ART clinics found that females had 21% higher odds of achieving VS (defined as VL <1000 copies/ml) than males. Those with a recent CD4 count >200 cells/µL at the last ART visit had nearly three times higher odds of VS than those with a recent CD4 count <200 cells/µL [110]. Other studies have reported similar factors associated with increasing odds of VS, including younger age at ART initiation, less advanced HIV disease (WHO stage 1 compared to 2 or higher), good adherence to ART, formal education, shorter duration on ART (between 6-12 months), being on first-line ART compared to second-line or higher, and having no co-morbidities [89, 92, 95, 111].

The studies reviewed in Table 1 report varying rates of VS among AHIV on ART, but none reported reaching the target of 95% VS among those on ART. This emphasises the vulnerability of adolescents living with HIV and underscores the importance of implementing targeted interventions to improve virologic outcomes in this age group.

2.3 Research gaps

The variations in virologic outcomes among different subgroups of AHIV highlight the need for tailored interventions. However, many HIV programmes still provide interventions not specifically designed for this population and follow a ‘one-size-fits-all’ approach. Some HIV programmes classify younger adolescents as children and older adolescents as adults or young adults without considering their unique needs [77]. The lack of standardised definitions for different age groups within the adolescent populations leads to inconsistent categorisations across studies and settings which makes comparing outcomes challenging. Moreover, limited evidence is available to comprehensively examine virologic response among AHIV in SSA.

In addition, there is limited evidence from the UTT era where all adolescents are eligible for ART. The transition notably impacted adolescents, given that a substantial proportion of them were previously ineligible for ART, and the group who became eligible under UTT may have different outcomes from previous studies [112, 113]. In recent times, there has been a growing number of adolescents with perinatally acquired HIV who would have started more effective ART earlier in life with the shift to earlier polymerase chain reaction (PCR) diagnosis and ART for all infants under two (2010) and then under five years of age (2015). Their outcomes may differ from APHIV from earlier periods who would have only started ART later in life and been a cohort of survivors from the pre-ART era.

2.4 Reported LTFU and outcomes among CAYHIV

Ensuring consistent and long-term engagement with the healthcare system is crucial for achieving optimal HIV treatment outcomes among CAYHIV [114]. However, a major obstacle to the expansion and improvement of HIV treatment programmes is the substantial proportion of CAYHIV reported as LTFU throughout the HIV continuum of care [115, 116]. CAYHIV who are no longer in care are likely not on ART, so they are at increased risk of VNS, disease progression and mortality [55, 70]. Most CAYHIV reported as LTFU get lost during the first year after ART initiation [117]. Reported LTFU, a commonly used indicator in most ART programmes, limits accurate ascertainment of programme outcomes as reported LTFU can mask a range of outcomes, including mortality, self-transfers, data management and entry errors within the facility, as well as stopping of ART and true LTFU [53-56]. There has been an upward trend in reported LTFU rates among pediatric and adult populations, underscoring the importance of addressing this challenge to attain optimal treatment outcomes and to know what actually happened to these patients [56, 118].

Table 2.2: Literature on reported loss to follow-up (LTFU) among children, adolescents and young adults with HIV (CAYHIV) and true outcomes from tracing studies of those reported as LTFU

Author, year	Country	Study/ ART initiation period	Sample size of CAYHIV[a]	Children (0-9 years)	Adolescents (10-19 years)	Young adults (20-24 years)	Definition of reported LTFU	Reported LTFU rate/ proportion	Mortality rate (without accounting for outcomes in those traced)	Number and proportion of those LTFU who were traced	Outcomes among traced
Leshargie et al., 2022 **[115]**	Systematic review and meta-analysis	2005-2020	285,564	-	10-19	-	Missed 3 health facility visits or ART pick-ups, OR ≥90 days without follow-up	15%	-	-	-
Fox and Rosen., 2015 **[55]**	Systematic review (LMIC)	2008-2013	55,904 at ART initiation	Mean age: <18	Mean age: <18	-	Each report's definition	63%	37%	-	-
Slogrove et al., 2018 **[11]**	12 Global cohorts	1982-2015	38,187 entered care before 10 years	-	10-15	-	No observed visit for more than 365 days before the last observed visit of the cohort	11% at 15 years	3% at 15 years	-	-
Leroy et al., 2013 **[119]**	Asia and Africa cohorts	-	13,611 at ART initiation	0-9	10-14 at	-	-	Asia: 4% Southern Africa: 9% East Africa: 14% West Africa: 22%	East Africa: 4% Asia: 5% Southern Africa: 6% West Africa: 7%	-	-
KIDS-ART-LINC, 2008 **[118]**	Multicentre study in SSA	-	2,405 at ART initiation	Median age: 2 (2.1-8.4)	-		No visit for ≥ 6 months from the last recorded visit and database closure date	10% at 2 years	7% at 2 years	-	-

Jerene et al., 2019 **[120]**	Ethiopia	2005-2013	2,058 at enrolment into HIV care	0-9	10-19	-	the patient did not have a follow-up visit for at least 30 days from the last scheduled appointment.	ON ART: 14%	6%	-	-
Chandiwana et al., 2018 **[121]**	South Africa	2005-2014	135 at ART initiation	0-9	10-12	-	Non-attendance at the clinic for ≥30 days but <90 days after the scheduled visit	36%	-	-	-
Kranzer et al., 2017 **[122]**	Zimbabwe	2005-2009	2,273 at ART initiation	5-9	10-19	-	Having a missed scheduled appointment by ≥2 months	8%	-	-	-
Davies et al., 2017 **[47]**	South Africa	2004-2014	460 at transfer	-	10-19	-	-	1 year: 10% 3 years: 16%	-	-	-
Ahonkhai et al., 2016 **[123]**	Nigeria	2009-2011	354 at ART initiation	-	15-19	20-24	Patients with > 3 months between consecutive visits	55%	-	-	-
Sengayi et al., 2013 **[62]**	South Africa	2004-2011	4,266 at ART initiation	0-9	10-12	-	≥6 months from the last contact with the clinic before the database closure	7%	-	-	-
Nglazi et al., 2012 **[28]**	South Africa	2002-2009	883 at enrolment into care	9	10-19	20-24	Not specified	7%	-	-	-

Chammartin et al., 2018 **[56]**	Systematic review (ssa)	2009-2015	7,377 at last clinic visit	2 studies included children	2 studies included children	20-24	The patient did not return to the clinic within 2 weeks to 3 months	Varying	-	Only among lost and traced	Died: 22% Alive and stopped art: 23% Transferred out: 15% Retained in care: 9% True ltfu: 32%
Abuogi et al., 2016 **[67]**	Systematic review (LMIC)	2006-2014	78,424 at ART initiation	ART initiation<10 years	-	-	As per the study definition	4082/5558 (73%)	1476/5558 (27%)	12/35 studies	-
Ballif et al., 2021[∞] **[52]**	Lesotho Malawi Mozambique South Africa Zambia Zimbabwe	2014-2017	1,098/ 3,256 at last clinic visit	0-9	10-19	20-24	Malawi: Missed appointment for ≥ 60 days Others: ≥90	all	-	2,294	In care: 34% out of care: 19% unknown care status: 4% Silent transfers: 17% Died: 9% True LTFU: 41%
Geng et al., 2015 **[70]**	Uganda Tanzania Kenya		(mostly adults) at last clinic visit	-	-	20-24	≥90 days late and not returned before database closure	3150 (18%)	-	579 (18%)	497 (86%) successfully traced Alive: 69% Corrected: In care: 69% Official Transferred: 4% Self-transfer: 10% Alive and out of care: 6% Died: 12%

Haghighat et al., 2021 **[86]**	South Africa	2000-2017	1,080 at ART initiation	-	10-19	-	Participants without any available clinical record	38%	-	-	Corrected LTFU (corrected for mortality and self-transfers):17 , corrected mortality (corrected for transfers): 3%
Mutanga et al., 2019 **[124]**	Zambia	2003-2015	1,039 at ART initiation	0-9	10-15	-	No clinical or pharmacy contact for ≥90 days from last missed visit	167 (16%)	7%	151/167 (90%)	Died: 26% Defaulted: 47% Self-transfer: 13% Continued treatment with gaps:14%
Saumu et al., 2019 **[117]**	Kenya	2010-2015	261 on follow-up	0-9	10-14	-	Not returned to care for ≥3 months	45 (17%)	5%	44/45 (98%)	Dropped out of care: 75%
Rachlis et al., 2015 **[125]**	Kenya	2009-2011	361/2,540 at last clinic visit	-	-	-	Missing a clinic visit for ≥ 3 months	-	-	-	Died: 21% Out of care: 29% Self-transfers:25 %
Ardura-garcia et al., 2015 **[116]**	Malawi	2006-2010	985 at ART initiation	0-9	10-15	-	Verified, missed, and scheduled appointment for ART collection of 3 weeks or more	251 (26%)	-	201/251 (80%)	Died: 11% Stopped ART:25% Transferred out:26% Still on ART:37%

[a]Enrolment varies for the different studies (some are at ART initiation, entry into HIV care, last visit at the clinic or at transfer), [∞] Parent study for the CAYHIV analysed in my study, ART: antiretroviral therapy, LMIC: Low and middle income countries, SSA: Sub-Saharan Africa

Reported LTFU among children aged (0-9 years, or 0-14 years)

In 2013, the global estimate of reported LTFU among CHIV was 14% and 28% after one and two years of ART, respectively [126]. In SSA, the IeDEA pediatric collaboration found an overall reported LTFU rate of 12% by 18 months after ART start among children who initiated ART between 1995-2009 aged <16 years, with estimates varying between 4% in Asia and 22% in West Africa [119]. A recent systematic review of 12 studies among CHIV in resource-limited settings reported LTFU rates that ranged from 5% to 29% during the first year of ART initiation [67]. In South Africa, reported LTFU rates varied greatly between studies among children who initiated ART aged ≤12 years, with one study reporting a 12-month cumulative probability of 7% for those who initiated ART between 2004-2011 and another reporting a cumulative probability of 36% for those who initiated ART between 2005-2014 [62, 121]. In Malawi, the overall proportion of reported LTFU among children initiating ART aged <15 years was 25%, with rates of 8%, 13% and 19% at six, 12 and 24 months respectively [116].

Reported LTFU among adolescents aged 10-19 years

Adolescents experience the highest rates of reported LTFU compared to children and adults [28, 120, 122]. The likelihood of reported LTFU among adolescents varies depending on their mode of infection and age [77], with older adolescents being more prone to LTFU than younger adolescents. The developmental and psychosocial changes during adolescence, such as increased sensitivity to peer pressure and fear of disclosing their HIV status to peers or sexual partners, can contribute to medication non-adherence and missed clinic appointments [122]. A systematic review and meta-analysis evaluating reported LTFU among adolescents found an overall pooled estimate of 15% [115]. Older adolescents aged 15-19 years were 43% more likely to experience LTFU compared to young adolescents aged 10-14 years. Another study in South Africa revealed that young adolescents (10-14 years) had a 57% lower likelihood of LTFU compared to adults, while older adolescents (15-19 years) and young adults (20-24 years) had a significantly higher likelihood of LTFU (78% and 63% respectively) compared to adults, specifically within 12 months from ART initiation [18]. Transition between treatment sites may also contribute to high reported LTFU in this population.

Davies et al. reported that a high proportion (81%) of adolescents successfully transitioned between facilities in adolescence, with the majority (95%) reaching their transfer site within 18 months. However, the proportion retained declined slightly between one and three years after the transfer, from 90% to 84% [47].

Reported LTFU among youth aged 15-24 years

Research in this population shows significant variation based on sex and mode of transmission. Those with HIV in this age group mostly have non-perinatally acquired HIV and most are female [5, 76, 77]. A study conducted in Nigeria comparing outcomes between youth and older adults (>25 years) found that 89% of the group were female, compared to 65% of the older adult group [123]. In this study, 67% of youth were reported to be out of care (defined as having more than three months gap between consecutive clinic visits) by the end of the follow-up period (median 1.8 years). In South Africa, youth had the worst outcomes compared to younger adolescents and adults [18]. The rate of LTFU among older adolescents was 41%, while for young adults, it was 35%. In Ethiopia, the highest risk of LTFU was among those aged 15-19 years, with an adjusted hazard ratio (aHR) of 3.1 compared to children aged 0-9 years [120].

2.5 Ascertained outcomes among CAYHIV reported as LTFU and subsequently traced or linked

To determine outcomes among those reported as LTFU, tracing and linkage have been used, but mostly among adult patients. A larger proportion of patients reported as LTFU may have actually died compared to those retained in care; hence, updating programme-level mortality estimates to account for the true outcomes of those LTFU is essential for obtaining accurate mortality estimates [56, 71].

Tracing is a labour-intensive exercise that involves contacting a sample or all of the patients who miss their scheduled visits through phone calls, text message reminders and home visits for those who cannot be reached by phone [52, 70, 124]. In sample-based tracing, researchers obtain a list of all PLWH who are reported as LTFU and

select a representative sample for tracing using an appropriate sampling design [127]. The tracing team can include peer patients, nurse counsellors and social and community workers. Among studies that traced children who were reported as LTFU, a substantial proportion were found to have died. For example, in a systematic review by Abuogi et al., 27% of traced LTFU children had died [67]. Similarly, in a study in a rural hospital in Kenya, a very high mortality rate of 14% was observed among traced children who were initially reported as LTFU [117]. Other outcomes among those reported as LTFU in this study included 75% being alive but out of care and 11% self-transferring to other facilities. In Zambia, among children who were traced (151/167), 26% had died, 47% had stopped treatment, 13% had self-transferred to other ART clinics, and 14% had continued treatment with gaps [124]. In a study among adolescents in South Africa, almost 40% of those reported LTFU had been misclassified, with 7% having died and 31% having self-transferred [86]. Among 201 children who were reported as LTFU and traced in Malawi, 11% had died, 25% had stopped ART, 26% had transferred out (officially or silently), and 37% were still on ART in the same facilities [116].

Linkage involves using unique patient identifiers or national identification numbers that can be linked to other health information exchanges or vital registration systems within a country [68, 128]. However, many countries in SSA lack robust vital registration systems and only a few have implemented unique patient identifiers and established health exchange information systems [128]. As a result, tracing is the most used method for determining patient outcomes.

Data on outcomes of CAYHIV reported as LTFU obtained through linkage to health registers are scarce. However, linkage effectively identifies successful official transfers and self-transfers within the healthcare system [47]. Given the increased rates of transfers or transitions between care providers in this population, it is crucial to gather accurate data on the true outcomes among those reported as LTFU.

2.6 Correcting mortality estimates by incorporating outcomes from tracing or linkage studies

CAYHIV account for approximately 5% of all PLWH but contribute 15% of AIDS-related deaths [43]. Mortality is an important measure of programme effectiveness, but facility-level mortality may be underestimated if true outcomes among those reported as LTFU are not accounted for [69, 71, 117]. In a study analysing data from several patient cohorts, it was reported that the probability of death four years after ART start was six times higher among patients who were reported as LTFU (21%) compared to those who were retained in care (3%) [56]. Policy decisions using estimates that do not account for the true outcomes of those reported as LTFU may be incorrectly informed and lead to the misallocation of scarce resources, for instance, as mentioned earlier, when used in the UNIADS SPECTRUM model which informs global HIV/AIDS targets [57-59]. Corrected mortality estimates among CAYHIV are important because CAYHIV may be reported as LTFU when in fact they died and were not able to attend their scheduled visit. Conversely, CAYHIV who become LTFU and are still alive at the time of their next scheduled visit but do not return, may face a higher risk of mortality since they are out of care and have discontinued ART.

Research among adults living with HIV has shown that site-reported mortality may be underestimated by about 50% [129]. Tracing studies have reported higher mortality and lower true LTFU after incorporating outcomes from tracing. For example, in an adult tracing study in Tanzania, site-reported mortality was 13% before accounting for tracing outcomes, and it increased to 35% after incorporating tracing outcomes [130]. Similarly, in a South African study of adolescents with HIV who initiated ART before 2015, reported mortality and LTFU rates were adjusted to account for transfers and unreported deaths. When these corrections were made, the adjusted mortality rate was 3%, while reported LTFU reduced from 38% to 17% after 12 months from ART initiation [86]. Among patients reported as LTFU, 7% were found to have died.

There are limited data on outcomes of CAYHIV who are reported as LTFU, resulting in likely underestimation of mortality rates in this population. A systematic review

published in 2016 examining the retention of children with HIV during their first 12 months on ART reported that out of 35 studies, only 12 reported any attempts to locate children who were LTFU [67]. Importantly, none of these studies ascertained outcomes among children reported as LTFU. In studies that do ascertain outcomes in CAYHIV reported as LTFU, few report corrected estimates incorporating outcomes from tracing. For instance, efforts were made to trace those reported as LTFU at a rural hospital in Kenya. The hospital reported facility-level mortality (5% (13/261)) and mortality from those traced (14%) [117], but they did not present corrected mortality estimates. Similarly, in Zambia, the estimated facility-level mortality was 7% (71/1039) before tracing those who were reported as LTFU in whom mortality was 26%, but no corrected mortality was reported [124]. Nonetheless, a study from Malawi incorporated deaths ascertained through tracing with an increase in estimated mortality from 1.3 to 2.4 per 100 child years [116]. In their study, Kassanjee and colleagues used a simulation model based on the same tracing data that we used to adjust mortality estimates derived solely from programme data for the African regions within IeDEA consortium. However, this simulation was limited to CAHIV age <15 years and to deaths occurring within 180 days of the last ART visit and thus in participants assumed to still be on ART and did not examine longer-term mortality. They also did not examine the effect of incorporating outcomes in those reported as LTFU on associations of different CAYHIV characteristics with mortality.

Correction analyses require unique methods to pool outcomes among those retained in care and those obtained from tracing or linkage exercises. Most of these methods have been developed and used in adult populations, but there has been limited use in pediatric populations. These methods include inverse probability weighting (IPW) using logistic regression models to upweight outcomes among successfully traced or linked individuals to represent those who were not found or not traced [127]. Others include the nomogram method that uses a correction factor based on the proportion of patients LTFU at specific periods after ART start [131], the Frangakis & Rubin (F&R) method that constructs weights equivalent to the inverse proportion of patients traced out of all patients LTFU [132], and more recently the multiple imputation (MI) method suggested

by Schomaker et al. [71]. The accuracy of these methods in correcting mortality estimates and associations of risk factors for mortality depends on the effectiveness of capturing, measuring, and ensuring the accuracy, completeness and availability of patient variables associated with the probability of being included in the tracing sample or successfully found by the tracer. It also depends on correct model specification and level of outcome ascertainment among those reported as LTFU. A comparative analysis may assist in clarifying the difference between the methods when applied to CAYHIV [53].

Factors associated with mortality and reported LTFU among CAYHIV

Several factors have been identified as predictors of mortality and LTFU among CAYHIV. Since most studies examne outcomes of reported LTFU rather than true LTFU, factors associated with reported LTFU include factors associated with mortality, as reported LTFU will include a varying amount of unascertained mortality. These factors include caregiver dynamics, sex, age at ART initiation, duration on ART, calendar year of ART start, advanced HIV disease, disclosure status, and transition of care.

Caregiver dynamics

The role of caregivers is crucial in the treatment and care of CAHIV. These caregivers are responsible for administering treatment and ensuring access to HIV care services [62, 117, 121, 133]. However, the dynamics of the caregiver-child relationship can complicate this process. Many CAHIV face challenges such as orphanhood and being cared for by relatives or non-biological caregivers instead of their biological parents, which may increase their vulnerability to LTFU [117]. Caregivers may have financial constraints, experience issues related to stigma and non-disclosure and find it challenging to adhere to clinic appointments [121, 124, 134]. Caregivers not living with HIV themselves may also face difficulties scheduling their lives around the child's treatment needs. This highlights the need to provide caregivers with psychosocial support and implement family-centered care approaches that allow caregivers to have treatment days aligned with the child's schedule, reducing the burden of multiple visits.

In some cases, despite interventions, some caregivers are unwilling to support the child's treatment, and the child may become LTFU [124]. Also, the caregiver's education level has been found to be predictive of LTFU [117].

Biological Sex

Sex is another factor that is associated with both mortality and LTFU, although studies among younger children and younger adolescents report no sex differences. For example, a study conducted by the Collaborative Initiative for Pediatric HIV Education and Research (CIPHER), which examined outcomes among APHIV aged 10-15 years, found no differences in mortality among males and females [98]. Conversely, older adolescents and young females have been reported to be disproportionately affected by HIV and have poorer treatment outcomes compared to their male counterparts [5]. In an Ethiopian study focusing on mortality and LTFU among adolescents (10-19 years) and young children (0-9 years), females were nearly twice as likely to be LTFU in both univariate and adjusted analyses. However, there were no sex differences in the mortality analysis in this study [120]. This pattern may be attributed to sociocultural differences, with young females being forced into early marriages and involved in intergenerational relationships while dealing with the challenges of a chronic illness [135]. The analysis did not distinguish by pregnancy status, which may impact LTFU in older female adolescents.

Age at ART start /diagnosis

Age at ART initiation has been reported as a predictor of mortality and LTFU, with the greatest risk among children who initiate treatment below two years of age, followed by older adolescents aged 15-19 years [62, 119, 124, 136]. In their systematic review, Abuogi et al. reported that infants (age <1 year at ART start) and younger children were at higher risk of both LTFU and mortality after ART initiation compared to older children [67]. Before the implementation of UTT, this phenomenon could be partly explained by infants and young children starting ART being those whose condition deteriorated rapidly enough to fulfil the criteria for ART eligibility and thus had more severe and rapidly progressive disease than those who survived to only become eligible for ART at

older ages. Additionally, this vulnerability in younger children may be attributed to their underdeveloped immune response, making them more susceptible to severe disease progression and a higher likelihood of mortality [137].

Among adolescents and young adults, the risk pattern differs. Younger adolescents are more likely to die, while older adolescents and young adults are more likely to be LTFU [120]. The higher reported LTFU among older adolescents may be linked to changing location/ addresses to access education and/or employment opportunities, increased autonomy over their health, greater peer pressure, and being more sensitive to stigma, as previously discussed concerning poorer virologic outcomes [74, 77]. A study in South Africa among children initiating ART aged ≤12 years found that older age was predictive of LTFU compared to younger age [121]. The differences in the risk of age at ART start/diagnosis likely reflect a combination of mode of HIV acquisition and the timing of diagnosis or access to care [138].

Duration on ART

Most patients who become LTFU or die after starting ART experience these outcomes within the first year after ART initiation [56] [137]. A South African study found that the highest incidence of LTFU occurred within the first three months of starting ART, with a rate of 13.6 (95% CI: 11.6-16.1) per 100 child years [62]. In an Ethiopian study, over two-thirds of reported deaths occurred in the first year of follow-up [120], with 56% of the children and 44% of adolescents who were LTFU being lost in the first year of ART. A 12-year prospective cohort analysis of early mortality among adults and children in Ethiopia found that 89% of 326 deaths during the follow-up period happened within the first 24 months after ART initiation [44]. In Kenya, 65% of infants had dropped out of care within the first 18 months of follow-up, with 43% of these occurring in the first two months following ART start [139].

Calendar year of ART initiation

In recent years, there has been a decrease in mortality risk among CAYHIV, likely due to improvements in ART regimens and HIV care services as well as earlier diagnosis

and better access to treatment, resulting in longer survival [74, 102]. However, during the same period, the risk of reported LTFU has increased progressively [62, 140, 141]. This increase in reported LTFU may be explained by the rapid expansion of ART services, which has led to higher workloads for health workers and facilities, potentially impacting the quality of care provided [5, 7, 62, 142]. As a response, decentralised models of care have been adopted to bring HIV care closer to patients. However, the lack of standardised transfer policies has resulted in many self-transfers, leading to challenges in tracking patients and potentially contributing to higher reported LTFU rates [28, 47, 143-145]. Reported LTFU may appear high at the original facility of ART initiation, while CAYHIV may, in fact, have self-transferred [56, 57], highlighting the need for integrated health exchange information systems.

Advanced HIV disease

CAYHIV who are reported as LTFU may only return to care if they experience HIV-related illnesses and often present with advanced HIV disease [11]. Advanced HIV disease, which may be reflected in having a very low CD4 count or CD4%, being in WHO clinical stages 3&4 or having lower weight-for-age Z (WAZ) scores, has been identified as a risk factor for mortality and a protective factor against the competing risk of reported LTFU [18, 46, 56, 119, 146]. Many children with advanced disease are diagnosed for the first time during hospitalisation, increasing their mortality risk [62, 124]. Abrams et al. found that over 60% of children enrolled in their study were diagnosed during hospitalisation, suggesting late diagnosis and advanced disease at the time of diagnosis and treatment initiation [147]. Advanced disease may be associated with high reported LTFU if the patient is lost because they have actually died or are too sick to return to care [71]. In contrast, patients may be LTFU because they feel well enough to not want to return to care but subsequently become ill and die because they are out of care and off ART [121]. Late presentation to care is associated with increased morbidity, faster progression to AIDS, accelerated immunological and clinical failure, increased risk of drug resistance and increased risk of early mortality [148].

Late or non-disclosure of HIV status

Delayed or non-disclosure of HIV status to children, adolescents, or caregivers is a risk factor for LTFU [134, 149]. Caregivers of children with perinatally acquired HIV may delay disclosure of the diagnosis to the child until adolescence, which could lead to denial and anger towards the caregiver and deteriorating retention [150]. Additionally, youth who have not disclosed their HIV status to their peers or sexual partners are at increased risk of LTFU due to fear of stigma and discrimination. Some may still be in denial of their HIV results. Studies that have reported non-disclosure status showed that CAYHIV not knowing their HIV status was associated with a nearly 25% higher likelihood of LTFU [115, 120, 124].

Transition of care

Transitioning of care from pediatric to general HIV care is increasingly common as ART services become more crowded and decentralised, with more sites providing care for children, and during adolescence and young adulthood, when patients may be more mobile and transfer to clinics closer to their school or work [144, 145]. The transition period from pediatric to adolescent or adult care is associated with high rates of LTFU, with varying rates between high-income and low-income countries [151]. Transition is a challenging period for many reasons, including breaking ties with pediatric clinic staff, psychosocial, developmental and logistical issues, work, the hesitancy of caregivers or parents to leave pediatric care, difficulty adjusting to the adult clinic environment, or, in family-centred primary care clinics, the difficulty of adjusting to increased autonomy for self-care [47, 152-154].

Other factors associated with LTFU and not necessarily mortality include structural barriers like lack of transport costs, long distances to the clinic, clinical barriers like long waiting times, unfriendly health workers, and psychosocial barriers like stigma [69, 70, 144].

2.7 Research gaps

Despite the significant proportion of CAYHIV who are reported as LTFU along the continuum of care, there is limited research on the extent of both reported and true LTFU in these populations. Additionally, there is a lack of consistency in the definition of LTFU across studies, resulting in varied results and interpretations. This makes comparing findings and drawing meaningful conclusions difficult [134, 155, 156]. Moreover, there are few studies among CAYHIV determining LTFU outcomes through tracing or linkage to health information exchanges and many studies broadly categorise CAYHIV using a binary variable (children aged 0-14 years and adults aged 15 years and above) without disaggregating into age groups. In a study of outcomes among patients reported as LTFU [56], only two studies [116, 125] included children, and only one study focused solely on children [116]. In addition, even when patients are traced and returned to care, they remain at high risk of attrition. Therefore, there is an urgent need for data-driven interventions tailored to those at high risk of LTFU [157].

CHAPTER 3 Virologic Response of Adolescents Living with Perinatally Acquired HIV Receiving Antiretroviral Therapy in the Period of Early Adolescence (10–14 Years) in South Africa

Citation: Nyakato P, Schomaker M, Sipambo N, Technau K-G, Fatti G, Rabie H, et al. Virologic response of adolescents living with perinatally acquired HIV receiving antiretroviral therapy in the period of early adolescence (10-14 years) in South Africa. AIDS, 2021;35(6):971.

Paper overview

This paper describes the trajectory of 75th quantile VL values among adolescents who initiated ART below the age of ten years, as a proxy for perinatal infection. We used quantile regression to analyse the 75th quantile VL values and examine predictors associated with increasing VLs in this population.

Contribution to the thesis and novelty

Many studies have reported poor virologic outcomes among APHIV regardless of whether they entered adolescence with a suppressed VL. However, no study has assessed at what point in the early adolescent period the VLs begin to increase and whether this increase differs by sex. We analysed the 75th quantile along the VL distribution curve as the most relevant point at which VL begin to rise, leading to negative outcomes among those entering adolescence with suppressed VLs. The results show that APHIV experience increasing 75th quantile VLs as they progress through early adolescence with no specific age at which this increase occurs and no difference by sex.

Role of the candidate

I was responsible for conceptualising the study and conducting all data analysis. I drafted the manuscripts, incorporated all relevant comments from co-authors, and finalised and submitted the manuscript. I subsequently addressed all reviewer comments and submitted the corrected manuscript for publication.

3.1 Abstract

Background and objectives: Adolescents living with perinatally acquired HIV (APHIV) on antiretroviral therapy (ART) have been noted to have poorer adherence, retention and virologic control compared to adolescents with non-perinatally acquired HIV (AnPHIV), children or adults. We aimed to describe and examine factors associated with longitudinal virologic response during early adolescence.

Design: A retrospective cohort study

Methods: We included APHIV who initiated ART before age 9.5 years in South African cohorts of the International epidemiology Databases to Evaluate AIDS-Southern Africa (IeDEA-SA) collaboration (2004-2016); with viral load values (VLs) <400 copies/mL at age ten years and at least one VL measurement after age ten years. We used a log-linear quantile mixed model to assess factors associated with elevated (75th quantile) VLs.

Results: We included 4,396 APHIV, 50.7% were male, with median (interquartile range) age at ART start of 6.5 (4.5, 8.1) years. Of these, 74.9% were on a non-nucleoside reverse transcriptase inhibitor (NNRTI) at age ten years. After adjusting for other patient characteristics, the 75th quantile VLs increased, with increasing age being 3.13-fold (95% CI: 2.66, 3.68) higher at age 14 versus age 10, 3.25-fold (95% CI: 2.81, 3.75) higher for patients on second-line protease-inhibitor (PI) and 1.81-fold for second-line NNRTI-based regimens (versus first-line NNRTI-based regimens). There was no difference by sex.

Conclusions: As adolescents age between 10 to 14 years, particularly if receiving 2nd-line PI or NNRTI-based regimens, they are increasingly likely to experience higher VL values. This warrants adherence support interventions for the adolescents.

Keywords: Virologic response; Antiretroviral therapy; HIV; perinatal infection; early adolescence

3.2 Introduction

The success of pediatric antiretroviral therapy (ART) has led to better survival with a growing number of adolescents living with perinatally acquired HIV (APHIV) surviving through to adulthood [11, 158, 159]. In 2018, there were 1.6 million (1.1 - 2.3 million) adolescents living with HIV (AHIV) worldwide, and of these, 1.5 million (970,000 – 2.0 million) were living in sub-Saharan Africa [160]. Despite these reported successes, APHIV who enter adolescence virologically suppressed may experience deteriorating outcomes as they progress through adolescence [98].

APHIV usually have long prior treatment histories and have been noted to have poorer adherence, retention and deteriorating virologic control as they start to become autonomous regarding their healthcare [32, 161]. Several studies have reported higher rates of non-adherence, virologic failure, drug resistance, faster disease progression, and higher rates of mortality and loss to follow-up (LTFU) among APHIV compared to either children or adults with non-perinatally acquired HIV [84, 162-165]. Among APHIV in Cameroon, only 36% self-reported being adherent to their medications in the previous 14 days, 71% achieved virologic suppression, and only 52% had sustained virologic suppression [93]. Among AYPHIV initiating ART before the age of 20 years in Europe, the cumulative incidence of triple-class virologic failure increased from about 10% within three years of follow-up to about 30% within five years compared to <9% among adults [162].

APHIV on second-line regimens have also been reported to be more likely to experience virologic failure compared to young children [78, 166]. For example, in a multicentre aggregate analysis of second-line treatment outcomes for children living with HIV, one in six children on second-line protease inhibitor-based (PI) therapy experienced virologic failure, with adolescents having higher failure rates than young

children [167]. Among older adolescents, boys may have poorer virologic response compared to girls [168, 169] but it is not clear if this is the same among younger adolescents, and especially among APHIV. There are also limited data on the age at which the virologic response begins to deteriorate and whether this differs by sex.

Most studies assessing virologic outcomes in this age group have either looked at the most recent viral load (VL), examined changes in mean VL, or considered the binary outcome of virologic suppression versus non-suppression [93, 162, 170]. VLs are time-varying and usually follow a bimodal distribution [171]. Therefore, analysing VL at a single time point or grouping data into a binary outcome will likely result in significant loss of information. Even modelling longitudinal VLs using normal linear models is inappropriate, given the bimodal distribution of VL measurements, and may not identify risk factors for the clinically relevant outcome escalating VLs. Our study aims to describe the longitudinal viral load trajectories of APHIV in the period of early adolescence (10-14 years). Our research will explicitly assess differences in virologic suppression between girls and boys along with other factors associated with elevated VL values during this period using log-linear quantile mixed methods which do not rely on the normal distributional assumptions of the linear mixed model framework.

3.3 Methods

Study population and inclusion criteria

We included data from APHIV who initiated ART from 2004-2016 at age <9.5 years (a proxy for perinatally acquired HIV infection [98]) at eight South African cohorts that contribute data to the International epidemiology Database to Evaluate AIDS-Southern Africa (IeDEA-SA) collaboration [73, 172]. These cohorts include both urban and rural populations across three provinces and have been described in detail elsewhere [173-180].

Patients eligible for this study had to be virologically suppressed (VL <400 copies/ml) at age ten years and have at least one VL measurement after ten years of age.

We, therefore, excluded all adolescents who had initiated ART after 9.5 years. We also excluded all adolescents who had a non-suppressed VL (≥ 400 copies/ml) at the start of adolescence and those that initiated ART before 2004 or after 2016.
ART was defined as a three-drug regimen containing two nucleoside reverse transcriptase inhibitors (NRTIs) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a PI. The outcome of interest was time-updated log_{10}VL, measured between 10.5-14.5 years of age.

Analysis

We used descriptive statistics of proportions, medians and interquartile ranges (IQRs), means and standard deviations to summarise the data [181]. We then used density plots to visualise the estimated probability distribution of VLs. VL values recorded as the lower limit of detection (LLD) were assigned the value of the assay LLD value minus one (e.g. 399 if the LLD was 400) or assigned a conservative value of 399 if the LLD value was not provided. Because the 75^{th} quantile of the log_{10} VL distribution marked approximately the start of virologic non-suppression (VL ≥400copies/ml) across all VL measurements, we chose to use this threshold as an outcome in a random intercept linear quantile mixed-effects model (LQMM) [182, 183]. Since the outcome is measured on a log-scale, the exponentiated coefficients of this model can be interpreted as relative changes in the 75^{th} quantile VL over time. The statistical model included the following explanatory variables: - sex, age, World Health Organization (WHO) clinical stage (Stages 1&2 and Stages 3&4), CD4 count, and calendar year of ART initiation as well as health care facility at ART start and time-varying age. In a sensitivity analysis, we restricted the cohort to APHIV who had been on treatment for at least two years to assess if increasing age remained a risk factor for elevated viral load in adolescents who had been on treatment for more extended periods and were more stable at the start of adolescence (Supplementary Table 3.1).

We used multiple imputation (MI) using the Amelia II package in R to account for missing observations of CD4 count and WHO stage, using the complete data in sex, age, cohort and calendar year of ART start in the MI model [184]. Results were

combined according to Rubin's rules [185]. The remaining analyses were performed in R and Stata 15.1.

Ethics statement

IeDEA-SA cohorts have ethical approval to collect and transfer anonymised patient data to the IeDEA Data Centres at the Universities of Bern and Cape Town. The data centres have approval from their respective institutions for curation and analysis of the combined anonymised data.

3.4 Results

Patient characteristics

Of 4,396 adolescents included, 50.7 % were male with a median age at ART start of 6.5 (IQR: 4.5, 8.1) years (Table 3.1). At ART start, 2,145 (66.2%) of the adolescents with WHO staging measures were in stage III/IV. The majority of adolescents had initiated ART between 2004-2009 (76.0%) and had been on treatment for at least two years. Over 85% of all adolescents had been initiated on an NNRTI-based regimen. By the age of 10 years, 570 (13.0%) had switched treatment to a second-line regimen, and the majority (2,457, 73.9%) had CD4 counts above 500 cells/μL. Median follow-up in the 10-14-year period was 2.2 (IQR: 1.0, 3.9) years.

Table 3.1: Characteristics of adolescents living with perinatally acquired HIV at antiretroviral therapy (ART) start and at start of adolescence (age 10 years)

Patient characteristics	Number (N=4,396)	Percentage
Sex		
Male	2,227	50.7%
Age at ART start, years, median (IQR)[a]	6.5 (4.5, 8.1)	
WHO[o] stage at ART start[#]		
I/II	1,093	33.8%
III/IV	2,145	66.2%
Missing	1,158	26.3%
Calendar year of ART start		
2004-2006	1,627	37.0%
2007-2009	1,718	39.1%
2010-2012	876	19.9%
2013-2016	175	4.0%
Time on treatment, years		
<1	699	15.9%
1-2	736	16.7%
3-5	1,730	39.4%
>5	1,231	28.0%
Third drug in regimen at ART start		
Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)	3,798	86.4%
Protease Inhibitor (PI)	598	13.6%
Ever switched from regimen by the age of 10 years		
Yes	570	13.0%
CD4 count (cells/ µL) at age 10 years[#]		
≤250	352	10.6%
251-350	138	4.2%
351-500	376	11.3%
≥500	2,457	73.9%
Missing	1,073	24.4%
Time of follow-up, years, median (IQR)	1.7 (0.5, 3.4)	
Third drug in regimen at age 10 years		
First line NNRTI	3,294	74.9%
First line PI	532	12.1%
Second line (PI to NNRTI)	65	1.5%
Second line (NNRTI to PI)	505	11.5%

[a]Interquartile range, [o]World Health Organization, [#]Denominator for the stage and CD4 count categories is those with complete records

Distribution and completeness of viral load measurements

Overall, 612 (13.9%) of the adolescents had at least one VL≥ 400 copies/ml. Among those followed up for four years or more, over 80% had five or more VL measurements (Figure 3-1). By 11 years of age, two-thirds of the adolescents had at least one VL measurement, with nearly a third having two measurements. For those followed up until age 14 years or longer, over 80% had at least five VL measurements. The median (IQR) number of VL measurements per year of follow-up was 1.89 (1.42, 2.49). Supplementary Figure 3-1 shows the bimodal distribution of VL measures stratified by sex with a cut-off line at VL=400 copies/ml. Overall, VL values increased with age with an emerging hump in the distribution of high viral load values between 10,000 and

100,000 copies/ml by the age of 14 years. There was no evidence of a crude difference in VL values by sex.

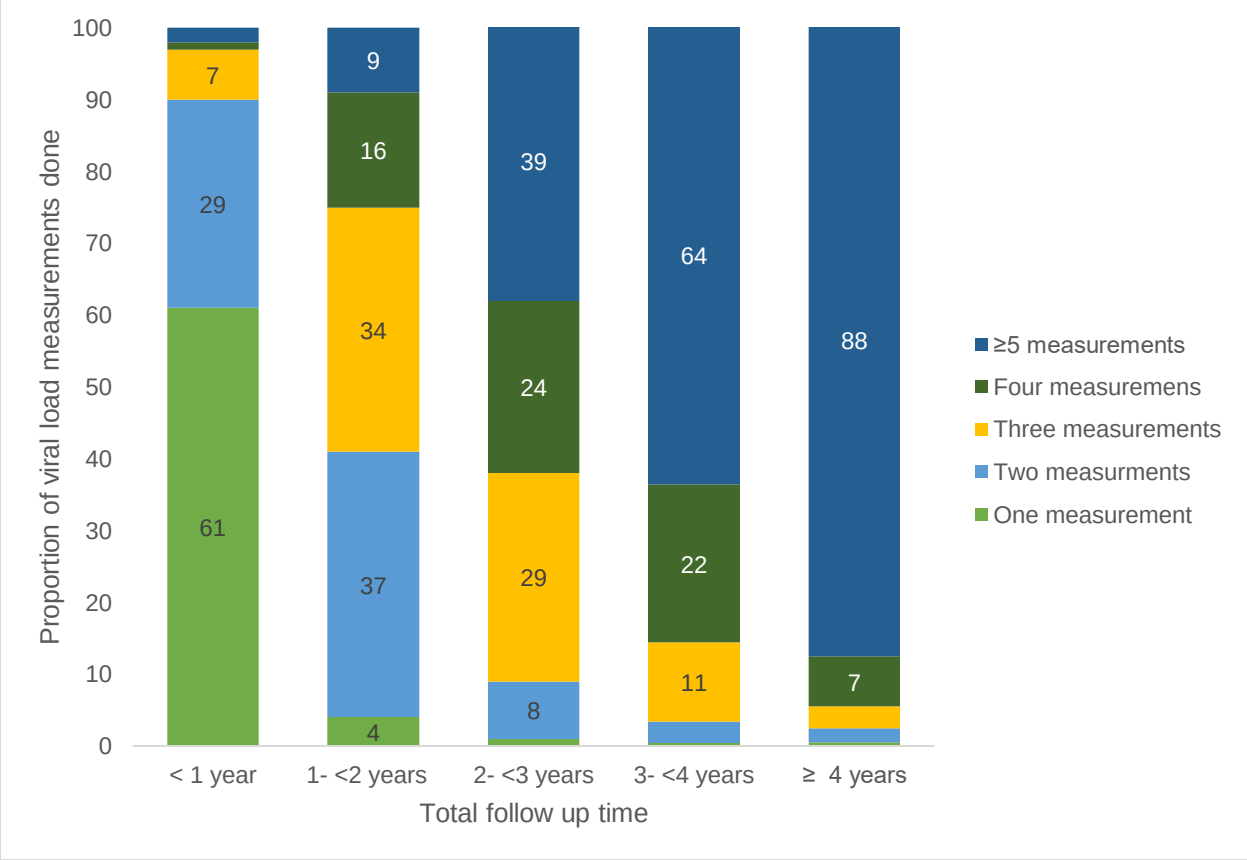

Figure 3-1:Proportion of viral load measurements done per year stratified by total follow-up time in the age 10-14 year period (Values >3% are shown)

Factors associated with high viral load values at the 75th quantile

There was a consistent increase in VLs as age increased (Table 2). Compared to age ten years, there was a 2.10-fold (95% Confidence Interval (CI): 1.89 to 2.33) increase in the 75th quantile VLs at 11 years, and a 3.13-fold (2.66, 3.68) increase in the 75th quantile VLs at 14 years, having adjusted for all other measured patient characteristics. The 75th quantile VL was similar for girls and boys (exponentiated β coefficient: 0.98 (95% CI: 0.92, 1.06)). In comparison to APHIV who were on NNRTI-based first-line regimens, those on other regimens had higher 75th quantile VL values as follows: first-line PI-based 1.29-fold higher (95%CI: 1.15; 1.45); NNRTI-based second-line 1.81-fold higher (95%CI: 1.48, 2.22) and second-line PI-based 3.25-fold higher (95%CI: 2.81,

3.75) There was an increase in the 75th quantile VLs among those starting ART in more recent years (2013-2016 versus 2004-2006, 1.48, 95% CI: 1.22, 1.78).

In a sensitivity analysis including only those who had been on ART for at least two years by age ten years, the effects of age, being on a second-line regimen, and calendar year on the 75th quantile VL were attenuated but similar to the primary analysis (Supplementary Table 3.1).

Table 3.2: Factors associated with high viral load (VL) values at the 75th quantile between 10-14 years of age

Patient characteristics	CR[a]: Adjusted relative changes* in 75th quantile VL (95% CI•)	MI[b]: Adjusted relative changes in 75th quantile VL (95% CI•)
Age, years		
10	1	1
11	1.65 (1.45, 1.88)	2.10 (1.89, 2.33)
12	1.73 (1.52, 1.99)	2.38 (2.12, 2.67)
13	1.88 (1.68, 2.10)	2.71 (2.39, 3.08)
14	2.10 (1.82, 2.39)	3.13 (2.66, 3.68)
Sex		
Male	1	1
Female	1.00 (0.93, 1.07)	0.98 (0.92,1.06)
WHO¶ clinical stage at ART start		
Stage 1&2	1	1
Stage 3&4	1.07 (0.92, 1.25)	1.06 (0.99, 1.14)
Calendar year of ART start		
2004-2006	1	1
2007-2009	1.09 (0.97, 1.23)	1.27 (1.17, 1.37)
2010-2012	1.51 (1.25, 1.84)	1.60 (1.38, 1.84)
2013-2016	1.60 (1.21, 2.10)	1.48 (1.22, 1.78)
"Third" drug in regimen at age 10 years		
First line non-nucleoside transcriptase reverse inhibitor (NNRTI)	1	1
First line protease inhibitor (PI)	1.15 (0.97, 1.36)	1.29 (1.15, 1.45)
Second line NNRTI	1.75 (1.39, 2.23)	1.81 (1.48, 2.22)
Second line PI	2.53 (2.16, 1.94)	3.25 (2.81, 3.75)
Time on treatment before age 10 years		
<1 year	1	1
1-2 years	1.07 (0.88, 1.31)	0.98 (0.85, 1.12)
3-5 years	1.05 (0.88, 1.25)	1.04 (0.91, 1.18)
>5 years	0.92 (0.89, 1.23)	1.11 (0.94, 1.31)
CD4 cell count (cells/uL) at age 10 years		
≤ 250	1	1
251-350	0.92 (0.73, 0.86)	1.01 (0.80, 1.26)
351-500	0.99 (0.77, 1.27)	0.96 (0.82, 1.14)
> 500	0.99 (0.81, 1.21)	0.87 (0.75, 1.00)

•Confidence interval, ¶World Health Organization, ƒ 612 (13.9%) adolescents experienced a non-suppressed VL, å Adjusted for health facility where the patient was receiving care, [a] Complete records analysis. [b] Multiply imputed analysis. *Number of times that the 75th quantile VL is bigger or smaller for different values of the independent variable.

3.5 Discussion

In our analysis, APHIV on ART entering adolescence with VL <400 copies/ml experienced increasing VLs with age up to 14 years. Adolescents on second-line PI-based regimens were especially vulnerable and had three-fold higher 75th quantile VL values compared to those on first-line NNRTI-based regimens. There was, however, no particular age at which the VLs sharply increased, and the virologic response was similar for boys and girls.

Our results are consistent with other studies which have found deteriorating virologic and immunologic outcomes among APHIV [84, 162, 163]. Although our study was restricted to APHIV who had a suppressed VL at the time they entered into adolescence, there was a progressive increase in the 75th quantile of the VL distribution between 10 and 14 years of age. Adherence challenges brought about by changes in HIV care offered, the increased responsibility for their own health decisions and the usual social and developmental changes of adolescence may partly explain the increasing VL. In a study among APHIV in Thailand, almost half reported having suboptimal adherence measured as a composite outcome of self-reported missed doses in the previous seven days and caregiver rating of overall adherence [186]. Similar to our study, 18% of the adolescents in that study were virally non-suppressed (VL≥1000 copies/ml). The main barriers to adherence in this age group, as highlighted by a systematic review done in low and middle-income countries, were non-disclosure to the adolescent themselves of serostatus, coming from a “broken” family structure or having non-biological parents as caregivers, the impact of burdensome ART regimens, having had missed clinic appointments in the past as well as coming from rural versus urban locations [45].

Other authors point out the need for greater adherence and psychosocial support during the adolescent period, especially as adolescents grow older and get more independent with their health care needs [32, 186]. Denison et al. also highlighted the importance of families and home environments in supporting adolescent adherence to treatment and disclosure in Zambia [187]. Conversely, a study in the USA did not find any association of age with virologic non-suppression among APHIV and adolescents with non-perinatally acquired HIV [188]. However, lack of

ascertaining an age-related association could be due to differences in study design, as the US study used a cross-sectional design, unlike our longitudinal design.

In our study, the 13% of adolescents who had switched to second-line regimens by age ten years experienced far greater increases in the 75th quantile VLs than those on first-line NNRTI-based regimens. This finding is in line with other studies that have reported APHIV being at high risk of treatment failure and multiclass drug resistance [78, 167]. Similar results were observed in a study done among Asian APHIV on stable ART to assess Incidence and predictors of post suppression virologic rebound; 13% of the adolescents experienced post-suppression virologic rebound at a rate of 3.4 (95% confidence interval: 2.9-3.9) per 100 person-years, which was consistent over time [189]. A Kenyan study reported over one-third of children experiencing virologic failure among those that underwent routine VL testing, with children that had switched ART regimen having higher odds of having unsuppressed VL [166]. In a Tanzanian study, among the 25% of children identified with virological failure, 90% had ART-associated drug resistance mutations, and almost 80% had multiclass resistance [190].

Notwithstanding, in our study, 88% of adolescents on second-line were on a PI-based regimen following NNRTI-based first-line and these children had the highest 75th quantile VL values, which may indicate non-adherence and not necessarily resistance. These adolescents probably had suboptimal adherence and viral failure before adolescence, which led to switching in regimens. For example, in a study done among Tanzanian children, suboptimal adherence to the first-line regimen was a predictor of suboptimal adherence to the second line [191]. In their study, Mocroft et al. also found that patients on the second line were more likely to experience virologic rebound compared to those on the first line [192]. Furthermore, even adolescents on first-line PI-based regimens had higher 75th quantile VL values compared to those on first-line NNRTI-based regimens, also suggesting non-adherence especially as there is a high genetic barrier to PI resistance. PI regimens have also been recorded to have severe side effects like gastrointestinal effects compared to NNRTIs [193].

The median number of VL measurements per year of follow-up was approximately two measurements/year of follow-up. This is in line with what the VL monitoring guidelines in South Africa recommend. This finding suggests that despite the increased number of patients in the health care system, on average, VL testing is being done as per guidelines.

It is concerning that adolescents who had started ART in more recent calendar years appear to have higher 75th quantile VL values compared to those who began ≤2006. However, a high proportion of the children who started in the first two-three years of ART roll-out were long term survivors of perinatally acquired HIV in the era before ART was widely available. Our finding may reflect a survival bias favouring the most adherent and least sick among that cohort. In addition, there was no evidence of a deteriorating trend in viral outcomes over calendar time beyond 2006. The children who initiated in more recent years may carry drug-resistant strains from being exposed to maternal ART hence having a higher risk of rebound. A study done in the UK and Ireland among children on antiretroviral therapy [194] showed this result, although they did not have sufficient power to evaluate this. Another plausible explanation is that in more recent years, with the overcrowding of the health system due to increased survival of patients, VL monitoring has targeted high-risk patients. This could mean that the stable patients may have their VLs done less frequently, and could have been excluded or be under-represented in our analysis due to our strict exclusion criteria.

Our study concurs with others which showed no strong association in virologic response between younger adolescent boys and girls [93]. A study comparing retention and virologic suppression among adolescents and young adults attending either an adolescent-friendly clinic or standard paediatric care reported no major differences by sex in either model of care, having adjusted for all other measured patient characteristics [195]. Sex differences in adolescent outcomes have mostly been reported among those with horizontally acquired HIV and in older adolescents of ≥15 years [169, 195].

Our study was limited by the lack of data on resistance, treatment interruptions and adherence; hence we were unable to assess an association between elevated VLs

and resistance or adherence in this population. We also made assumptions about the actual VL value when VL was reported as below the LLD. Although the LLD of assays has dropped in more recent years, it is unlikely to have affected the 75th quantile values themselves as the 75th quantile value from 11 years of age onwards was >400, the lowest LLD. A further limitation is our use of starting ART before age 9.5 years as a proxy for perinatally acquired HIV as there may be adolescents commonly referred to as “slow progressors” who were missed in our definition of perinatal infection [32, 196]. The inclusion of children who survived into adolescence and had a VL measurement in the 10-14-year age period may have introduced selection and survival bias and hence an over-estimation of the high VL trajectories. However, there was no difference in the median number of VL measurements/year of adolescent follow-up by calendar year of ART start suggesting minimal/no selection bias by calendar year in those whose VL was measured.

We used linear quantile mixed regression modelling that considers the bimodal distribution as the longitudinal nature of the VL data instead of cross-sectional analyses, modelling of dichotomised virologic outcomes (VL suppression versus non-suppression) or longitudinal analyses based on assuming a normal distribution of VL measures. We also used multiple imputation for missing observations. We presented both results from complete record analysis (CR) and multiple imputation (MI), which provides a more robust comparison and generalizability of the results [185]. Our analysis is further strengthened by the large sample size and the broad geographic coverage of our cohort, comprising adolescents from a wide range of public-sector patients from hospitals and health centres in three provinces of South Africa. The results may be generalisable to other routine care settings in Sub-Saharan Africa, where VL monitoring is available.

Conclusions

In our study, APHIV experienced deteriorating viral load outcomes as they aged from 10-14 years, especially if on any second-line or a PI-based first-line regimen with no major/relevant differences by sex. Using the quantile regression allowed for a more granular understanding of the factors that cause higher VL values in the most clinically relevant upper end of the range. Adherence support in early adolescence is

critical, with a particular focus on ensuring regular VL monitoring and adherence interventions for those on second-line treatment.

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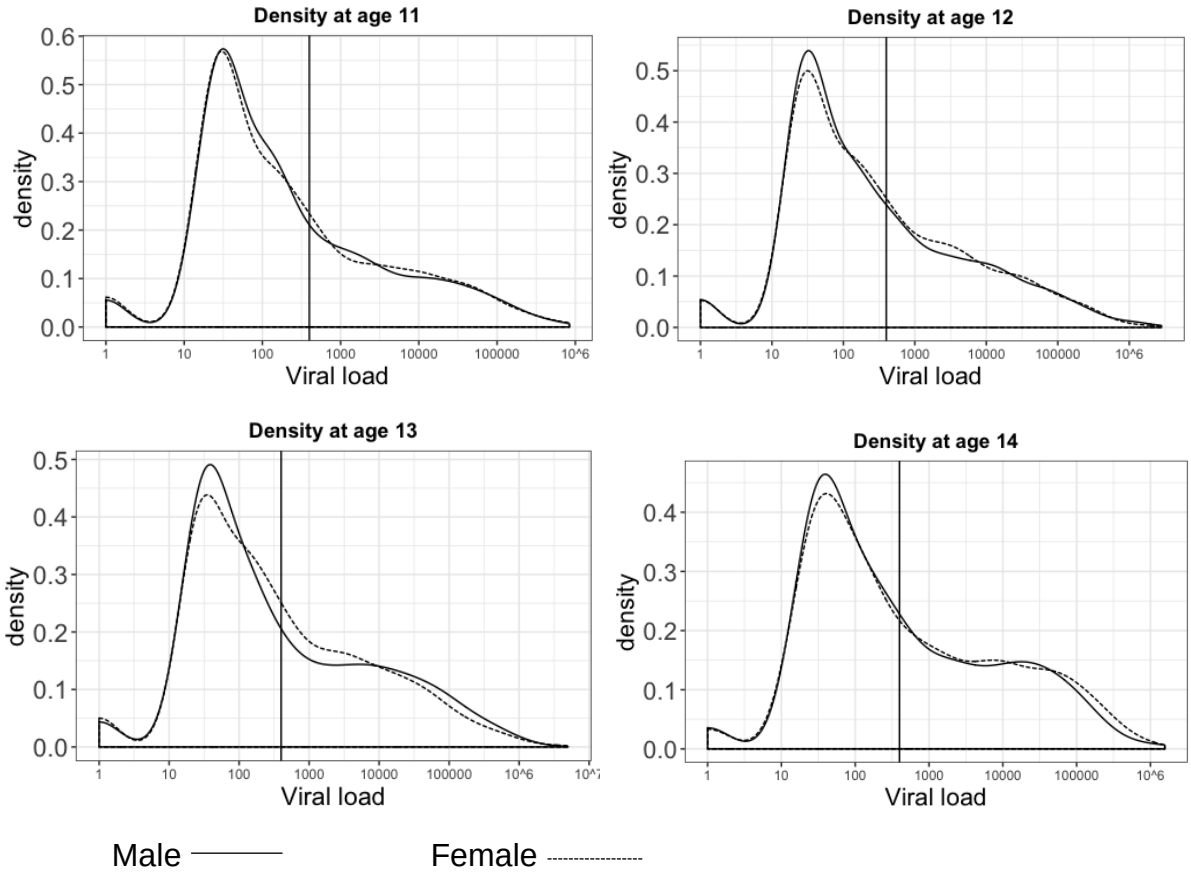
3.6 Supplementary materials

Supplementary Table 3.1: Factors associated with high viral load (VL) values at the 75th quantile among patients between 10-14 years of age who had been on treatment for at least two years by age 10 years

Patient characteristics	CR†[a]: Adjusted relative difference in 75th quantile VL[§] (95% CI[ᵠ])	MI†[b]: Adjusted relative difference in 75th quantile VL[§] (95% CI[ᵠ])
Age, years		
10	1	1
11	1.60 (3.74, 8.50)	1.94 (1.71, 2.20)
12	1.67 (1.42, 1.80)	2.12 (1.88, 2.40)
13	1.88 (1.48, 1.88)	2.46 (2.19, 2.76)
14	2.12 (1.63, 2.14)	2.64 (2.20, 3.16)
Sex		
Male	1	1
Female	1.01 (0.94, 1.08)	1.04 (0.95, 1.13)
WHO clinical stage at ART start		
Stage 1&2	1	1
Stage 3&4	1.17 (1.02, 1.36)	1.10 (0.97, 1.25)
Calendar year of ART start		
2004-2006	1	1
2007-2009	1.06 (0.97, 1.16)	1.11 (0.99, 1.24)
2010-2012	1.45 (0.14, 0.61)	1.59 (1.32, 1.91)
2013-2016	1.31 (0.95, 1.82)	1.12 (0.87, 1.44)
"Third" drug in regimen at age 10 years		
First line non-nucleoside transcriptase reverse inhibitor (NNRTI)	1	1
First line protease inhibitor (PI)	1.17 (1.03, 1.32)	1.17 (1.03, 1.32)
Second line NNRTI	1.70 (1.32, 2.20)	1.77 (1.41, 2.22)
Second line PI	2.29 (1.86, 2.77)	2.83 (2.35, 3.41)
Time on treatment before adolescence		
<1 year	-	-
1-2 years	-	-
2-5 years	1	1
>5 years	1.007 (0.92, 1.09)	1.04 (0.94, 1.15)
CD4 cell count (cells/uL) at 10 years		
≤ 250	1	1
251-350	1.09 (0.77, 1.54)	1.14 (0.84, 1.54)
351-500	1.22 (0.90, 1.67)	1.14 (0.88, 1.48)
> 500	1.16 (0.90, 1.52)	1.05 (0.85, 1.31)

†Adjusted for health facility where the patient was receiving care, [a] Complete records analysis, [b] Multiply imputed analysis, [§]Viral load, [ᵠ]Confidence interval



Supplementary Figure 3-1: Density plots of viral loads in copies/ml on $\log_{10}$ scale between ages 11-14 years stratified by sex

CHAPTER 4 Virologic Non-Suppression and Early Loss to Follow-Up Among Pregnant and Non-Pregnant Adolescents Aged 15-19 years Initiating Antiretroviral Therapy in South Africa: A Retrospective Cohort Study

Citation: Nyakato P, Schomaker M, Fatti G, Tanser F, Euvrard J, Sipambo N, et al. Virologic non-suppression and early loss to follow up among pregnant and non-pregnant adolescents aged 15–19 years initiating antiretroviral therapy in South Africa: a retrospective cohort study. Journal of the International AIDS Society. 2022; 25(1):e25870.

Paper overview

This paper examines poor virologic outcomes and early LTFU among older adolescents who initiated ART between the ages of 15-19 years with a sub-analysis among adolescents initiating during pregnancy. We analysed the two outcomes using competing risk regression analysis. We also explored the predictors of these outcomes.

Contribution to the thesis and novelty

Previous studies have often combined older adolescents with young adults (20-24 years) or younger adolescents (10-14 years) when examining treatment outcomes, resulting in a limited understanding of the specific challenges older adolescents face. However, even in these studies, older adolescents have consistently been reported to have higher rates of VNS and LTFU compared to either younger adolescents or young adults. Furthermore, there is a disproportionate prevalence and incidence of HIV among girls compared to boys in this age group. This further increases their vulnerability with regard to pregnancy. Contrary to what many other studies have found, we found lower rates of VNS but a very high rate of early LTFU within the first 24 months from ART initiation.

Role of the candidate

I was responsible for conceptualising the study with the support of Professor Mary-Ann Davies and conducted all data analysis. I drafted the manuscripts, incorporated all relevant comments from co-authors, and finalised and submitted the manuscript. I

subsequently addressed all reviewer comments and submitted the corrected manuscript for publication.

4.1 Abstract

Introduction: Older adolescents aged 15-19 years continue to have high rates of loss to follow-up (LTFU), and high rates of virologic non-suppression (VNS) compared to younger adolescents and adults. Adolescent females are at risk of pregnancy, which puts those living with HIV at a dual vulnerability. Our study assessed the factors associated with VNS and LTFU in older adolescents (including pregnant females) who initiated antiretroviral therapy (ART) in South Africa.

Methods: We included adolescents aged 15-19 years initiating ART between 2004-2019, with ≥ one viral load (VL) measurement between 4-24.5 months, and ≥ six months follow-up, from six South African cohorts of the International epidemiology Databases to Evaluate AIDS-Southern Africa (IeDEA-SA). We defined VNS as VL ≥400 copies/ml and LTFU as the first gap in care of ≥180 days after ART start and not known as transferred out of the clinic or dead in the first 24 months on ART. We examined factors associated with VNS and LTFU using Fine & Gray competing risks models.

Results: We included a total of 2,733 adolescents, 415 (15.2%) males, median (IQR) age at ART start of 18.6 (17.3, 19.4) years. Among females, 585/2318 (25.2%) were pregnant. Over the 24-month follow-up, 424 (15.5%) of all adolescents experienced VNS: range (11.1% pregnant females, 20.5% males). Over half of all adolescents were LTFU before any other event could occur. The hazard of VNS reduced with increasing age and CD4 count above 200 cells/μL at ART initiation among all adolescents having adjusted for all measured patient characteristics (adjusted sub-distribution hazard ratio (aSHR) 19 vs 15 years: 0.50 (95% CI: 0.36, 0.68), aSHR: >500 vs ≤200 cells/μL: 0.22 (95% CI: 0.16, 0.31)). The effect of CD4 count persisted in pregnant females. Increasing age and CD4 count >200 cells/μL were risk factors for LTFU among all adolescents.

Conclusions: Older adolescents had a high risk of LTFU shortly after ART start and a low risk of VNS, especially those initiating treatment during pregnancy. Interventions addressing adherence and retention should be incorporated into

adolescent-friendly services to prevent VNS and LTFU and endeavor to trace lost adolescents as soon as they are identified.

4.2 Introduction

In 2019, about 1.7 (1.1-2.4) million adolescents aged 10-19 years and 3.4 million young people aged 15-24 years were living with HIV worldwide [1], with the vast majority living in sub-Saharan Africa (SSA). In recent years, adolescent-friendly HIV programmes have increased as antiretroviral therapy (ART) programmes become more decentralised [154, 197]. Despite these efforts, older adolescents aged 15-19 years continue to have high rates of loss to follow-up (LTFU), less than optimal adherence and high rates of virologic non-suppression (VNS) compared to younger adolescents aged 10-14 years and adults [34, 164, 198].

Behavioural and patient characteristics play an important role in adherence to ART and retention in care among adolescents living with HIV. Adolescence is when sexuality, gender norms, and sexual relationships are explored while experiencing major physical, and physiological changes [32, 169]. These changes often influence adolescents' health-related behavior, including clinic attendance and long-term adherence to HIV medication, which affects virologic suppression (VS) [30]. In Gauteng, South Africa, older adolescents (15-19 years) and young adults (20-24 years) were more likely to have VNS and virologic failure compared to either younger adolescents (10-14 years) or adults [18]. Transition to adult care generally happens during later adolescence, and in some settings, older adolescents are often treated as adults [161, 199]. In these situations, they would be expected to make health care decisions without understanding the importance of sustained adherence and retention in care. Among South African adolescents who had successfully transferred, older adolescents were more likely to have VNS and CD4 count cells ≤500 cells/μL compared to younger adolescents at one- and two-years post transfer [47].

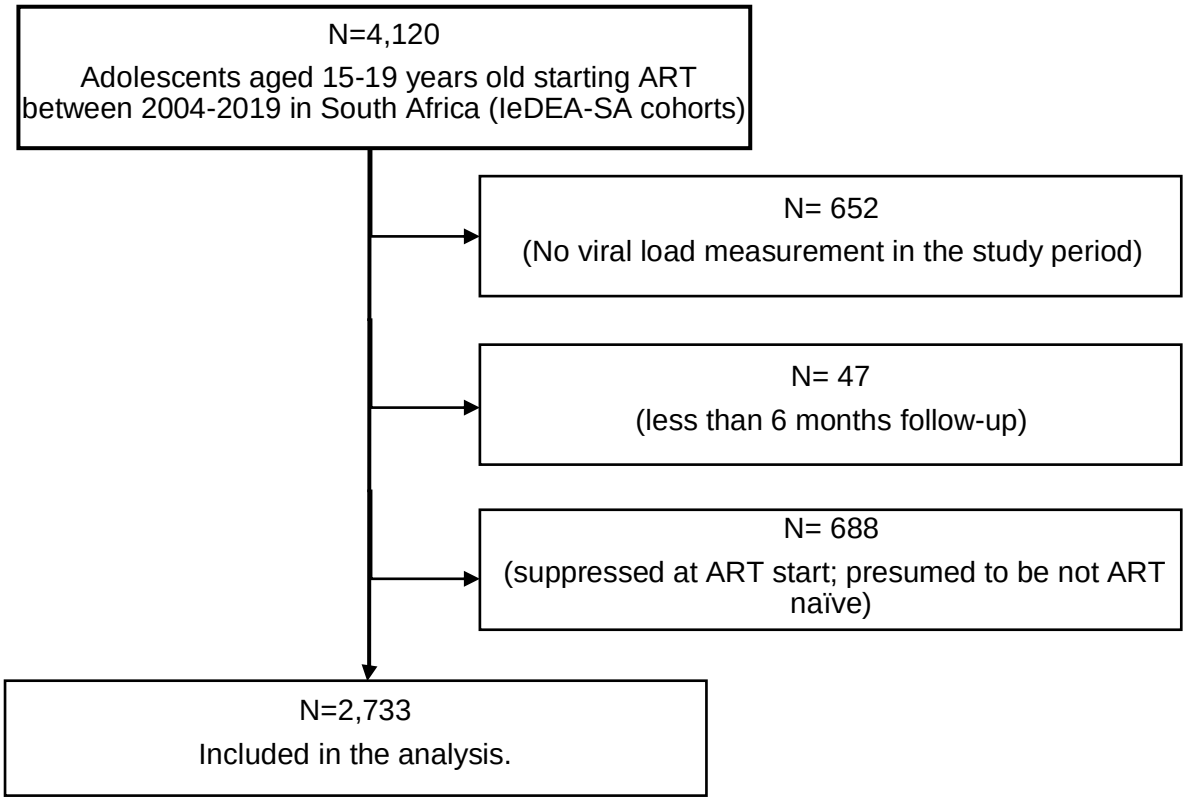
Globally, adolescent girls and young women aged 15-24 years continue to be disproportionately affected by HIV compared with their male counterparts. Adolescent girls are at a higher risk of acquiring HIV compared to adolescent boys

[197], with twice the HIV prevalence of boys and young men in the same age range [1]. Girls are also at risk of pregnancy, which puts those living with HIV at a dual vulnerability, dealing with a chronic illness and the physical and emotional changes that occur during pregnancy [6, 37]. VNS among adolescent girls living with HIV is of particular concern due to the high risk of virologic failure, morbidity and mortality, and the potential for HIV transmission to an unborn child should they become pregnant [37]. Studies have reported high rates of LTFU among pregnant and breastfeeding women which are associated with a high risk of VNS [200, 201]. To date, however, there are limited data on VNS among adolescents (pregnant and non-pregnant) who initiate ART between the ages of 15-19 years in SSA [163, 202]. Our study aimed to assess the factors associated with VNS and LTFU in older adolescents (including pregnant females) who initiated ART between 2004-2019 in the South African cohorts of IeDEA-SA.

4.3 Methods

Study population and inclusion criteria

We included all ART-naïve (defined as not being on any ART regimen) adolescents aged 15-19 years initiating ART between 2004-2019 from six South African cohorts of the International epidemiology Databases to Evaluate AIDS-Southern Africa (IeDEA-SA) collaboration [172]. These cohorts are in both rural (Hlabisa) and urban (Harriet Shezi, Themba Lethu, Khayelitsha, Kheth'Impilo and AfA) locations entailing public hospitals (Harriet Shezi, Themba Lethu), a public sector primary health care centre (Khayelitsha), not-for-profit organisations (Kheth'Impilo, Hlabisa) and one private sector managed-care HIV programme (AfA), across three South African provinces, and the individual cohort profiles have been described elsewhere [173-175, 178, 203, 204]. All these facilities have a mix of pediatric and adult populations except for Harriet Shezi, a pediatric hospital. To be included in the analysis, these adolescents had to have at least one viral load (VL) measurement between 4-24.5 months on ART, and at least six months follow-up on ART. We excluded 688 adolescents with a suppressed VL at ART start (VL<400 copies/ml) as they were unlikely to be ART-naïve.



ART: antiretroviral therapy

Figure 4-1: Flow chart showing the inclusion and exclusion criteria of adolescents aged 15-19 years old in International epidemiology Databases to Evaluate AIDS-South African (IeDEA-SA) cohorts

Outcome definitions

The main outcome of interest was the first non-suppressed VL (VNS) within 4-24.5 months from ART start. We defined VNS as any VL ≥400 copies/ml (cpm). The choice of the 400cpm cut off is based on historical accuracy of the test: VL assays used to only be reliable at around 400cpm for some of the years included. Competing outcomes: the competing outcomes we considered were LTFU (defined as the first gap in care of ≥180 days from ART start and not known as having transferred out of the clinic or died in the first 24 months on ART with no consideration for patients cycling in and out of care in this period), all-cause mortality and official transfers. Most of these facilities trace patients who are lost as part of routine procedure and mortality is defined as all-cause mortality. We examined these outcomes among all adolescents and separately among pregnant females. Pregnancy is routinely collected and recorded in patient files and electronic databases.

Analysis

We used descriptive statistics of proportions, medians, interquartile ranges (IQRs), rates and cumulative incidence functions (CIF) to summarize the data stratified by sex (males, non-pregnant females and pregnant females) [205]. We examined factors associated with VNS using Fine & Gray competing risks regression models among all adolescents and separately among pregnant females [206]. We included characteristics recorded at ART initiation (sex, World Health Organization (WHO) stage, CD4 count, health facility, calendar year of ART start and age at ART start) in the model. We report adjusted sub-distribution hazard ratios. In our secondary analysis, we examined factors associated with being LTFU in the presence of death and official transfers as competing events among all adolescents and separately among pregnant females. Under Option B, rolled out in South Africa from 1 April 2013 - 31 December 2014, ART was only recommended for pregnant and breastfeeding females. It is relatively uncommon for adolescent mothers to breastfeed for an extended period as most need to return to school. To address this issue, we censored the analysis at nine months for women who initiated ART during the roll-out of Option B in South Africa [207].

We assumed all missing data were missing at random (MAR) and we multiply imputed (15 times) missing baseline CD4 count and WHO stage data using multiple imputation (MI) with a chained equations approach [208]. Results were then combined using Rubin's rules [53]. We report the multiple imputation-adjusted results among all adolescents and pregnant females, respectively for both outcomes of VNS and LTFU. Analysis and data management were performed in STATA version 15.1 (Stata Corporation, College Station, TX, USA).

Ethics statement

The data used in this analysis is collected as part of the standard routine procedure at the facilities; patients or caregivers have given consent to the collection of the data. IeDEA-SA cohorts have also obtained ethical approval to collect and transfer anonymized data through their respective Institutional Review Boards (IRBs). The IeDEA-SA data centre has approval from the University of Cape Town's IRB (Human Research Ethics Committee (HREC)) to receive and analyze these anonymized data.

4.4 Results

Patient characteristics

We included a total of 2,733 adolescents, 415 (15.2%) males, with a median (IQR) age at ART start of 18.6 (17.3, 19.4) years (Table 4.1). Among the females, 585/2318 (25.2%) were pregnant at ART initiation. While nearly one in five adolescents were in WHO stages 3&4, the proportion ranged from 4.1% among pregnant females to 31.3% among males. Similarly, among adolescents with recorded CD4 count, 17.3% had CD4 count ≤ 200 cells/μL, with the highest proportion found among males (29.9%) and the lowest in pregnant females (7.9%). Most adolescents had initiated ART between 2013-2019. The majority (56.1%) of adolescents were from Kheth'Impilo cohort, ranging from 44.1% males to 63.6% pregnant females. The median (IQR) number of VL measurements per patient was 1(1,2) with a range between one and five measurements for all sex categories.

Table 4.1: Patient characteristics of adolescents 15-19 years old at antiretroviral therapy (ART) initiation and outcomes (virologic non-suppression, loss to follow-up, mortality, transfers) at 24 months after ART initiation

Patient characteristics	Total, n(%)[a] (N=2,733)	Male, n(%)[a] (N=415)	Non-pregnant females, n(%)[a] (N=1,733)	Pregnant females, n(%)[a] (N= 585)
Age at ART start, years, median (IQR)	18.6 (17.3, 19.4)	17.2 (16.0, 18.8)	18.6 (17.4, 19.4)	18.9 (18.0, 19.5)
Age at ART start, years				
15	272 (10.0)	99 (23.9)	152 (8.8)	21 (3.6)
16	310 (11.3)	87 (21.0)	188 (10.9)	35 (6.0)
17	433 (15.8)	66 (15.9)	280 (16.2)	87 (15.0)
18	696 (25.5)	74 (17.8)	443 (25.6)	179 (30.6)
19	1022 (37.4)	89 (21.5)	670 (38.6)	263 (45.0)
WHO[£] stage				
Stage 1&2	1850 (67.7)	204 (49.2)	1136 (65.5)	510 (87.2)
Stage 3&4	537 (19.7)	132 (31.3)	383 (22.1)	24 (4.1)
Missing	346 (12.7)	81 (19.5)	214 (12.4)	51 (8.7)
CD4 count ,(cells/µL) at ART start				
≤200	472 (17.3)	124 (29.9)	284 (16.4)	46 (7.9)
201-350	762 (27.9)	119 (28.7)	431 (24.9)	155 (26.5)
351-500	598 (21.9)	71 (17.1)	393 (22.7)	142 (24.6)
≥500	807 (29.5)	89 (21.5)	568 (32.8)	215 (36.8)
Missing	94 (3.4)	12 (2.9)	57 (3.3)	25 (4.3)
Calendar year of ART start				
2004-2006	96 (3.5)	14 (3.4)	76 (4.4)	6 (1.0)
2007-2009	277 (10.1)	50 (12.1)	201 (11.6)	26 (4.4)
2010-2012	656 (24.0)	124 (29.9)	438 (25.3)	94 (16.0)
2013-2015	801 (29.3)	89 (21.5)	479 (27.6)	233 (39.8)
2016-2019	903 (33.0)	138 (33.3)	539 (31.1)	226 (38.6)
Current age[¢], years, median (IQR)	19.5 (18.2, 20.4)	18.7 (17.5, 20.0)	19.9 (18.7, 20.8)	19.9 (19.1, 20.8)
Health facility				
AfA	135 (4.9)	49 (11.8)	79 (5.1)	7 (1.2)
Harriet Shezi	76 (2.8)	39 (9.4)	37 (2.1)	0 (0.0)
Hlabisa	384 (14.1)	64 (15.4)	235 (13.2)	85 (14.5)
Khayelitsha	496 (18.2)	51 (12.3)	328 (18.5)	117 (20.0)
Kheth'Impilo	1,532 (56.1)	183 (44.1)	977 (55.0)	372 (63.6)
Thembalethu	110 (4.0)	29 (7.0)	77 (4.3)	4 (0.7)
Virologic non-suppression[*]	424 (15.5)	85 (20.5)	274 (15.8)	65 (11.1)
Secondary outcomes				
In care	747 (27.3)	102 (24.6)	317 (18.3)	147 (25.1)
Transferred out	520 (19.0)	104 (25.1)	382 (22.1)	94 (16.1)
Dead	48 (1.8)	10 (2.4)	37 (2.1)	2 (0.3)
Lost to follow-up	1,418 (51.9)	199 (48.0)	997 (57.5)	342 (58.5)

[a] Column percentages are reported, [*]VLs ≥400copies/ml, [£]World Health Organization, [¢]Current age= age at last visit, IQR: Interquartile range

Over the 24-month follow-up period, 424 (15.5%) of the adolescents experienced VNS (Table 4.1, Figures 4-1&4-2): range, 11.1% among pregnant females to 20.5% among males. At the end of the study period, the estimated mortality was low for all groups (1.8%), and lowest among pregnant females (0.3%). In total, 1,418 (51.9%) adolescents were LTFU before any other event could occur, range: 48.0% among males to 58.5% among pregnant females. Overall, 67.4% of all adolescents were either LTFU or had a non-suppressed VL and 66.5% of all pregnant females were either LTFU or had a non-suppressed VL within 24 months on ART start.

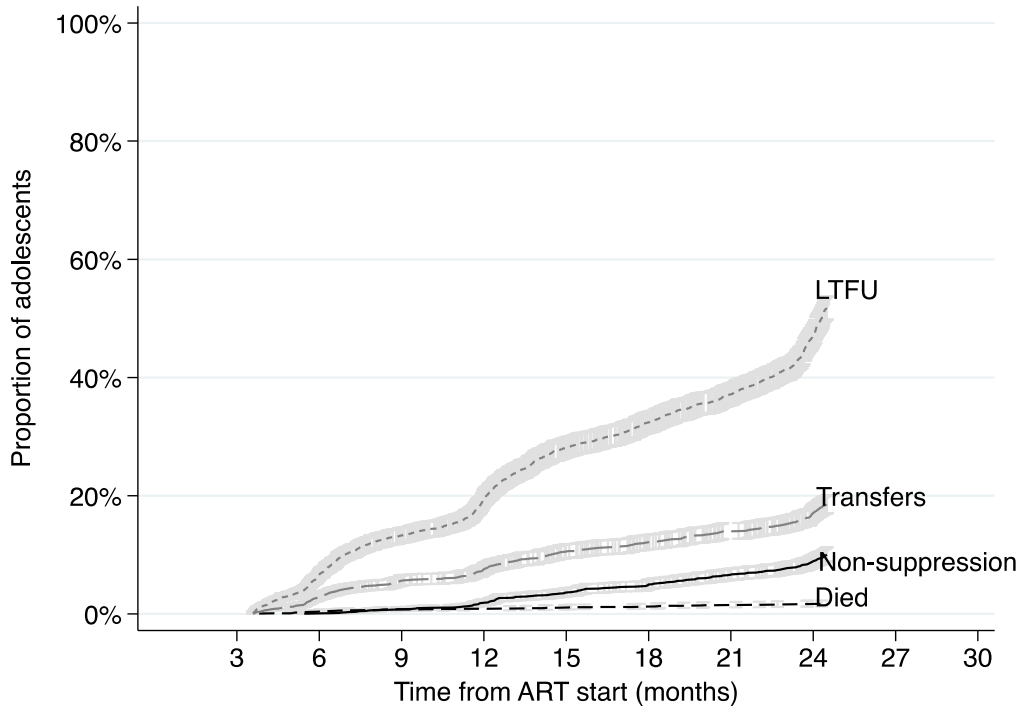


Figure 4-2: Cumulative incidence functions with 95% confidence intervals of virologic non-suppression, loss to follow-up (LTFU), transfers and mortality among all adolescents 4-24.5 months from antiretroviral therapy (ART) start

The overall estimated rate of VNS among all adolescents was 0.96 (95% Confidence Interval (CI): 0.88, 1.06) per 100 person-months (pm) with 44,045 months total time at risk. The estimated rate of VNS among males, non-pregnant females, and pregnant females were: 1.24 (95% CI: 1.00, 1.54), 0.95 (0.84, 1.07) and 0.77 (0.61, 0.99) per 100 pm with 8,396 months total time at risk respectively. The overall estimated rate of LTFU was 3.22 (95% CI: 3.06, 3.39) per 100 pm, highest among

pregnant females: 3.86 (3.46, 4.30) per 100 pm and lowest among males: (2.68 (2.32, 3.10)) per 100 pm.

Factors associated with virologic non-suppression and early loss to follow-up within 24 months after ART initiation among all adolescents

The hazard of VNS at 24 months reduced with increasing age at ART initiation from 16 to 19 years among all adolescents compared to 15 years, having adjusted for all measured patient characteristics (adjusted sub distribution hazard ratio (aSHR) 19 vs 15 years: 0.50 (95% CI: 0.36, 0.68)) (Table 4.2). The incidence of VNS decreased with increasing CD4 count above 200 cells/μL at ART initiation among all adolescents (aSHR: >500 vs ≤200 cells/μL: 0.22 (95% CI: 0.16, 0.31)).

Table 4.2: Factors associated with virologic non-suppression and loss to follow-up at 24 months on antiretroviral therapy (ART) among adolescents that initiate ART at the ages of 15-19 years

	Virologic non-suppression		Loss to follow-up	
Patient characteristics	**Adjusted sub-distribution hazard ratios (aSHR)[§]**	**95% confidence interval**	**Adjusted sub-distribution hazard ratios (aSHR)[§]**	**95% confidence interval**
Sex[•]				
Male	1		1	
Female (non-pregnant)	1.14	0.88, 1.46	0.97	0.82, 1.14
Female (pregnant)	1.21	0.85, 1.72	1.00	0.82, 1.22
Age, years, at ART initiation				
15	1		1	
16	0.70	0.50, 0.99	1.17	0.92, 1.48
17	0.57	0.40, 0.81	1.19	0.94, 1.50
18	0.62	0.45, 0.86	1.28	1.03, 1.59
19	0.50	0.36, 0.68	1.24	1.01, 1.53
WHO[£] stage at ART initiation				
1&2	1		1	
3&4	1.29	0.98, 1.68	0.91	0.79, 1.06
CD4 count (cells/μL) at ART initiation				
≤200	1		1	
201-350	0.56	0.44, 0.71	1.31	1.10, 1.56
351-500	0.41	0.31, 0.55	1.43	1.19, 1.72
>500	0.22	0.16, 0.31	1.35	1.13, 1.62
Year of ART initiation				
2004-2006	1		1	
2007-2009	0.86	0.54, 1.39	1.41	1.00, 1.99
2010-2012	1.20	0.77, 1.88	1.40	1.01, 1.95
2013-2015	1.08	0.69, 1.70	1.84	1.32, 2.56
2016-2019	1.22	0.74, 1.98	2.55	1.81, 3.57

[§]Adjusted for health facility where the patients initiated ART, [•]Sex of adolescents refers to the field in the individual patient health record/file, [£]World Health Organization

After adjusting for other patient characteristics, the hazard of LTFU was higher among adolescents who initiated ART with a CD4 count above 200 cells/μL at ART start (aSHR: >500 vs ≤ 200 cells: 1.24 (95% CI: 1.01, 1.53)), aged 18 or 19 years compared to 15 years and among those who initiated ART between 2013-2019 compared to 2004-2006 (aSHR: 2016-2019 vs 2004-2006:2.55 (95% CI: 1.81, 3.57) (Table 4.2).

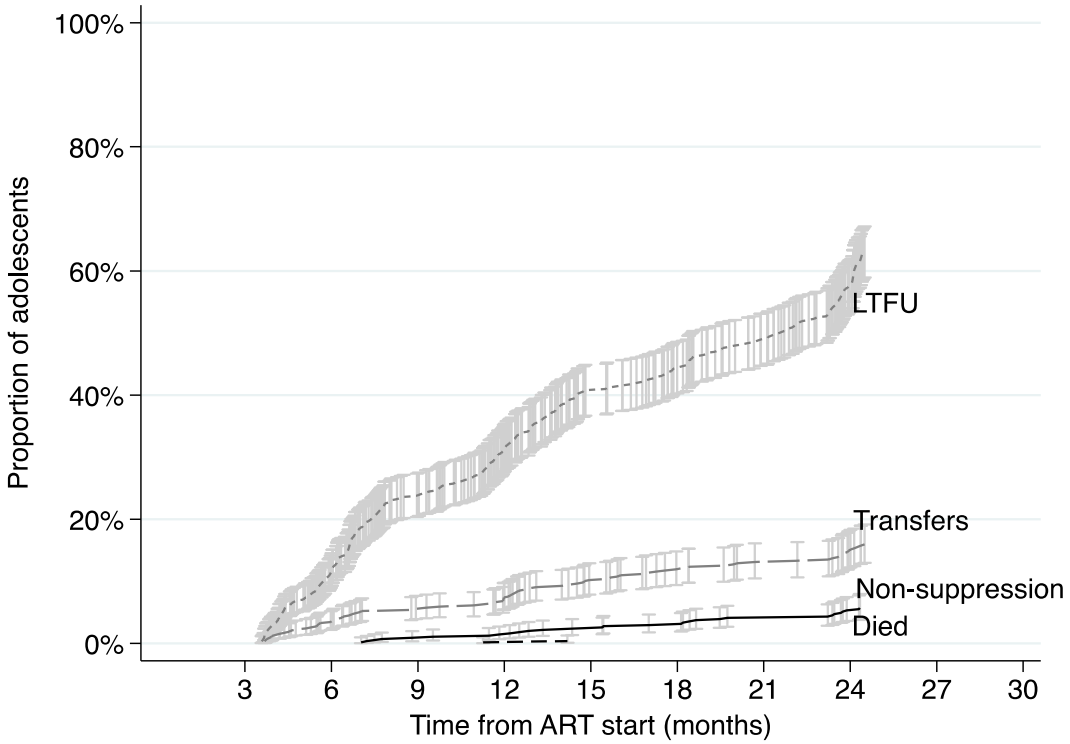


Figure 4-3: Cumulative incidence functions of virologic non-suppression, loss to follow-up (LTFU), transfers and mortality among pregnant females 4-24.5 months from antiretroviral therapy (ART) start

Factors associated with virologic non-suppression and LTFU at 24 months after ART initiation among pregnant females

Pregnant females who initiated ART with a CD4 count above 350 cells/μL at ART start had lower hazards of VNS compared to those initiating with a CD4 count ≤200 cells/μL (aSHR: >500 vs ≤ 200 cells: 0.11 (95% CI: 0.05, 0.27) having adjusted for all measured patient characteristics (Table 4.3). Pregnant females initiating ART in WHO stages 3&4 had a lower hazard of LTFU compared to those initiating in WHO stages 1&2 (aSHR: 0.52; 95% CI: 0.28, 0.99)).

Table 4.3: Factors associated with virologic non-suppression and loss to follow-up at 24 months among pregnant females that initiate antiretroviral therapy (ART) at the ages of 15-19 years

	Virologic non-suppression		Loss to follow-up	
Patient characteristics	**Adjusted sub-distribution hazard ratios (aSHR)***	**95% confidence interval**	**Adjusted sub-distribution hazard ratios (aSHR)***	**95% confidence interval**
Age, years, at RT initiation				
15-17 years	1		1	
18 years	0.66	0.34, 1.29	1.17	0.86, 1.58
19 years	0.66	0.36, 1.21	0.99	0.74, 1.33
WHO£ stage at ART initiation				
1&2	1		1	
3&4	1.25	0.37, 4.28	0.52	0.28, 0.99
CD4 count (cells/µL) at ART initiation				
≤200	1		1	
201-350	0.62	0.33, 1.18	0.88	0.56, 1.37
351-500	0.31	0.15, 0.65	1.29	0.83, 2.03
≥500	0.11	0.05, 0.27	1.43	0.93, 2.20
Year of ART initiation				
2004-2012	1		1	
2013-2015	1.73	0.69, 4.34	0.88	0.62, 1.26
2016-2019	2.07	0.78, 5.43	1.11	0.76, 1.61

*Adjusted for health facility where the patients initiated ART [72], £World Health Organization

4.5 Discussion

In our study looking at VNS and early LTFU among pregnant and non-pregnant adolescents initiating ART aged 15-19 years, we found that over 10% of adolescents experienced VNS and more than half were LTFU during the first 24 months from ART start. One in four females had initiated ART during pregnancy. There were differences in characteristics by sex and pregnancy status: males were most likely and pregnant females least likely to experience VNS; while pregnant females were most likely, and males least likely, to be LTFU. We found that initiating ART at older ages and CD4 counts >200 cells/μL were protective against VNS but increased the hazard of LTFU in all adolescents. Among pregnant females, initiating ART at CD4 counts >200 cells/μL reduced the hazard of VNS, and initiating in WHO stages 3&4 reduced the hazard of LTFU. Adolescents who initiated ART in more recent calendar years were more likely to be LTFU than those initiating ART in 2004-2006.

It is encouraging to see low proportions of VNS in our study although this still falls short of the third UNAIDS 2030 target, that no more than 5% of those on treatment should be virally non-suppressed [209]. Nonetheless, this proportion was lower than has been reported in other studies which range from 19% -73% [84, 168, 195, 210] but concurs with a South African study [195] which found similar rates of VNS for adolescents attending an adolescent friendly clinic. VNS is widely used as a proxy for poor adherence [211]. Sutton et al. showed that adherence ≥80% is required for VS for those on single-tablet regimens and 90% for those on multiple tablet regimens [212]. Our results may therefore suggest good adherence, although we were unable to assess this association due to lack of adherence data. Notably, good adherence is associated with low rates of VNS, hence high rates of VS, which in turn reduces the risk of advanced disease and mortality [213]. Part of the recommended approaches is expansion of adolescent friendly services within the health system like peer support, viral load monitoring and adherence clubs [214]. MacPherson et al., further identified that adolescent friendly services like offering individual and group education and counselling were promising interventions to improve outcomes [215]. We also recommend that future studies collect both adherence and VS data to assess the association between VS and optimal adherence levels in this age group.

The low proportion of VNS among pregnant females is important in low and middle-income countries, where more than 50% of adolescent births occur [216]. The low rates of VNS translate to a reduced risk of disease progression for the adolescents, and of HIV transmission to both the unborn baby and their sexual partners [13, 217]. Our results concur with a recent population-based HIV Impact Assessment (PHIA) survey in seven African countries, which reported similar rates of VNS (18%) among adolescent girls and young women living with HIV on ART [218]. However, our results should be interpreted with caution. Due to the high rate of early LTFU in our study, we were unable to observe and measure VS among nearly half of our sample. If we assumed that all pregnant females who were LTFU had VNS, the rates of VNS may have been higher, as reported in the overall rate of VNS (45%) in the PHIA surveys among all adolescent girls and young women regardless of whether they were on ART [219].

Our study confirms that 15- to 19-year-olds living with HIV are a vulnerable population with high rates of LTFU, especially in the first 24 months after ART initiation [18, 136, 220-222]. In East Africa, the cumulative incidence of LTFU at five years among young adolescents, older adolescents and young adults was 26.6%, 44.1% and 29.3% respectively [136]. In a South African study, only 29% of adolescents aged 15-19 years were retained in care 24 months after ART initiation [220]. These high rates of LTFU among adolescents are driven by several factors including but not limited to: stigma and discrimination, substance use, school, work and family responsibilities, non-disclosure of HIV, drug toxicity and high costs of transport to the facility, compounding adolescent concerns about body image, peer pressure, first sexual experience, mental health concerns and developmental changes [32] [11, 221]. Adult clinics do not offer services that are as adolescent-friendly as pediatric clinics and adolescents may not be ready to be responsible for their own health needs [223-226]. We, therefore, recommend targeted support for adolescents and integration of adolescent friendly services like mental health services, adolescent sexual and reproductive health across the health system.

The high rate of LTFU among pregnant females is of particular concern given that a quarter of the female adolescents in our study were pregnant, and over half were lost to care within 24 months. Pregnancy in an adolescent with HIV may be a sign of

systemic or societal failure: a failure to prevent both pregnancy and HIV, even with available prevention measures [216]. Similar results have been found across different settings among pregnant women on life-long treatment (Option B+) [136, 227]. In a multi-site analysis, adolescents who were pregnant at ART initiation had almost three times higher risk of LTFU than adults or young adolescents [136]. Within services to prevent mother-to-child transmission of HIV in Cape Town, women initiating ART during pregnancy had more than 50% higher hazard of being LTFU compared to those who were already on ART [227]. Some of the observed LTFU is likely due to silent transfers. For example, in Malawi, a study tracing women LTFU on Option B+ found that many patients had actually self-transferred to other clinics [201]. Similarly, in sample-based tracing of patients LTFU, a substantial number had transferred to other clinics [53, 70]. Pregnant adolescent girls who are newly diagnosed with HIV represent a vulnerable population urgently requiring linkage into targeted care, to prevent early LTFU. Paediatric ART programmes should also put in place integrated services that cater to the unique needs of pregnant adolescent girls like PMTCT.

In our study, older age at ART start was protective against VNS for all adolescents. In contrast to our findings, other studies have documented an increased risk of VNS with increasing age [211, 212, 221, 228]. This difference may be due to differences in comparison groups: most other studies compared older adolescents (15-19 years) with younger adolescents (10-14 years), young adults (20-24 years) and adults, but did not include 15- to 19-year-olds as a group [47]. It is likely that as adolescents grow older, they become more responsible, more adherent to medication and consequently less likely to experience VNS. This is reassuring especially as adolescents transition to adult care where there is less parental or health care worker control.

Adolescents who were healthier at ART initiation, with higher CD4 counts, were less likely to experience VNS but more likely to experience LTFU than peers with more advanced HIV disease. Our finding makes intuitive sense as adolescents with high CD4 counts may feel healthy and unmotivated to attend clinic visits and may become lost to care. Because LTFU is associated with an increased risk of poor adherence, VNS, disease progression and mortality [18, 164], adolescent-friendly clinics and

health care systems should develop innovative ways of targeting adolescents aged 15-19 years, particularly those starting in pregnancy, and those with more advanced HIV disease. Such strategies could include differentiated service delivery for both pregnant and non-pregnant females, adherence clubs, peer support for pregnant adolescent girls as part of the peer mentorship programme, and continued counselling to improve treatment outcomes [229]. With the introduction of universal Test and Treat [230], many countries including South Africa no longer measure CD4 count at ART start since there is no eligibility requirement for ART initiation. However, given that CD4 count predicted both VNS and LTFU in adolescents 15-19 years old, CD4 count at ART start should still be used to identify vulnerable patients in this age group and provide them with additional support to be retained in care and adherent to medication.

Finally, the increased risk of LTFU among adolescents enrolled in more recent years could be due to crowded health systems or silent transfers due to decentralization of the health system [136, 231]. HIV care services should therefore provide additional support to ensure that adolescents starting treatment in more recent years remain in care [232].

To the best of our knowledge, this is the first study looking at HIV treatment outcomes among 15–19-year-old adolescents, and within pregnant females in this age group. Our study is strengthened by the large sample size, wide geographical coverage, and the inclusion of public and private located in both rural and urban public health facilities in South Africa, making the results generalizable to similar resource-limited routine care settings with VL monitoring in SSA. Our study's major limitation was the lack of data on adherence, preventing us from assessing an association between adherence and VNS. We addressed the issue of missing data, a common challenge in observational studies, using multiple imputation. Our results may be subject to selection bias, as adolescents who stayed in care long enough to have VLs taken were already adherent to treatment, hence the low rates of VNS observed. We did not undertake time-updated analysis and could not assess incident pregnancies and re-engagement in care for those that may have returned after the first gap in care. Results should be interpreted cautiously due to the potential for outcome misclassification of deaths and “silent” transfers as LTFU. A further

limitation is that we did not have data on transmission mode and were unable to differentiate between perinatally infected adolescents (who would probably be slow progressors) [196, 233] and non-perinatally infected adolescents, who may have different barriers to retention. We could not assess if the high rate of LTFU among pregnant females was pre- or postpartum.

Conclusions

Our study showed that older adolescents initiating ART aged 15-19 years had a high risk of LTFU shortly after ART start and a low hazard of VNS, especially those initiating treatment during pregnancy. Given the heterogeneity in treatment outcomes across these age bands, age-disaggregated outcomes among adolescents (10-14 vs 15-19) and young adults (20-24) should be reported. Interventions addressing adherence and retention should be incorporated into adolescent-friendly services to prevent VNS and LTFU and endeavor to trace lost adolescents as soon as they are identified. Paediatric ART programmes should also put in place integrated services that cater to the unique needs of pregnant adolescent girls like PMTCT.

Competing interests: All authors have no conflicts of interest.

Authors' contributions

PN, MS, and MD conceptualized the study idea. P.N performed the data analysis with guidance and contributions from MS. PN, MC, MD drafted the article with revisions and comments from all authors. GF, FT, JE, NS, MF, AH collected the data. All authors have read and approved the final article.

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CHAPTER 5 High Unreported Mortality in Children and Youth (< 25 Years) Living with HIV who were Lost To Care from Antiretroviral Therapy Programmes in Southern Africa: Results from a Multi-Country Tracing Study

Citation: Nyakato P, Christ B, Anderegg N, Muhairwe J, Jefferys L, van Dijk J, et al. High unreported mortality in Children and Youth (< 25 Years) living with HIV who were lost to care from antiretroviral therapy programmes in Southern Africa: Results from a multi-country tracing study. Journal of Acquired Immune Deficiency Syndromes. 2022; 91(5):429-433.

Paper overview

This paper describes outcomes among CAYHIV who were traced following being reported as LTFU at their original facilities of ART initiation. We used two-stage IPW to determine mortality among those initially reported as LTFU by incorporating mortality data obtained from tracing. We then used weighted Cox regression models to assess mortality predictors among those successfully traced.

Contribution to the thesis and novelty

Previous global mortality estimates among children and youth have relied heavily on facility-level estimates since limited studies have traced CAYHIV considered LTFU. However, as many adult studies have shown, these estimates are biased, especially in the presence of non-ignorable LTFU. This is the first large tracing study among CAYHIV who are LTFU and gives valuable updated insights on CAYHIV LTFU outcomes and informs more accurate mortality estimation.

Role of the candidate

I was responsible for all data analysis. I drafted the manuscripts, incorporated all relevant comments from co-authors, and finalised and submitted the manuscript. I subsequently addressed all reviewer comments and submitted the corrected manuscript for publication.

5.1 Abstract

Background: Antiretroviral therapy (ART) programme mortality maybe underestimated if deceased patients are misreported as lost.

Methods: We used two-stage inverse probability weighting to account for probability of being: sampled for tracing and found by the tracer.

Results: Among 680 children and youth aged <25 years on ART who were lost and traced in Southern Africa between October 2017-November 2019, estimated mortality was high at 9.1% (62/680). After adjusting for measured covariates and within-site clustering, mortality remained lower for young adults aged 20-24 years compared to infants aged <2years (adjusted Hazard ratio (aHR): 0.40 (95% confidence interval (CI): 0.31, 0.51)).

Conclusions: Our study confirms high unreported mortality in children and youth who are lost and the need for tracing to assess vital status among those who are lost to accurately report on programme mortality.

5.2 Introduction

Despite significant progress in pediatric HIV care and treatment, outcomes of children, adolescents, and young adults living with HIV (CAYHIV) aged <25 years continue to lag behind those in adults aged ≥25 years [15, 16]. CAYHIV have substantial loss to follow-up (LTFU) and mortality, especially in the first year after starting antiretroviral therapy (ART). LTFU hampers accurate outcome estimation as outcomes among those LTFU are unknown, which may bias the reporting of programme performance.

Most studies reporting programme outcomes estimate mortality at site-level from patient files, which are often incomplete or inaccurate. The International epidemiology Databases to Evaluate AIDS in Southern Africa collaboration (IeDEA-SA) has previously found that site-reported adult mortality can underestimate true mortality by up to 50% [129], with many undocumented deaths misreported as LTFU.

It is unclear whether the level of undocumented mortality among CAYHIV is similar, particularly given high rates of LTFU and the role of caregivers in retention of CAYHIV [55]. In a large analysis of African and Asian pediatric programmes, only 12/35 studies reported efforts to trace children LTFU, and none reported on outcomes among these children [67]. We examined mortality from a large tracing study among CAYHIV considered LTFU in Southern Africa [52].

5.3 Methods

Setting and sampling

We used data from a multi-country stratified sampling tracing study of adults and children among seven ART programmes in IeDEA-SA in both rural and urban centres [52, 172, 234]. For this analysis, we included CAYHIV aged ≤24 years initiating ART between 2004-2017 from seven sites in five countries (Lesotho (1), Malawi (2), Mozambique (1), Zambia (1), and Zimbabwe (2)). The target sample number of adults and children was 500 participants per clinic, with pre-defined strata of age at last visit, sex, and time since ART initiation, but for clinics with fewer patients LTFU, the entire group were sampled (Supplementary Table 5.1) [66]. Tracing was done using SMS, phone calls and home visits between October 2017-November 2019 (Supplementary Figure 5-1) [52]. We defined children and youth as all children, adolescents and young adults aged 0-24 years. We defined immunosuppression as per the WHO 2016 guidelines [230] and defined ART as being on at least three antiretroviral therapy drugs.

Outcomes

Our outcome of interest was all-cause mortality. We defined LTFU as having no recorded visit for ≥60 days (Malawi) and ≥ 90 days (all other sites) before start of tracing in keeping with local guidelines, and not known as deceased or transferred out. Death information was obtained through interviewing close informants including relatives or caregivers.

Analysis

We summarised data using proportions, medians, interquartile ranges (IQRs), and rates [181]. We used multivariate logistic regression to assess the factors associated

with being found by the tracer. We applied weighted Weibull models to examine predictors of all-cause mortality with shared-frailty terms to account for the clustering within sites. Weights consisted of two-stage inverse probability weights to upweight those successfully traced accounting for the sampling strategy and likelihood of being found by the tracer to make results representative of all lost CAYHIV (methods to construct weights are explained elsewhere) [54, 66, 71]. We measured follow-up time from the last clinic visit to 1) death date if informed to have died, or 2) site specific tracing date if found alive. We assumed all missing immune-suppression data (variable constructed from CD4 count/percent and age) were missing at random (MAR) and multiply imputed these data with a chained equation approach [235]. Results were combined using Rubin's rules [236]. Analysis was performed in Stata version 17 (Stata Corporation, College Station, TX, USA).

Ethics statement

The tracing study received ethical approval from the respective site/country Institutional Review Boards (IRBs) for tracing and to transfer anonymised data to IeDEA-SA, which has approval from the University of Cape Town's Human Research Ethics Committee to receive and analyse these anonymised data.

5.4 Results

Patient characteristics

Of 972 CAYHIV recorded as lost and sampled for tracing, 121 (12.4%) were misreported as lost but were in care at the facility, 171 (17.6%) had missing files and both groups were therefore not included in the study. Among the remaining 680 CAYHIV traced, three in five were female, median age at last visit was 17.0 years (interquartile range (IQR): 5.4, 21.7) and nearly half (317, 46.6%) had been on ART for at least 12 months (Table 5.1). Health facilities were equally distributed between urban (344, 50.6%) and rural (336, 49.4%) areas and the majority were receiving ART at a health centre (494, 67.3%) (Supplementary Table 5.1).

Table 5.1: Patient characteristics at antiretroviral therapy (ART) start and last visit in routine and tracing data

Variable	Traced (N=680)	Vital status not confirmed (Remained LTFU) (N=218)	Vital status confirmed (alive/dead) (N= 462)	P-value[&]
	n (%)	n (%)	n (%)	
Sex				0.560
Male	273 (40.2)	91 (41.7)	182 (39.4)	
Female	407 (59.9)	127 (58.3)	280 (60.6)	
Age at last visit, median (Interquartile range (IQR)) years	17.00 (5.40, 21.66)	15.68 (4.44, 21.61)	17.58 (6.31, 21.80)	0.306
0-<2	72 (10.6)	24 (11.0)	48 (10.4)	
2-<10	154 (22.7)	54 (24.8)	100 (21.7)	
10-<20	203 (29.9)	62 (28.4)	141 (30.5)	
≥20	251 (36.9)	78 (35.8)	173 (37.5)	
CD4 count at last visit, cells/μL	414 (253.5, 675)	464 (291, 610)	407.5 (233, 680)	0.516
0-199	54 (7.9)	11 (5.1)	43 (9.3)	
200-349	60 (8.8)	13 (6.0)	47 (10.2)	
350-499	63 (9.3)	16 (7.3)	47 (10.2)	
≥500	107 (15.7)	28 (12.8)	79 (17.1)	
Missing	396 (58.2)	150 (68.8)	246 (53.3)	
Year of ART start				0.074
2004-2013	127 (18.7)	31 (14.2)	96 (20.7)	
2014-2015	372 (54.7)	131 (60.1)	241 (52.2)	
2016-2017	181 (26.6)	56 (25.7)	125 (27.1)	
Duration on ART at last visit, months				0.001
0-<6	263 (38.7)	114 (52.3)	141 (30.5)	
6-<12	100 (14.7)	41 (18.8)	63 (13.6)	
≥12	317 (46.6)	63 (28.9)	258 (55.8)	
Country				<0.0001
Lesotho	38 (5.2)	13 (6.0)	25 (5.4)	
Malawi	265 (36.1)	84 (38.5)	181 (39.2)	
Mozambique	131 (17.9)	22 (10.1)	109 (23.6)	
Zambia	136 (18.5)	87 (5.5)	49 (10.6)	
Zimbabwe	110 (15.0)	12 (5.5)	98 (21.2)	

LTFU: Loss to follow-up, [&]P-value between those traced and found and those who were not found,

Tracing outcomes

Overall, 246 (36.2%) remained LTFU, had missing contact details or were not found in person (vital status was confirmed through an informant), 111 (16.3%) were alive and in care elsewhere (silent transfers), 141 (20.7%) had officially/silently transferred to other clinics, 120 (17.7%) were alive and out of care and 62 (9.1%) had died (Supplementary Table 5.1). Patient characteristics between those traced and found and those who were not found were similar except for CD4 count at last visit, duration on ART and site of ART initiation (Table 5.1). Three in five participants found (confirmed vital status) and included in further analysis were female, median age at last visit was 17.6 years (IQR: 6.3, 21.8), the majority started treatment in 2014-2015, and over half had been on ART for at least 12 months. Longer duration on ART and initiating ART after 2013 were associated with higher odds of being successfully traced. The success of tracing also differed by country of ART initiation (Supplementary Figure 5-2).

Mortality predictors

Overall, 462 participants had their vital status ascertained through the tracing and included in the analysis for mortality. Males had higher mortality than females (unadjusted rate: 13.3 (95% confidence interval (CI): 8.4, 21.9) and 8.6 (95% CI: 4.4, 19.3) per 100 py (Table 5.2). Mortality was highest for those who started ART at 0-<2 years old (16.5 (95% CI: 8.0, 34.1)) per 100 py and declined with higher age groups (20-24 years: 3.2 (95% CI: 1.1, 13.2) per 100 py). Children and youth who were immune suppressed at last visit also had higher mortality rates compared to those who were not (21.8 (95% CI: 10.7, 56.3 vs 8.9 (95% CI: 2.3, 64.9)). Mortality rates were lowest for those ≥12 months on ART.

After adjusting for measured covariates and within-site clustering, mortality remained lowest for young adults aged 20-24 years compared to infants aged <2years (adjusted Hazard ratio (aHR): 0.4 (95% confidence interval (CI): 0.3, 0.5)).

Table 5.2: Predictors of mortality among children, adolescents and young adults living with HIV who are successfully traced

Patient characteristics	Crude rates (per 100 person years) (95% CI*)	Crude HR¶ (95% CI*)	Adjusted HR¶£ (95% CI*)
Sex			
Male	19.42 (13.80, 27.31)	Ref	Ref
Female	11.58 (8.05, 16.67)	2.35 (0.20, 27.33)	1.88 (0.28, 12.53)
Age at last visit, years			
0-<2	47.63 (29.61, 76.62)	Ref	Ref
2-<10	19.28 (12.44, 29.89)	2.03 (0.55, 7.44)	2.13 (0.13, 35.40)
10-<20	10.91 (6.46, 18.42)	2.25 (0.33, 14.91)	2.13 (0.45, 10.09)
20-24	7.21 (3.99, 13.02)	1.38 (1.00, 1.91)	0.58 (0.15, 2.20)
Immunosuppression at last visit			
No	8.67 (3.25, 23.11)	Ref	Ref
Yes	15.39 (9.43, 25.13)	3.77 (0.82, 17.31)	3.03 (0.33, 27.74)
Duration on ART, months			
0-<6	22.46 (13.54, 37.25)	Ref	Ref
6-<12	52.60 (29.87, 92.62)	9.56 (1.94, 47.22)	0.04 (0.01, 0.20)
≥12	10.58 (7.60, 14.74)	0.16 (0.01, 2.10)	0.02 (0.01, 0.07)
Location of health facility			
Rural	15.12 (11.09, 20.62)	Ref	Ref
Urban	17.89 (11.78, 27.18)	4.53 (0.42, 49.43)	6.04 (0.93, 39.07)

ART: Antiretroviral therapy, *CI: confidence interval, ¶Hazard ratio, £Adjusted for country where health facility is located

5.5 Discussion

In our study, we were unable to ascertain through tracing the vital status of nearly 40% of CAYHIV because they could not be traced, nearly 20% were alive and out of care, 21% had silently transferred to other clinics and about a tenth had died. The estimated mortality was high at 9.1% (62/680). We also found that longer duration on ART and initiating ART after 2013 were associated with higher odds of being successfully traced. The success of tracing also differed by country of ART initiation. Higher mortality rates were found among infants aged below 2 years compared to young adults aged 20-24 years.

To the best of our knowledge, this is the first multi-country tracing study among CAYHIV considered LTFU. The high rates of unreported mortality are consistent with results from a systematic review [55], and a multi-regional tracing study [140], although mortality in our study was lower than a Zambian tracing study in which 26% of children had died [124]. The children in the Zambian study were younger (0-15 years) compared to those in our study (0-24 years) and as reported, younger children have a higher risk of mortality compared to older children. Mortality estimates among adults who are LTFU and traced vary across settings from 6% in Mozambique [237] to 30% in Malawi [238] with other studies reporting no differences [57]. The high mortality among children and youth LTFU could be patients were too ill to return to care and died immediately after being lost (i.e. they are lost because they have actually died), or may have stopped taking ART after their missed appointment, leading to non-suppression, disease progression and mortality (i.e. they died because they are lost and no longer on treatment) [71]. In our study, most of the children and youth died within one year from their last visit (median (IQR): 0.4 (0.2, 1.3) years) suggesting that they were disengaged from care despite being ill. There 27/62 (44%) of deaths that occurred within the first 3 months from the last clinic visit, and since visits are scheduled three-monthly, these appear to have missed their visits because they were deceased. The most common risk factors associated with LTFU in the literature, are psychosocial, structural and clinical barriers. Psychosocial barriers include denial of HIV status, non-disclosure, structural barriers include economic factors like lack of transport costs, long distance between

clinic and patient's home and clinical factors may include drug stockouts, long waiting times at the clinic, health care workers' attitudes [124] [238].

Mortality was highest among the youngest children. Infants are more vulnerable to severe disease progression and HIV-related complications. Without ART, only half survive to their second birthday [221, 239, 240]. Despite the introduction of early infant diagnosis (EID) and earlier initiation of ART, many children are only diagnosed during hospital admission with advanced disease and a high risk of mortality [147]. ART programmes focussed on EID and retention of these children should be strengthened to reduce mortality. Our study provides additional evidence that the first six months on ART are critical for survival [38, 119]. Longer duration on ART would also imply sustained viral suppression and hence reduced risk of mortality in this age group. ART programmes should ensure that CAYHIV achieve and maintain high CD4 counts and stay on ART, and trace those who are lost as soon as they miss a clinic visit. ART programmes should also prioritise children and youth who enter care with severe disease to ensure improved survival in the first six months on ART. Interventions to prevent LTFU among the youngest children and in the first six months after ART start are urgently needed.

Our study was strengthened by the large sample of traced CAYHIV from five countries in Southern Africa. Our results should be generalizable to pediatric HIV programmes with high rates of LTFU and mortality in low- and middle-income countries. Our study was limited by missing CD4 count/percent measurements, which we addressed using multiple imputation. We didn't have data on the causes of deaths and were also unable to link to national registers for any deaths that may have occurred among those that we were unable to find through tracing.

In conclusion, our study adds much-needed evidence on outcomes of CAYHIV who are LTFU, confirms high mortality in those lost and the need for tracing to assess vital status among those who are lost to accurately report on programme mortality. Treatment programmes must prioritize retaining CAYHIV who start ART below two years old and those in the first year of initiating ART, and actively trace them should they miss a clinic visit.

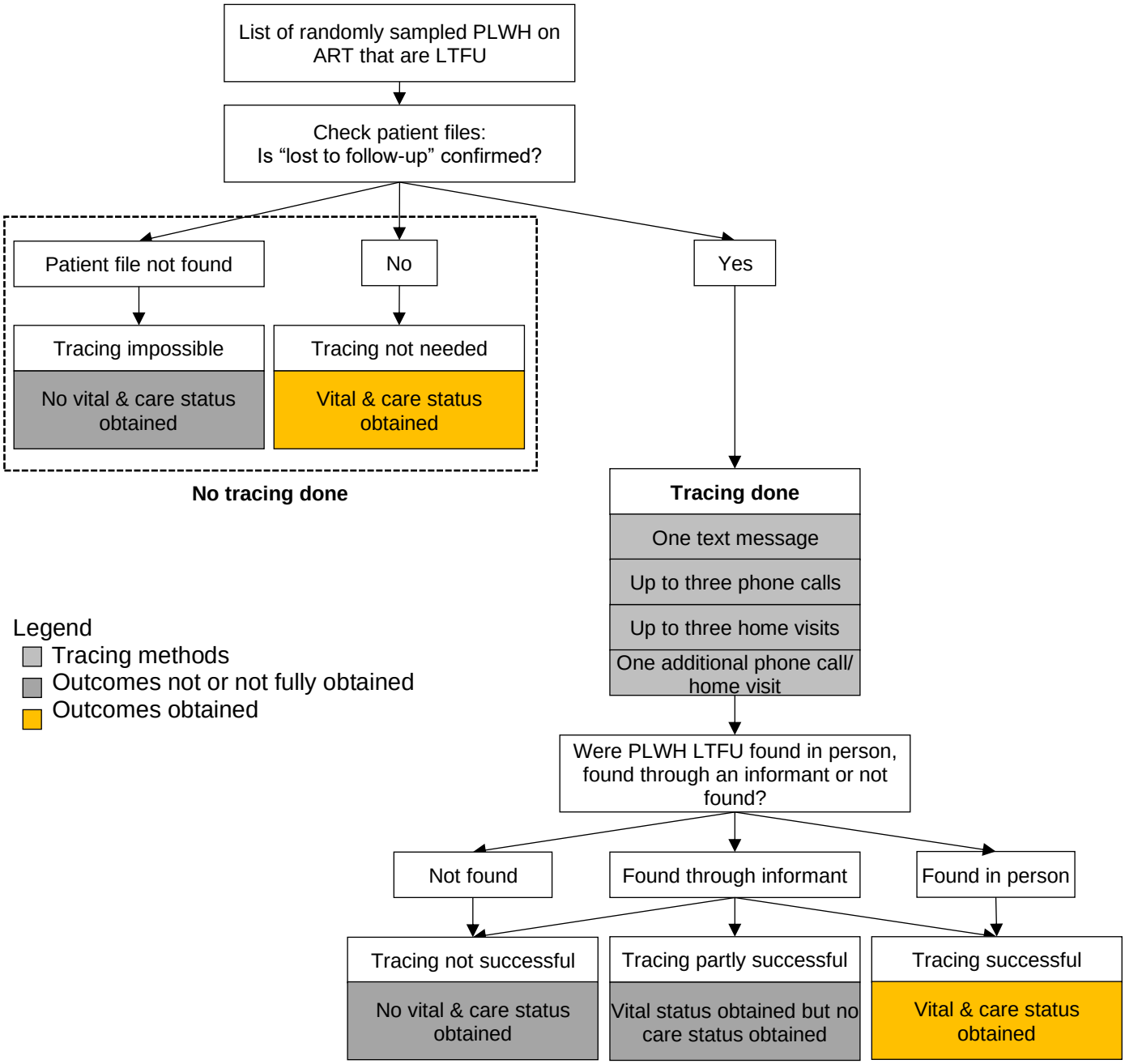
Author contributions: P.N performed the analyses and drafted the manuscript. B. C., N. A., M. B., and M. E. designed the study. N, A., performed the sampling. R. K., and M. S., and provided statistical support. M. C., and M-A. D., provided mentorship support. J. M., L. J., J. H., J. v. D., M. J. V., M. v. L., C. C., S. J. P. reviewed the study design and oversaw data collection. All authors reviewed, revised, and approved the final manuscript.

5.6 Supplementary materials

Supplementary Table 5.1: Description of tracing variables among children, adolescents and young adults living with HIV (CAYHIV) that were traced

	Number (N=680)	Percentage (%)
Location of the health facility		
Rural	336	49.4%
Urban	344	50.6%
Level of care at health facility		
Health centre	494	67.3%
District hospital/health centre	186	25.3%
Regional, provincial or university hospital	54	7.4%
Method of tracing used		
SMS (text messages)	96	13.8%
Phone call	139	27.7%
Home visit	407	58.5%
Ascertained tracing outcomes		
Dead	62	9.1%
Retained in care	111	16.3%
Transfer-out (self/official)	141	20.7%
Out of care	120	17.7%
Unknown care status but known to be alive	28	4.1%
Unknown (not found in person/missing contact details/LTFU)	218	32.1%
Tracing outcome details among those known to be alive		
Patient never missed a clinic visit	32	8.0%
Patient returned to care at the facility	79	19.8%
Patient in care at another facility	141	35.3%
Patient stopped taking ART	117	29.3%
Patient never started ART	3	0.8%
Patient/caregiver refused to be interviewed	3	0.8%
Tracing attempted but patient not found in person	25	6.3%
Care giver relationship with CAYHIV		
Parent	72	27.5%
Grand parent	46	17.6%
Spouse/ sexual partner	20	7.6%
Sibling	64	24.4%
Child	9	3.4%
Other relative	14	5.3%
Other	28	10.7%
Missing	9	3.4%
Time not seen from last visit until study start, months		
0-5	39	5.8%
6-11	79	11.8%
12-23	238	35.4%
24-35	150	22.3%
≥ 36	166	24.7%

ART: Antiretroviral therapy, LTFU: Loss to follow-up



LTFU: Loss to follow-up, PLWH: People living with HIV

Supplementary Figure 5-1: Flow chart showing the tracing process

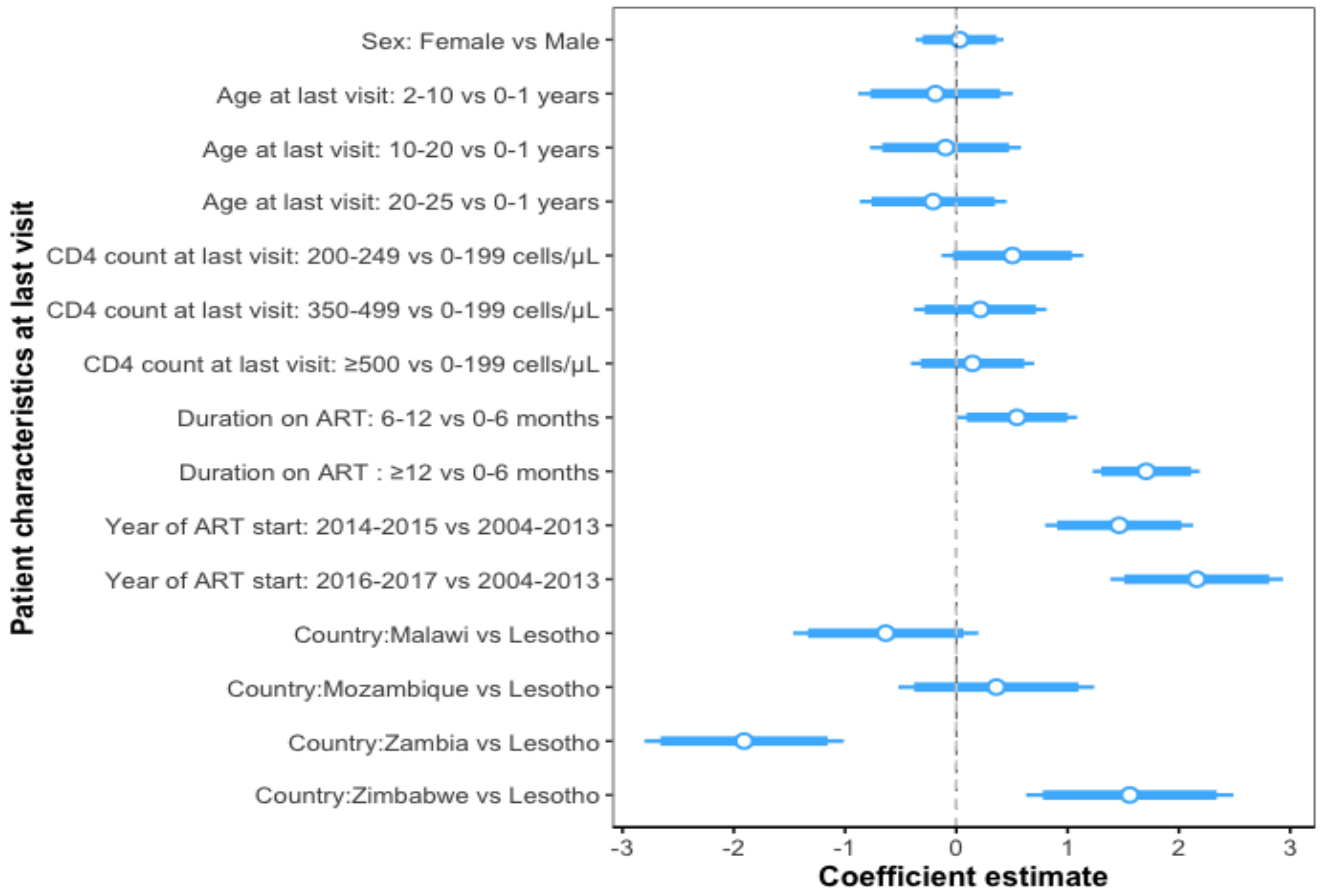


Figure 5-1: Factors associated with being found by the tracer using logistic regression models

CHAPTER 6 Self-transfers, Hospital Admissions and Mortality among Children and Adolescents Lost to Follow-up from Antiretroviral Therapy Programmes in the Western Cape, South Africa between 2004-2019: Linkage to Provincial Records

Paper overview

This paper describes outcomes among CAHIV who were initially reported as LTFU at four IeDEA-SA WC sites by linking their patient records to the WCPHDC. We used cause-specific Cox regression models to assess predictors of all the outcomes identified from the linkage.

Contribution to the thesis and novelty

This is the first study that uses linkage to a health register to assess outcomes of CAHIV initially reported as LTFU. The study gives insight into patient movements across the healthcare system, revealing a high proportion of self-transfers and hospital admissions among these children. It also highlights the value of integrated health exchange information systems that simplify patient transfers and provide patient-centered care.

Role of the candidate

I was responsible for conceptualising the study with the support of Professor Mary-Ann Davies and conducted all data analysis. I drafted the manuscripts, incorporated all relevant comments from co-authors, and finalised and submitted the manuscript.

Publication status: under review

This manuscript is currently undergoing the peer review process at the Pediatric Infectious Diseases Journal. It was initially submitted in April 2023, received an invitation for resubmission and has been accepted for publication.

6.1 Abstract

Background: Paediatric programmes face a high rate of loss to follow-up (LTFU) among children and adolescents living with HIV (CAHIV). We assessed true outcomes and their predictors among CAHIV who were LTFU using linkage to the Western Cape Provincial Health Data Centre (WCPHDC) at WC sites of the International epidemiology Databases to Evaluate AIDS-Southern Africa (IeDEA-SA) collaboration.

Methods: We examined factors associated with self-transfer, hospitalisation, and mortality using competing risks regression in a retrospective cohort of CAHIV initiating ART <15 years old between 2004-2019 and deemed LTFU (no recorded visit at the original facility for ≥180 days from the last visit date before database closure and not known to have officially transferred out or deceased).

Results: Of the 1,720 CAHIV deemed LTFU, 802 (46.6%) had self-transferred and were receiving care elsewhere within the WC, 463 (26.9%) had been hospitalised, and 45 (2.6%) CAHIV had died. The overall rates of self-transfer, hospitalisation, mortality, and LTFU were 9.4 (95% confidence interval (CI): 8.8, 10.1), 5.4 (95% CI: 5.0, 6.0), 0.5 (95% CI: 0.4, 0.7) and 4.8 (95% CI: 4.4, 5.3) per 100 person-years respectively. Increasing duration on ART before LTFU was associated with self-transfers, while male sex, older age at last visit (≥10 years vs younger) were associated with hospitalisation and immune-suppression at last visit was associated with five times higher mortality.

Conclusion: Nearly half of CAHIV reported as LTFU had actually self-transferred to another health facility, a quarter had been hospitalised, and a small proportion had died.

6.2 Introduction

Despite remarkable progress in preventing and treating paediatric HIV infection, the treatment of children and adolescents living with HIV (CAHIV) lags behind that of adults [15]. A major challenge is the high loss to follow-up (LTFU) rate, with reported LTFU on antiretroviral (ART) varying from about 5%-29% in the first year of ART initiation [67]. LTFU may represent unascertained mortality, hospitalisation, self-transfers (patient transferred but not documented by the original site, also called a silent or undocumented transfer), true disengagements from care or administrative errors from incorrectly recording patients who are still in care as LTFU [53, 63, 241]. In a study in Western Kenya, 16% of children LTFU had died, over 50% were out of care, and 11% had self-transferred [242]. LTFU biases programme performance reporting when outcomes among those considered lost are unknown [70]. For example, Kassanjee et al. recently conducted a study updating mortality estimates among children living with HIV on a global scale, and their findings revealed a decline in mortality over time. However, when they incorporated data from tracing those who were LTFU, mortality estimates increased, and the observed temporal reductions were somewhat diminished [140].

While physical tracing of all patients LTFU is valuable to accurately ascertain programme outcomes and reengage CAHIV in care, it is laborious, expensive and time-consuming. In 2007, South Africa's Western Cape (WC) Province consolidated the use of unique patient identifiers in all public sector services to integrate patient-level data for use by clinicians and other stakeholders responsible for patient follow-up (Supplementary Figure 1) [68]. The Western Cape Provincial Health Data Centre (WCPHDC) combines data on hospital visits or primary care facilities, laboratory and pharmacy data and electronic HIV and TB registers. If sufficiently complete, linkage of patient data to WCPHDC would be cheaper and more efficient than physical tracing for estimating HIV programme outcomes. Such linkage would also allow ongoing outcomes assessment in those LTFU, which is impossible in a once-off tracing exercise. Among CAHIV considered LTFU at WC sites of the International epidemiology Databases to Evaluate AIDS-Southern Africa (IeDEA-SA), we aimed to assess true outcomes and their predictors by linkage to the PHDC.

6.3 Methods

Study population and inclusion criteria

This was a retrospective cohort study of CAHIV initiating ART below the age of 15 years, between 2004-2019, at four IeDEA-SA WC sites (Khayelitsha, Gugulethu, Tygerberg and Red Cross) [172] who were recorded as LTFU at the facility of ART initiation. Khayelitsha and Gugulethu are primary healthcare facilities; Tygerberg and Red Cross are tertiary hospitals in urban areas.

Using the unique patient identifier used across public health services in the WC for CAHIV in our study, the WCPHDC provided the relevant sites with data that could indicate they were not truly lost. Data provided included HIV or non-HIV encounters such as health visits, pharmacy, laboratory tests, hospitalisations or death at a health facility. After linkage, the de-identified linked data were shared with IeDEA-SA for analysis. Using this data, we could identify if a patient had been hospitalised, died or was receiving routine HIV care at another WC facility, hence actually retained in care.

Study variables

Demographic, clinic and laboratory data from ART initiation to the last clinic visit were obtained from the IeDEA-SA database. Variables included sex, age, last visit (CD4 cell count and percentage measurement within six-18 months before the last visit), death date, last visit viral load (VL) copies/ml, ART and clinic history. Linked data comprised all health visits, including acute/emergency hospitalisations, death and death date, laboratory, pharmacy and other health encounters between 2004-2021. We generated the variable ‘immune-suppression’ based on the World Health Organisation (WHO) definition, using CD4 cell count for individuals over 60 months of age and CD4 percentage for those under 60 months [243]. If both measurements were available, we used whichever measure placed the child in the severe immune-suppressed category. In the multivariable analysis, we included biological sex, characteristics at last visit before LTFU (ART duration, age, immune-suppression, VL) ART start year and the ART registration site.

Definitions

We defined LTFU as having no recorded visit at the original facility for ≥180 days from the last visit date before the database closure and not known to have transferred out or died, with the last visit date before meeting the LTFU definition being considered the LTFU date. We defined virologic suppression as VL<400 copies/ml based on the lowest detection limit used in the facilities.

We defined the following outcomes of interest:

Self-transfers: having a visit at another facility (routine care, outpatient visit, laboratory results, or pharmacy ART pick-up) and was the first outcome to occur from the last clinic visit.

Hospitalisation: being admitted to the hospital subsequent to being recorded as LTFU, with hospitalisation being the initial outcome following the last clinic visit, unless the CAYHIV died during the hospitalisation in which case they were classified within the mortality category. Hospitalisations were also not considered self-transfers because we lacked confirmatory ART programme retention data.

Mortality: any patient with a recorded death date from the site or WC hospital outside the site or occurred during a hospitalisation and was the first outcome to occur from the last clinic visit.

“True” gap in care: no evidence of contact within the WC health system and no record of death after linkage.

Analysis

We used descriptive statistics (proportions, medians, interquartile ranges (IQRs)), rates and cumulative incidence functions (CIF) to summarise the data [181]. Patient characteristics (demographic and at the last visit) were stratified by outcomes from linkage (mortality, self-transfers, hospitalisations and true LTFU). We used multivariable cause-specific Cox proportional hazards models to assess factors associated with the outcomes of interest.

We assumed missing data were missing at random and imputed (10 times) missing CD4 cell counts, CD4 percentage and VLs using multiple imputation (MI) with a chained equation approach [235]. Results were then combined using Rubin's rules [236]. We report the MI-adjusted results. Analysis and data management were performed in Stata version 17 (Stata Corporation, College Station, TX, USA).

Ethical considerations

IeDEA-SA cohorts have obtained ethical approval to collect and transfer anonymised data through their respective Institutional Review Boards (IRBs). The IeDEA-SA data centre has approval from the University of Cape Town's IRB (Human Research Ethics Committee (HREC)) to receive and analyse these anonymised data. Cohort data were linked to WCPHDC by a staff member of the WCPHDC who has permission to access identified patient data. The linked data were de-identified before transfer to the IeDEA-SA data centre at UCT for analysis.

6.4 Results

Patient characteristics at the last visit with the original clinic

We included 1,720 CAHIV reported as LTFU, of whom 815 (47%) were males (Table 6.1). The total time at risk following LTFU was 8,503 person-years. At the last visit to the original clinic, the median age was 10.9 (IQR: 4.6, 16.7) years. More than one in four (454 (26.2%)) CAHIV were immune-suppressed, and 634 (36.9%) had a non-suppressed VL (Table 6.1). Most (1,201 (70%)) had been on ART for more than 24 months at the last visit before LTFU.

Table 6.1: Characteristics of children and adolescents living with HIV who initiated antiretroviral therapy (ART) between 2004-2019 in the Western Cape and were lost to follow-up (N=1,720)

Patient characteristics	N (%) or Median (IQR)
Sex, n(%)	
Male	815 (47.4)
Duration on ART, months, n(%)	
0-<6	247 (14.4)
6-≤24	272 (15.8)
>24	1,201 (69.8)
Year of ART start	
2004-2008	698 (40.6)
2009-2013	645 (37.5
2014-2019	377 (21.9)
Age at last visit, median (IQR) years	10.85 (4.61, 16.65)
Age at last visit, years, n(%)	
0-<2	200 (11.6)
2-<10	606 (35.2)
10-15	426 (24.7)
>15	488 (28.4)
CD4 percent at last visit (aged 0-5 years, n=539), median (IQR)	23.0 (13.9, 31.5)
CD4 percent at last visit (aged 0-5 years, n=539), n(%)	
<5	17 (3.2)
5-10	48 (8.9)
11-15	44 (8.2)
16-20	54 (10.0)
21-24	68 (12.6)
25-30	54 (10.0)
>30	103 (19.1)
Missing	151 (28.0)
CD4 count at last visit (aged >5years, n=1,181), cells/μL, median(IQR)	759.9 (411, 1205)
CD4 count at last visit (aged >5years, n=1,181), cells/μL, n(%)	
0-<200	96 (8.1)
200-<350	111 (9.4)
350-<500	134 (11.4)
≥500	718 (60.8)
Missing	122 (10.3)
Immune-suppressed at last visit[$]	
No	1,095 (63.7)
Yes	454 (26.4)
Missing	171 (9.9)
Viral load at last visit, copies/ml	
<400	634 (36.9)
≥400	634 (36.9)
Missing	452 (26.3)
Median time to contact with health facility in days (IQR)[^]	1500 (63, 2944)
Health facility of ART start	
Site 1	403 (23.4)
Site 2	665 (38.7)
Site 3	345 (20.1)
Site 4	307 (17.9)

IQR: Interquartile range, [$]Based on World Health Organization (WHO) 2006 definition of immune-suppression, [^] time from last visit at the original facility to first event after linkage

True outcomes of CAHIV after linkage to the WCPHDC

After linkage to the WCPHDC, 45 (2.6%) CAHIV had died, 463 (26.9%) had been admitted to the hospital, and 802 (46.6%) CAHIV had self-transferred and were receiving care elsewhere within the WC (Table 6.2, Figure 6-1). Overall, 410 (23.8%) of the CAHIV were truly LTFU, meaning no recorded outcomes were determined from linkage with their records. The median time from the last visit to each outcome was: death: 276 (IQR: 10, 1,219) days, hospitalisation: 1,788 (IQR: 97, 4,690) days and self-transfer 202 (IQR: 31, 1,834) days. The overall rates of mortality, hospitalisation, self-transfer, and LTFU were 0.5 (95% CI: 0.4, 0.7), 5.4 (95% CI: 5.0, 6.0), 9.4 (95% confidence interval (CI): 8.8, 10.1), and 4.8 (95% CI: 4.4, 5.3) per 100 person-years respectively. A greater proportion of those who had self-transferred were on ART for >24 months compared to other outcomes. The proportion with immune-suppression at the last visit was highest in those who died (57.8%) and lowest in those who had self-transferred (22.2%) (Table 6.2). There was higher mortality in the earlier years compared to later years, while there were fewer self-transfers in the earlier years relative to other outcomes but more transfers and true LTFU in later years. However, we expect we are less likely to ascertain outcomes through linkage for children whose last visit before LTFU was in more recent years, as they had less time to have subsequent health visits than those in the earlier years.

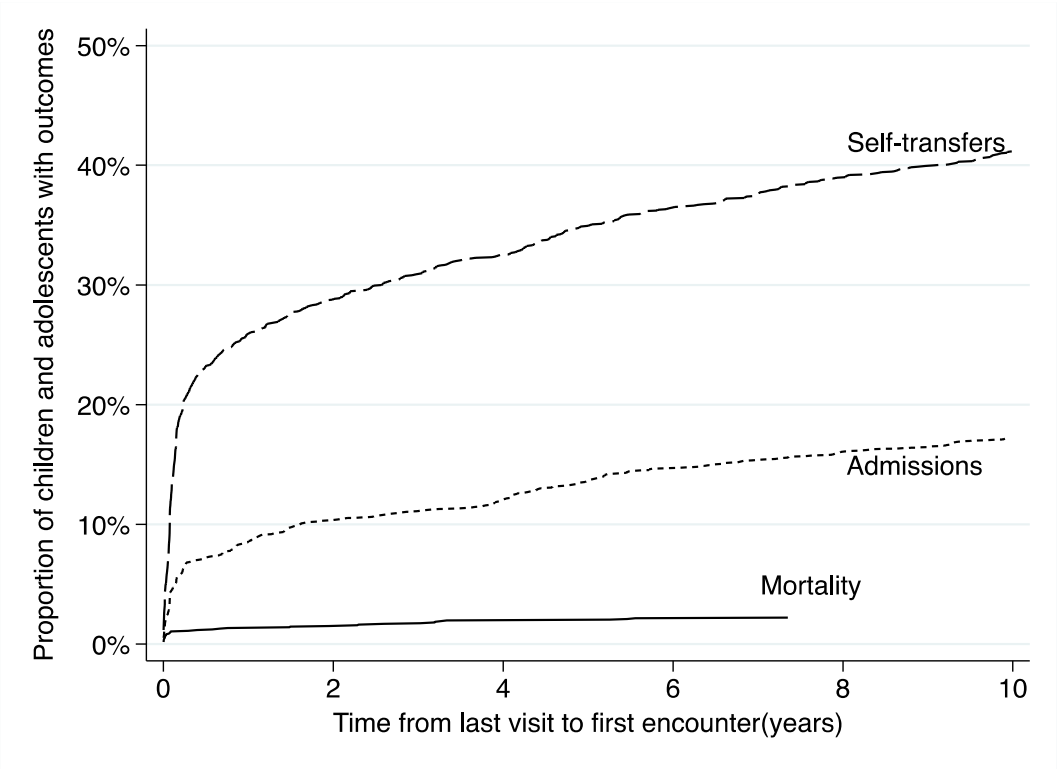


Figure 6-1: Competing risks cumulative incidence functions of mortality, hospital admission and self-transfer among children and adolescents living with HIV considered lost to care in the Western Cape between 2004-2019

Table 6.2: Characteristics of children and adolescents living with HIV who initiated antiretroviral therapy (ART) between 2004-2019 in the Western Cape and were lost to follow-up, stratified by outcomes after linkage to the Western Cape Provincial Health Data Centre

Patient characteristics	Mortality, n(%) (45 (2.6))	Hospitalisation, n(%) (463 (26.9))	Self-transfer, n(%) (802 (46.6))	Lost, n(%) (410 (23.8))	Total
Sex					
Male	22 (48.9)	248 (53.6)	356 (44.4)	189 (46.1)	815 (47.4)
Age at last visit, years					
0-<2	9 (20.0)	48 (10.4)	54 (6.7)	89 (21.7)	200 (11.6)
2-<10	8 (17.8)	124 (26.8)	267 (33.3)	207 (50.5)	606 (35.2)
10-≤15	8 (17.8)	119 (25.7)	214 (26.7)	85 (20.7)	426 (24.8)
>15	20 (44.4)	172 (37.2)	267 (33.3)	29 (7.1)	488 (28.4)
Duration on ART, months					
0-<6	9 (20.0)	107 (23.1)	52 (6.5)	79 (19.3)	247 (14.4)
6-≤24	6 (13.3)	89 (19.2)	86 (10.7)	91 (22.2)	272 (15.8)
>24	30 (66.7)	267 (57.7)	664 (82.8)	240 (58.5)	1201 (69.8)
Immune-suppressed at last visit[$]					
No	15 (33.3)	302 (65.2)	551 (68.7)	227 (55.4)	1095 (63.7)
Yes	26 (57.8)	114 (24.6)	178 (22.2)	136 (33.2)	454 (26.4)
Missing	4 (8.9)	47 (10.2)	73 (9.1)	47 (11.5)	171 (9.9)
Viral load at last visit, copies/ml					
<400	10 (22.2)	159 (34.3)	317 (39.5)	148 (36.1)	634 (36.9)
≥400	18 (40.0)	194 (41.9)	270 (33.7)	152 (37.1)	634 (36.9)
Missing	17 (37.8)	110 (23.8)	215 (26.8)	110 (26.8)	452 (26.3)
Median time to contact with health facility or death, days (IQR)	276 (10, 1219)	1788 (97, 4690)	202 (31, 1834)	1878 (1574, 3010)	1500 (63, 2944)
Time to contact with health facility or death, years					
≤ 1 year	0 (0.0)	23 (51.1)	146 (31.5)	445 (55.5)	614 (35.7)
1-2 years	1 (0.2)	3 (6.7)	32 (6.9)	50 (6.2)	86 (5.0)
>2years	409 (99.8)	19 (42.2)	285 (61.6)	307 (38.3)	1020 (59.3)
Year of ART start					
2004-2008	26 (57.8)	265 (57.2)	314 (39.2)	93 (22.7)	698 (40.6)
2009-2013	14 (31.1)	154 (33.3)	313 (39.0)	164 (40.0)	645 (37.5)
2014-2019	5 (11.1)	44 (9.5)	175 (21.8)	153 (37.3)	377 (21.9)

IQR: Interquartile range, [$]Based on WHO 2006 definition of immune-suppression

Factors associated with self-transfers, hospitalisation and mortality among CAHIV recorded as LTFU in the Western Cape between 2004-2019

In multivariable analyses, we found several patient characteristics associated with each patient outcome (Table 6.3).

Self-transfer: The hazard of self-transfer increased with increasing duration on ART beyond six months (>24 months vs 0-<6 months (aHR: 6.53 (95% CI: 2.66, 16.04)).

Hospitalisation: Females had a 21% lower hazard of hospitalisation than males (aHR; 0.79 (95% CI: 0.68, 0.92)) and adolescents (≥10 years at last visit) had a higher hazard compared to infants (>15 vs 0-<2 years: aHR: 4.93 (95% CI: 2.97, 8.20)). CAHIV who were immune-suppressed at the last visit had a 20% lower hazard of admission compared to those who were not immune-suppressed (aHR: 0.80 (95% CI: 0.67, 0.97)).

Mortality: CAHIV who were immune-suppressed at their last visit had nearly five times the mortality hazard compared with those who were not immune-suppressed (aHR: 4.87 (95% CI; 3.11, 7.63)).

True LTFU: Longer duration on ART compared to being on ART for <6 months was associated with ≥two-fold risk of being truly lost (6-≤24 months vs <6 months: aHR: 1.95 (95% CI: 1.06, 3.60)) (Supplementary Table 6.1).

Table 6.3: Cause-specific univariate and multivariable models of mortality, hospitalisation and self-transfers among children and adolescents living with HIV who initiated antiretroviral therapy (ART) between 2004-2019 in the Western Cape and were lost to follow-up (LTFU)

	Mortality		Hospitalisation		Self-transfer	
Patient characteristics	**Crude HR* (95% CI¢)**	**Adjusted HR*,∞ (95% CI¢)**	**Crude HR* (95% CI¢)**	**Adjusted HR*,∞ (95% CI¢)**	**Crude HR* (95% CI¢)**	**Adjusted HR*,∞ (95% CI¢)**
Sex						
Male	Ref	Ref	Ref	[Ref	Ref	Ref
Female	0.96 (0.69, 1.33)	0.94 (0.71, 1.24)	0.81 (0.72, 0.92)	0.79 (0.68, 0.92)	1.15 (1.07, 1.23)	1.04 (0.95, 1.14)
Duration on ART, months						
0-<6	Ref	Ref	Ref	Ref	Ref	Ref
6-≤24	0.68 (0.27, 1.71)	1.24 (0.52, 2.98)	0.85 (0.75, 0.96)	0.90 (0.68, 1.19)	1.71 (0.97, 3.01)	2.05 (1.14, 3.70)
>24	1.40 (0.88, 2.23)	2.13 (0.86, 5.29)	1.61 (0.99, 2.61)	1.07 (0.52, 2.21)	6.02 (2.67, 13.54)	6.53 (2.66, 16.04)
Age at last visit, years						
0-<2	Ref	Ref	Ref	Ref	Ref	Ref
2-<10	0.36 (0.13, 1.04)	0.40 (0.15, 1.04)	1.04 (0.87, 1.25)	1.02 (0.63, 1.65)	1.68 (1.37, 2.06)	0.71 (0.45, 1.11)
10-≤15	0.67 (0.36, 1.27)	0.65 (0.34, 1.26)	2.38 (1.35, 4.21)	2.24 (1.57, 3.18)	3.05 (1.19, 7.80)	1.06 (0.61, 1.79)
>15	1.76 (0.75, 4.17)	2.04 (0.98, 4.17)	3.89 (2.57, 5.89)	4.93 (2.97, 8.20)	4.09 (2.00, 8.36)	1.56 (0.94, 2.61)
Immune-suppressed at last visit$						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	3.67 (2.89, 4.79)	4.87 (3.11, 7.63)	0.70 (0.54, 0.92)	0.80 (0.67, 0.97)	0.65 (0.52, 0.82)	0.97 (0.84, 1.12)
Viral load at last visit, copies/ml						
<400	Ref	Ref	Ref	Ref	Ref	Ref
≥400	1.33 (0.59, 3.01)	0.99 (0.63, 1.57)	0.87 (0.66, 1.16)	1.09 (0.89, 1.32)	0.71 (0.57, 0.89)	0.94 (0.76, 1.17)

*HR: Hazard ratio, ¢ CI: confidence interval, ∞Adjusted for health facility where a patient was in care before LTFU and year of ART start, $ Based on WHO 2006 definition of immune-suppression

6.5 Discussion

In this study of 1,720 CAHIV recorded as LTFU at the original ART initiation facility, we found that the majority had been misreported as lost. After linkage to WCPHDC, nearly 80% of the CAHIV could be found, with most having self-transferred, a small proportion having died, one quarter hospitalised, and less than one quarter truly lost. Most self-transfers and deaths occurred within the first year of stopping care at the original facility, with a median time of 202 and 276 days, respectively. In adjusted analyses, mortality was almost five times higher among immune-suppressed patients. Risk factors for hospitalisation following LTFU were male sex, being ≥10 years old and not being immune-suppressed. CAHIV with more than six months on ART were more likely to self-transfer.

Most CAHIV reported as LTFU had self-transferred within the first year of stopping care at the original ART initiation facility. Longer duration on ART for ≥six months increased the likelihood of self-transfer, peaking nearly seven-fold after 24 months on ART. Our study provides evidence that most patients considered LTFU are in care elsewhere, especially with longer durations on ART. This could be due to changes across the patient's life course and extended treatment trajectories characteristic of HIV management. It is a normal expectation that CAHIV may relocate for reasons such as caregiver's work, school or address changes during the course of treatment [244]. Treatment interruptions and cycling in and out of care are expected [245].

Self-transfer may, therefore, be considered a relatively good outcome among those with a short (≤ 270 days) gap between the last visit at the original facility and the first subsequent visit at another facility within the province. It suggests that there may be no/minimal gap in care, and it is possible that these CAHIV sought treatment from facilities closer to them rather than the original ART registration facility. It is positive that patients appear to have sought care elsewhere and have not completely disappeared from the care system. Apparent self-transfer with a longer gap is concerning because it may mean that CAHIV might have been out of care for longer durations. Nonetheless, this situation remains more favourable than a complete disappearance from the healthcare system, where outcomes remain unknown.

Furthermore, since there is some migration between provinces, it is also possible that some of these CAHIV with apparent long gaps have been in care continuously but receiving care in another province. The high rates of self-transfer may also reflect what is happening in practice with increased decentralisation of the ART programme and healthcare system in recent years [201]. Additionally, two facilities included in this analysis are referral facilities where children who are very sick and/or young initiate ART. Once stable, they are intentionally transferred to health facilities closer to their home. If the recording of transfers is incomplete at the original facility, LTFU may appear to be high, while most children who initiated ART there are retained in care at another facility. Having integrated health exchange systems like the WCPHDC could support easy transfer and tracking of CAHIV from one site to another and allow for accurate estimates of patient retention across all facilities without burdening facilities with the capture of this data [68]. Tracing is important for establishing outcomes of those who are LTFU, especially those who have been on ART for ≤24 months, as a substantial proportion reported as LTFU in this period are either still in care or deceased. However, in the absence of health information exchanges where transfers can be identified, tracing all CAHIV LTFU is important.

Hospitalisation of people living with HIV is an important outcome which may indicate morbidity, mortality risk and impacts healthcare utilisation [246]. While hospitalisation may not necessarily indicate retention in care, it indicates retention within the healthcare system since the patient is known to be alive and seeking care. Hospitalisation was higher in males than females and significantly shifted to adolescents, with a five-fold higher risk in those older than 15 years. Conversely, Frigati et al. found no association between hospitalisation and sex. They found that older adolescents had a lower incidence rate of hospitalisation than younger adolescents in South African adolescents [247]. While hospitalisation among adolescents may indicate poorer treatment adherence and increased AIDS-related morbidity, it also includes non-AIDS-related admissions like violence exposure, traffic accidents, mental health issues and pregnancies, highlighting the need to strengthen adolescent care holistically [247]. In South Africa, young boys and men have a three-fold higher level of violence exposure than girls [248]. While we did not have data on admission reasons, Dicko et al. reported that 62% of hospitalisations in children with HIV in West Africa were AIDS-related. This proportion may be higher than in our

study as they included admissions in children not previously diagnosed or on ART [246], while we only included CAHIV who started ART previously. High adolescent hospitalisation rates may result from unique developmental, behavioural, psychosocial, and infrastructural factors necessitating tailored approaches to support them to optimise their treatment outcomes [228]. Strengthening adolescent-friendly programmes can improve adherence and retention, potentially reducing hospitalisation rates.

We observed far lower mortality compared to children that were traced in Malawi (2.6% vs 11%) and six southern African countries (2.6% vs 9%) [116, 249]. Mortality may be lower in the WC than in Malawi or other southern African countries due to better access to health care, nutrition and less poverty [64, 67, 119, 250]. Conversely, our study may have underestimated mortality because of limited death ascertainment outside the WC [128]. Mortality risk was nearly five times higher among immune-suppressed CAHIV than non-immune-suppressed CAHIV. This may suggest delayed diagnosis and/or ART initiation, and poor adherence, given that nearly half of the deaths occurred among adolescents aged ≥15 years [119, 250]. Other studies have reported similar results: in a study among nearly 4,000 CAHIV on ART in Europe and Thailand, severe immune-suppression was associated with a higher risk of death ≥six months after ART initiation [251]. This highlights the increased vulnerability of CAHIV, especially if diagnosis and/or the start of treatment is delayed, and the ongoing importance of identifying and testing CAHIV most at risk [147] [252]. Pediatric HIV programmes, including prevention of vertical transmission and early infant diagnosis, must be strengthened to ensure early ART initiation, adolescent adherence counselling, regular immune-suppression testing, and targeted tracing of immune-suppressed individuals. Although we did not have the cause of death recorded in our study, the EuroCoord study found that HIV-related infections and bacterial/sepsis-related infections were the commonest causes of death [251].

Only a quarter of CAHIV reported as LTFU were truly lost, implying that LTFU is non-ignorable, and analyses that censor LTFU patients may be biased [71]. Ignoring outcomes among those who are LTFU may lead to under-ascertaining retention and mortality estimates, two of the main indicators of programme effectiveness [71]. Our

results are consistent with tracing studies in pediatric and adult populations [53, 54, 58, 70]: for instance, in three East African countries (Uganda, Kenya and Tanzania), of 579 adult patients who were LTFU and traced, 69% were alive; of these, 82% had self-transferred and had their care status updated [70]. This suggests that programmes are doing well in patient retention but highlights the need for streamlined patient monitoring and smooth transfer between sites through user-friendly health exchange information systems.

To the best of our knowledge, this is the first study that has used linkage to a health information exchange to assess outcomes of CAHIV considered LTFU from the original clinic of ART initiation. Our results show that linkage to health information exchange data may be more efficient than manual tracing of all LTFU patients. We found information on at least 75% of patients who were LTFU; in tracing, only a sample of patients who are LTFU are traced. However, those truly lost still need to be traced so they can be reengaged in care. Linkage also allows the ascertainment of unrecorded and/or unreported transfers and deaths and the assessment of the burden of hospitalisations in patients with gaps in care [65, 128]. Furthermore, linkage for health outcomes assessment and monitoring holds significant promise for other health outcomes beyond HIV care and treatment. For example, the WCPHDC is crucial in providing readily accessible data to clinicians and individuals tasked with monitoring patients with specific health conditions like HIV, diabetes or tuberculosis daily. These data are made available to government clinicians to aid them in fulfilling their patient care responsibilities [68].

Our study was limited as we only explored linkage within the WC province, with a unique health identifier system in place. The CAHIV we could not find may have moved to other provinces or countries. Furthermore, there may be some underestimation of out-of-facility deaths due to limited linkage to the national population registry. There is also a possibility of over-estimation of self-transfers in cases where the outpatient visit was not HIV-related and HIV status not disclosed. Our study requires good health surveillance records, which may not be present in many resource-limited settings in sub-Saharan Africa with high HIV burdens. We could not assess temporal trends in true outcomes of those LTFU as CAHIV who were lost more recently would have had less time to present at a health facility than

those whose last visit was several years previously, biasing any analysis of the association with the calendar year of ART initiation.

Conclusion

We found that nearly half of CAHIV reported as LTFU at their original ART site had actually self-transferred to another health facility, while a quarter had been hospitalised and a small proportion had died. This is encouraging for pediatric HIV programmes as half of CAHIV misreported as lost are still in care. It also emphasises the importance of health information exchange data to accurately assess programme retention, mortality and LTFU and reduce the number of CAHIV needed to be traced for re-engagement in care. We recommend allocating resources to those most vulnerable to poor outcomes and leveraging health information exchange data to update programme estimates of retention, mortality and LTFU for better health outcomes for CAHIV. Furthermore, we recommend investigating the underlying reasons behind self-transfers, hospitalisations, and mortality among CAHIV.

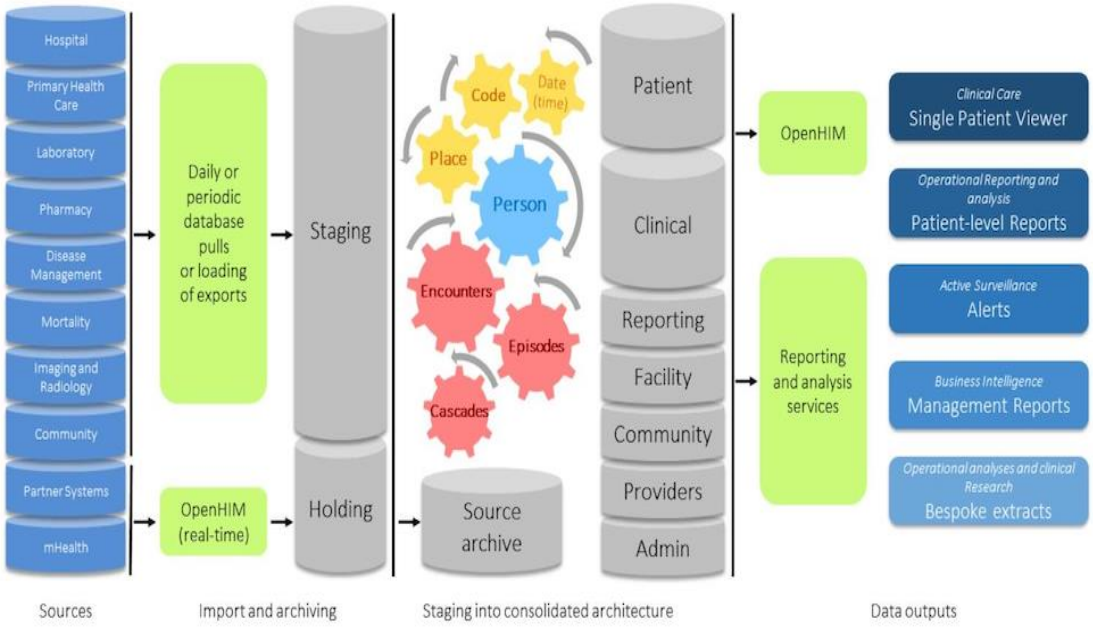
Author contributions: PN performed the analyses and drafted the manuscript. MC and M-AD provided mentorship support. AB, RW, BE, HR, ME, and CTY, reviewed the study design and oversaw data collection. All authors reviewed, revised, and approved the final manuscript.

6.6 Supplementary materials

Supplementary Table 6.1: Cause-specific univariate and multivariable models of true loss to follow-up among children and adolescents living with HIV who initiated antiretroviral therapy (ART) between 2004-2019 in the Western Cape and were lost to follow-up

	True LTFU	
Patient characteristics	**Crude HR (95% CI¢)**	**Adjusted HR*,∞ (95% CI¢)**
Sex		
Male	Ref	Ref
Female	1.12 (1.01, 1.24)	1.14 (0.98, 1.32)
Duration on ART, months		
0-<6	Ref	Ref
6-≤24	1.25 (0.88, 1.78)	1.95 (1.06, 3.60)
>24	2.18 (1.13, 4.22)	11.98 (5.97, 24.05)
Age at last visit, years		
0-<2	Ref	Ref
2-<10	1.16 (0.65, 2.09)	0.77 (0.68, 0.87)
10-≤15	1.01 (0.28, 3.64)	0.82 (0.34, 1.98)
>15	0.48 (0.12, 1.96)	0.50 (0.18, 1.39)
Immune-suppressed at last visit$		
No	Ref	Ref
Yes	1.00 (0.46, 2.18)	1.05 (0.74, 1.49)
Viral load at last visit, copies/ml		
<400	Ref	Ref
≥400	0.80 (0.41, 1.58)	0.88 (0.45, 1.70)

*HR: Hazard ratio, ¢ CI: confidence interval, ∞Adjusted for health facility where patient was in care before LTFU, $ Based on WHO 2006 definition of immune-suppression



Supplementary Figure 6-1: The architecture of the Western Cape Provincial Health Data Centre (WCPHDC)

CHAPTER 7 Correcting Mortality Estimates among Children and Youth on Antiretroviral Therapy in Southern Africa: A Comparative Analysis between a Multi-Country Tracing Study and Linkage to a Health Information Exchange

Paper overview

This paper examines the disparities in mortality outcomes using facility-level estimates and those obtained through tracing and linkage studies. Additionally, the paper explores programme-level mortality estimates using both uncorrected and corrected statistical methods and predictors of mortality when incorporating data from the tracing and linkage approaches.

Contribution to the thesis and novelty

In line with numerous studies conducted in adults, facility-level mortality and retention estimates based solely on patient databases or files at an individual facility often underestimate mortality rates if no additional data is ascertained among those reported as LTFU. To obtain more accurate estimates, it is necessary to incorporate outcomes among those LTFU using appropriate statistical methods. This study provides valuable insight into the differences observed between facility-reported mortality and corrected programme-level mortality estimates incorporating data obtained from tracing and linkage approaches. It highlights the importance of employing both tracing and linkage approaches, whenever feasible, as tracing revealed a higher number of deaths while linkage revealed a higher number of self-transfers.

Role of the candidate

I was responsible for conceptualising the study and conducting all data analysis. I drafted the manuscripts, addressed comments from co-authors and submitted to the journal.

Publication status: under review

This manuscript has been submitted to the Tropical Medicine and International Health journal as of October 2023.

7.1 Abstract

Objectives: To assess outcomes of children, adolescents and young adults (CAYHIV) reported as lost to follow-up (LTFU), correct mortality estimates for all CAYHIV for unascertained outcomes in those LTFU based on tracing and linkage data separately and assess predictors of corrected mortality using data from the International epidemiology Databases to Evaluate AIDS in Southern Africa (IeDEA-SA).

Methods: We included data from two different populations of CAYHIV; 1) clinical data from CAYHIV aged ≤24 years from Lesotho, Malawi, Mozambique, Zambia and Zimbabwe. Outcomes of patients LTFU were available from a tracing study; and 2) clinical data from CAYHIV aged ≤14 years from the Western Cape (WC) in South Africa. Outcomes of patients reported as LTFU were available from linkage to a health information exchange. For both populations, we compared six different methods for correcting mortality estimates for all CAYHIV and assessed predictors of mortality using weighted Cox models.

Results: We found substantial variations of mortality estimates among CAYHIV reported as LTFU versus those retained in care. Ascertained mortality was higher among lost and traceable CAYHIV and lower among lost and linkable than those retained in care (mortality: 13.4% (traced) vs. 12.6% (retained-other Southern Africa countries); 3.4% (linked) vs 9.4% (retained-WC)). A high proportion of CAYHIV reported as LTFU had self-transferred (21.0% and 47.0%) in the traced and linked samples respectively). The uncorrected method of non-informative censoring yielded the lowest mortality estimates among all methods for both tracing (6.0%) and linkage (4.0%) approaches at 2 years from ART start. Among the corrected methods using ascertained data, multiple imputation, incorporating ascertained data (MI(asc.)) and inverse probability weighting with logistic weights were most robust for the tracing approach. In contrast, for the linkage approach with low mortality ascertainment, MI(asc.) was the most robust.

Conclusions: Our findings emphasise that LTFU is not ignorable and both tracing and linkage improved outcome ascertainment: tracing identified substantial mortality

in those reported as LTFU. While linkage did not identify out-of-facility deaths, it showed that a large proportion of those reported as LTFU were self-transfers.

7.2 Introduction

Accurate estimation of mortality among children, adolescents and young adults with HIV (CAYHIV) is essential for HIV care programme evaluation. However, reported loss to follow-up (LTFU) remains a challenge as it may obscure several true outcomes. Mortality may differ between lost and retained patients, with many patients reported as LTFU having died; hence mortality may be high in programmes with high reported LTFU [69]. Furthermore, some patients reported as lost at one facility may have self-transferred to a different facility and still be receiving care [53-56]. Not accounting for outcomes in those reported as LTFU may result in underestimation of mortality and retention [57-59], impacting policy decisions.

Despite complexities surrounding reported LTFU, most routine settings assess mortality and retention from facility-level information in paper-based and/or electronic patient files/databases, which may be incomplete/ inaccurate, especially without tracing to assess outcomes among those reported as LTFU [71]. Site-reported mortality among adults living with HIV may be underestimated by up to 50% when not accounting for mortality in those reported as LTFU [129]. Limited data are available on outcomes among CAYHIV reported as LTFU, who may have different reasons for appearing LTFU compared to adults due to dependence on caregivers and mobility for education or employment. A systematic review of retention of children with HIV in the first 12 months on ART reported that only 12/35 studies described efforts to trace LTFU children, and none documented outcomes of traced children [67].

To generate unbiased mortality estimates, we need data on outcomes in a representative sample of those reported as LTFU. This can be obtained through tracing or linkage to other health information exchanges recording all health service encounters. These additional data need to be analysed alongside outcomes of retained CAYHIV. While there have been numerous analyses in adult populations [53, 69, 237], there is a dearth of research on CAYHIV. We assessed outcomes of

CAYHIV reported as LTFU through tracing and linkage, corrected mortality estimates for all CAYHIV and assessed predictors of mortality with six methods using data from the International epidemiology Database to Evaluate AIDS in Southern Africa (IeDEA-SA).

7.3 Methods

This study comprised two separate components (tracing-informed and linkage-informed studies) utilising data from six Southern African countries with ART cohorts that contribute to IeDEA-SA. IeDEA-SA is one of seven regions in the global IeDEA research consortium that collects and harmonises HIV/AIDS data [72].

Tracing-informed study in five Southern African countries

Study population and inclusion criteria

This was a retrospective cohort study among CAYHIV aged ≤24 years initiating ART between 2004-2017 in seven IeDEA-SA ART programmes in five countries (Lesotho, Malawi, Mozambique, Zambia and Zimbabwe).

Tracing sample

A multi-country tracing study was conducted among all people living with HIV (PLWH) reported as LTFU from selected IeDEA-SA programmes between October 2017-November 2019 [52, 66]. From the traced sample of 3,256 PLWH, we analysed a subsample of 680 CAYHIV with no recorded visit for ≥180 days or LTFU according to the sites' definition and not transferred out or deceased. Tracing used text messages, phone calls and home visits, reported elsewhere [52, 66].

Linkage-informed study in Western Cape (WC), South Africa

Study population and inclusion criteria

This was a retrospective cohort study among all CAYHIV who initiated ART aged <=14 years between 2004-2019 at four IeDEA-SA Western Cape (WC) sites [72, 172]. All sites are in Cape Town: two primary healthcare facilities (Khayelitsha and Gugulethu) and two tertiary hospitals (Tygerberg and Red Cross).

Linking records to the Provincial Health Data Centre

We identified CAYHIV aged 0-14 years at ART start reported as LTFU (no recorded visit at clinic of ART initiation for ≥180 days before database closure and not recorded as transferred out or deceased, with the last visit date before meeting the LTFU definition deemed the LTFU date). The province uses unique patient identifiers in all public health services. Utilising the unique identifier, the Western Cape Provincial Health Data Centre (WCPHDC) [68] provided sites with additional data on patients reported as LTFU, including any HIV or non-HIV-related encounters within the WC (health visits, pharmacy, laboratory tests, hospitalisation or death in a health facility). The de-identified linked data were shared with IeDEA-SA, allowing us to determine if a patient had been hospitalised, died or was receiving routine HIV care at another facility within the WC and retained, or was truly lost.

Outcomes

We defined **all-cause mortality** as having a recorded death date at the clinic or confirmed to have died through tracing, with information obtained through interviewing close informants, relatives or caregivers or through linkage to the WCPHDC.

We defined **self-transfer** as either a patient/informant reporting (tracing study) or having electronic evidence (linkage study) of a visit at another facility, ART pick-up, laboratory test, or hospitalisation after being reported as LTFU at the original ART initiation facility.

We defined **true LTFU** as previously reported LTFU with no evidence (reported or from linkage) of a healthcare visit or death.

Analysis

Analyses were performed in R version 4.2.2 and Stata v17 (Stata Corp., College Station, TX, USA). We summarised patient characteristics and outcomes using proportions, medians, and interquartile ranges (IQRs) [181]. ‘Immune-suppression’ was based on the World Health Organisation definition, using CD4 cell count/μL (<350 cells/μL) for individuals aged ≥60 months and whichever of CD4 percentage

(CD4% <30 for those under 12 months, <25 for those aged 12-35 months and <20 for those aged 36-59 months) or count was available for those aged <60 months [243].

Correcting mortality estimates for LTFU

We compared Kaplan Meier (K-M) curves/outputs for six methods (3 'uncorrected' and 3 'corrected') to estimate mortality. 'Corrected' methods accounted for unascertained mortality in those reported as LTFU.

'Uncorrected' methods

These methods were:

Complete cases (CC): discarding observations for CAYHIV reported as LTFU.

Non-informative censoring (NIC): censoring CAYHIV reported as LTFU from last contact date. NIC is used in most analyses of programme outcomes that do not trace LTFU patients.

Multiple imputation (MI(naïve)) of survival times and event status using a joint modelling approach [184] (with all measured variables included in the imputation model (Supplementary documentation)). This method assumes mortality can be imputed without additional tracing/linkage data, but this may be problematic if outcomes differ between those lost and in care.

'Corrected' methods

These methods were:

MI(asc.): multiple imputation after including the ascertained (asc.) data (outcomes from tracing/linkage) with indicators of missingness and ascertainment (successfully traced/linked) included in the imputation model [71].

Conventional inverse probability weights (IPW), weighting those LTFU and traced/linked by the inverse probability of being found/linked to represent all those who are lost using a null logistic model (IPW(asc.,cw)).

IPW(asc.,lw) as in (5) but the probability to be found modelled as:- Two logistic regression models: demographic and clinic characteristics associated with being sampled for tracing if reported as LTFU, and characteristics associated with being found by the tracer ('two-stage IPW') for tracing. One logistic model weighted for demographic and clinic characteristics associated with being successfully linked as all LTFU patients were in the linked sample ('one-stage IPW').

We used multivariable weighted Cox proportional hazards regression to assess factors associated with all-cause mortality using uncorrected and corrected methods.

Ethics

IeDEA-SA cohorts have ethical approval to collect and transfer anonymised data through their respective Institutional Review Boards (IRBs). The IeDEA-SA data centre has approval from the University of Cape Town's Human Research Ethics Committee (HREC) to receive and analyse these de-identified data. Cohort data were linked to WCPHDC by a WCPHDC staff member who has permission to access identified patient data. The linked data were de-identified before transfer to the IeDEA-SA data centre at UCT for analysis.

7.4 Results

Patient Characteristics in the five Southern African countries excluding South Africa (routine patients and tracing sample)

All routine patients (both retained and lost)

Among the 79,876 CAYHIV (33,187 (42%) retained, 46,689 (58%) reported as LTFU), 29% were males, with a median age at ART start of 18.7 (IQR: 7.9, 22.5) years (Table 7.1). Less than half were immune-suppressed at ART initiation, and 55% initiated ART between 2004-2013. At last visit, median age was 20.3 (IQR: 11.4, 23.9) years, with nearly 50% immune-suppressed and 44,588 (56%) on ART for ≥12 months. Before tracing a sample of lost participants, there were 4,164/33,187 (12.6%) reported deaths among patients retained in care. Compared to retained patients, those reported as LTFU were older at ART start (19.1 (IQR: 8.3, 22.5) vs. 17.9 (IQR: 7.4, 22.4) years), more likely immune-suppressed at ART start and last

visit (53% vs. 30% and 57% vs.38%, respectively), and less likely to have been on ART for ≥12 months at their last visit (54% vs. 58% respectively). In a sensitivity analysis, we restricted to CAYHIV aged 0-14 years at last visit totalling 25,384. In this subset, among those who remained in care, mortality was 16.1% (1,824/11,350) and 21.0% (43/205) among those who were lost and traceable.

Table 7.1: Patient characteristics at antiretroviral therapy (ART) start and last visit in routine and tracing data

Variable	All Routine patients (N=79,876)	Retained in care (N=33,187)	Lost patients (N=46,689)	Tracing sample (from lost) (N= 680)	Vital status confirmed (alive/dead) (N=462)	Vital status not confirmed (remained LTFU) (N=218)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Sex						
Male	23,316 (29.2)	10,246 (30.9)	13,070 (28.0)	273 (40.2)	182 (39.4)	91 (41.7)
Age at ART start, median (IQR) years	18.67 (7.90, 22.46)	17.90 (7.41, 22.37)	19.11 (8.26, 22.52)	16.57 (4.73, 21.10)	14.38 (4.31, 20.68)	14.13 (3.82, 21.08)T
Age at ART start, years						
0-<2	7,734 (9.7)	3,452 (10.4)	4,282 (9.2)	114 (16.7)	75 (16.2)	39 (17.9)
2-<10	16,286 (20.4)	7,066 (21.3)	9,220 (19.8)	136 (20.0)	92 (19.9)	44 (20.2)
10-<20	21,099 (26.4)	8,960 (27.0)	12,139 (26.0)	209 (30.7)	144 (31.2)	65 (29.8)
20-24	34,745 (43.5)	13,709 (41.3)	21,036 (45.1)	209 (30.7)	142 (30.7)	67 (30.7)
Age at last visit, median (IQR) years	20.33 (11.43, 23.95)	20.09 (11.22, 24.00)	21.03 (12.67, 24.59)	17.00 (5.40, 21.66)	17.58 (6.31, 21.80)	21.08 (12.74, 24.62)
Age at last visit, years						
0-<2	3,088 (3.9)	1,360 (4.1)	1,728 (3.7)	72 (10.6)	48 (10.4)	24 (11.0)
2-<10	14,313 (17.9)	5,984 (18.0)	8,329 (17.8)	154 (22.7)	100 (21.7)	54 (24.8)
10-<20	21,370 (26.8)	9,158 (27.6)	12,212 (26.2)	203 (29.9)	141 (30.5)	62 (28.4)
≥20	41,105 (51.5)	16,685 (50.3)	24,420 (52.3)	251 (36.9)	173 (37.5)	78 (35.8)
Immune-suppression at last visit*						
No	1,516 (1.9)	359 (1.1)	1,157 (2.6)	82 (12.1)	61 (13.2)	21 (9.6)
Yes	39,069 (48.9)	12,597 (38.0)	26,472 (56.7)	177 (26.0)	135 (29.2)	42 (19.3)
Missing	39,291 (49.2)	20,231 (61.0)	19,060 (40.8)	421 (61.9)	266 (57.6)	155 (71.1)
Year of ART start						
2004-2013	44,268 (55.4)	16,452 (49.6)	27,816 (59.6)	127 (18.7)	96 (20.7)	31 (14.2)
2014-2015	18,318 (22.9)	6,170 (18.6)	12,148 (26.0)	372 (54.7)	241 (52.2)	131 (60.1)
2016-2017	17,290 (21.7)	10,565 (31.8)	6,725 (14.4)	181 (26.6)	125 (27.1)	56 (25.7)
Duration on ART at last visit, months						
0-<6	27,589 (34.5)	10,906 (32.9)	16,683 (35.7)	263 (38.7)	141 (30.5)	114 (52.3)
6-<12	7,699 (9.6)	3,011 (9.1)	4,688 (10.0)	100 (14.7)	63 (13.6)	41 (18.8)
≥12	44,588 (55.9)	19,270 (58.1)	25,318 (54.2)	317 (46.6)	258 (55.8)	63 (28.9)
Country						
Country A	2,251 (2.8)	868 (2.6)	1,383 (3.0)	38 (5.2)	25 (5.4)	13 (6.0)
Country B	19,755 (24.7)	10,353 (31.2)	9,402 (20.1)	265 (36.1)	181 (39.2)	84 (38.5)
Country C	5,012 (6.3)	742 (2.2)	4,270 (9.2)	131 (17.9)	109 (23.6)	22 (10.1)
Country D	40,550 (50.8)	14,010 (42.2)	26,540 (56.8)	136 (18.5)	49 (10.6)	87 (5.5)
Country E	12,308 (15.4)	7,214 (21.7)	5,094 (10.9)	110 (15.0)	98 (21.2)	12 (5.5)

[§]tracing sample forms part of a larger traced sample (n= 3,256) that was sampled and traced including adult patients [52], IQR: Interquartile range, LTFU: Loss to follow-up, *Based on WHO 2006 definition of immune-suppression

Vital status confirmed (alive/dead) vs. not confirmed (true LTFU) in the tracing sample

Among 680 patients reported as LTFU, 462/680 (68%; 39% males) were found (successfully traced) with vital status ascertained, and 218/680 (32%; 42% males) remained LTFU (Table 7.1). Of patients with ascertained vital status, 62/462 (13.4%) had died and the remainder were confirmed alive although their retention status could not always be ascertained.

The median (IQR) age at ART start was similar among CAYHIV whose vital status was and was not ascertained in the tracing sample. However, at last visit, patients with ascertained vital status were younger (17.6 (IQR: 6.3, 21.8) vs. 21.1 (IQR: 12.7, 24.6) years), more likely immune-suppressed (29% vs. 19%) and more likely to have been on ART for ≥12 months (56% vs. 29%) than those who could not be traced. Mortality was slightly higher among those reported as LTFU and traceable than those remaining in care (13.4% vs. 12.6%), with great variability across countries (Table 7.2).

Table 7.2: Summary of the data used in the tracing-informed study of children, adolescents and young adults living with HIV (CAYHIV)

COUNTRY	CAYHIV	LTFU (N(%))	TRACED* (N(%))	NON- LTFU DIED	TRACEABLE LTFU DIED
COUNTRY A	2,251	1,383 (61.4)	38 (1.7)	19.6%	4.8%
COUNTRY B	19,755	9,402 (47.6)	265 (1.3)	7.7%	41.9%
COUNTRY C	5,012	4,270 (85.2)	131 (2.6)	63.8%	30.6%
COUNTRY D	40,550	26,540 (65.5)	136 (0.3)	14.3%	8.1%
COUNTRY E	12,308	5,094 (41.4)	110 (0.9)	10.1%	14.5%
TOTAL	**79,876**	**46,689 (58.5)**	**680 (0.9)**	**12.6%**	**13.4%**

LTFU: Loss to follow-up

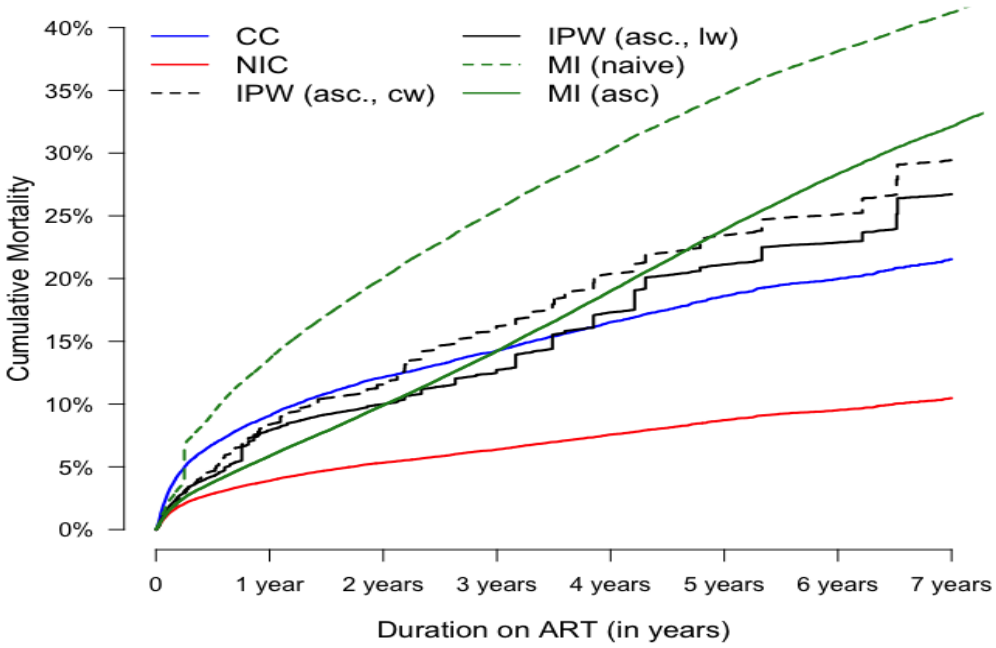
Table 7.3: Adjusted Cox regression models of mortality after correcting for loss to follow-up (LTFU) among those who were traced and found using different weighting methods

	CC	NIC	MI(naïve)	IPW(asc.,cw)	IPW(asc.,lw)	MI(asc)
Patient characteristics	**aHR£ (95% CI*)**	**aHR£ (95% CI*)**	**aHR£ (95% CI*)**	**aHR£ (95% CI*)**	**aHR£ (95% CI*)**	**aHR£ (95% CI*)**
Sex						
Male	Ref	Ref	Ref	Ref	Ref	Ref
Female	0.93 (0.85, 1.01)	0.87 (0.80, 0.95)	1.04 (0.98, 1.10)	1.02 (0.94, 1.09)	1.02 (0.94, 1.09)	1.02 (0.94, 1.09)
Age at last visit, years						
0-<2	Ref	Ref	Ref	Ref	Ref	Ref
2-<10	0.09 (0.08, 0.11)	0.05 (0.04, 0.06)	0.22 (0.20, 0.24)	0.20 (0.18, 0.22)	0.20 (0.18, 0.22)	0.20 (0.18, 0.22)
10-<20	0.05 (0.04, 0.06)	0.03 (0.03, 0.04)	0.14 (0.13, 0.16)	0.13 (0.12, 0.15)	0.13 (0.12, 0.15)	0.13 (0.12, 0.15)
≥20	0.08 (0.07, 0.10)	0.05 (0.04, 0.06)	0.19 (0.17, 0.21)	0.18 (0.16, 0.20)	0.18 (0.16, 0.20)	0.18 (0.16, 0.20)
Immune-suppression at last visit*						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.14 (0.92, 1.42)	1.98 (1.59, 2.45)	1.02 (0.91, 1.15)	1.07 (0.96, 1.18)	1.07 (0.96, 1.18)	1.07 (0.96, 1.18)
Year of ART start						
2004-2013	Ref	Ref	Ref	Ref	Ref	Ref
2014-2015	0.30 (0.26, 0.35)	0.33 (0.28, 0.38)	0.91 (0.84, 0.97)	0.83 (0.75, 0.92)	0.83 (0.75, 0.92)	0.83 (0.75, 0.92)
2016-2019	0.14 (0.11, 0.18)	0.20 (0.15, 0.26)	0.98 (0.89, 1.07)	0.79 (0.73, 0.85)	0.79 (0.73, 0.85)	0.79 (0.73, 0.85)

*CI: confidence interval, £Adjusted for country where health facility is located, CC: complete case, NIC: non-informative censoring, MI(naïve): Multiple imputation before ascertainment, IPW(asc.,cw): inverse probability weighting with constant weights, IPW(asc.,lw): inverse probability weighting with logistic weights, MI(asc.): multiple imputation incorporating ascertained data, *Based on WHO 2006 definition of immune-suppression

Comparison of K-M curves and Cox-model parameter estimates using uncorrected and corrected statistical methods of mortality ascertainment

Methods incorporating ascertained data produced higher mortality rates than uncorrected methods except for the MI(naïve) method, which imputed high mortality in those LTFU and estimated the highest mortality (Figure 7-1). The NIC method yielded the lowest mortality estimates. Among the corrected methods, IPW(asc.,cw) yielded higher estimates than IPW(asc.,lw). MI(asc.) yielded similar estimates to IPW(asc.,lw) until two years, whereafter MI(asc.) estimates were consistently higher.



ART: Antiretroviral therapy

Figure 7-1: Comparison of Kaplan-Meier survival curves using naïve methods: complete case (CC), non-informative censoring (NIC), inverse probability weighting (constant weights, IPW(asc.,cw)), inverse probability weighting (regression weights, IPW(asc.,lw)), multiple imputation, MI(naïve) and corrected methods: multiple imputation with ascertainment (MI(asc) in Southern Africa data. Additional outcome ascertainment of those lost to follow-up was obtained through tracing.

Estimates of associations with mortality from corrected methods were attenuated compared to uncorrected methods (Table 7.3) due to relative differences in mortality in traced vs. retained patients for different patient characteristics. For example, the association between age <2 years at last visit with mortality vs. age 2 to <20 years was attenuated, as the relative mortality difference in the traced vs. retained CAYHIV was greater for those aged 2 to <20 years (Supplementary Table 7.1). Similarly, the

apparent lower mortality of recent calendar years of ART initiation (2014-2017) vs. earlier years was attenuated due to relatively more unreported deaths in recent years vs. earlier years among those who were traced than those retained.

Patient characteristics in Western Cape, South Africa (routine patients and linked data)

All routine patients (both retained and lost)

Among 6,728 CAYHIV (5,008 (74%) retained, 1,720 (26%) reported as LTFU) with age at ART start <15 years, 48% were males, with median age at ART start of 1.5 (IQR: 0.4, 5.5) years (Table 7.4). At ART initiation, over 50% were immune-suppressed. At last visit, median age was 7.2 (IQR: 2.4, 13.2) years, with a quarter immune-suppressed. Most (58%) CAYHIV initiated ART between 2004-2009 with nearly two-thirds on ART for ≥12 months. Before linkage, there were 468/5008 (9.4%) reported deaths among those retained in care. Compared to retained patients, fewer of those reported as LTFU were immune-suppressed at ART start (42% vs. 61%) and at last visit they were older (median age 10.9 (IQR: 4.6, 16.7) vs. 6.2 (IQR: 1.9, 12.0) years) with a greater proportion on ART for ≥12 months; 76% vs. 54%).

Table 7.4: Patient characteristics at antiretroviral therapy (ART) start and last visit among children and adolescents who initiated treatment between 2004-2019 in Western Cape, South Africa

Variable	All routine patients (N=6,728)	Retained in care (N=5,008)	Lost patients (N= 1,720)	Vital status confirmed (alive/dead) (N=1,310)	Vital status not confirmed (remained LTFU) (N=410)
	n (%)	n (%)	n (%)	n (%)	n (%)
Sex					
Male	3,258 (48.4)	2,443 (48.8)	815 (47.4)	626 (47.8)	189 (46.1)
Age at ART start, median (IQR) years	1.54 (0.41, 5.47)	1.42 (0.38, 5.26)	1.88 (0.54, 6.22)	2.07 (0.62, 6.61)	1.52 (0.41, 5.02)
Age at ART start, years					
0-<2	3,723 (55.3)	2,841 (56.7)	882 (51.3)	646 (49.3)	236 (57.6)
2-<10	2,381 (35.4)	1,746 (34.9)	635 (36.9)	498 (38.0)	137 (33.4)
10-<15	624 (9.3)	421 (8.4)	203 (11.8)	166 (12.7)	37 (9.0)
Immune-suppression at ART start*					
No	2,165 (32.3)	1,392 (27.8)	773 (44.9)	670 (51.2)	103 (25.1)
Yes	3,774 (56.1)	3,052 (60.9)	722 (42.0)	488 (37.3)	234 (57.1)
Missing	789 (11.7)	564 (11.3)	225 (13.1)	152 (11.6)	73 (17.8)
Age at last visit, median (IQR) years	7.20 (2.39, 13.20)	6.18 (1.87, 12.0)	10.85 (4.61, 16.65)	12.92 (6.05, 18.21)	5.48 (2.48, 11.21)
Age at last visit, years					
0-<2	1,514 (22.5)	1,314 (26.2)	200 (11.6)	111 (8.5)	89 (21.7)
2-<10	2,642 (39.3)	2,036 (40.7)	606 (35.2)	399 (30.5)	207 (50.5)
10-<15	1,589 (23.6)	1,163 (23.2)	426 (24.8)	341 (26.0)	85 (20.7)
≥15	983 (14.6)	495 (9.9)	488 (28.4)	459 (35.0)	29 (7.1)
Immune-suppression at last visit					
No	3,675 (54.6)	2,580 (51.5)	1,095 (63.7)	868 (66.3)	227 (55.4)
Yes	1,759 (26.1)	1,305 (26.1)	454 (26.4)	318 (24.3)	136 (33.2)
Missing	1,294 (19.2)	1,123 (22.4)	171 (9.9)	124 (9.5)	47 (11.5)
Viral load at last visit (copies/ml)					
<400	2,874 (42.7)	2,240 (44.7)	634 (36.9)	486 (37.1)	148 (36.1)
≥400	2,661 (39.6)	2,027 (40.5)	634 (36.9)	482 (36.8)	152 (37.1)
Missing	1,193 (17.7)	741 (14.8)	452 (26.3)	342 (26.1)	110 (26.8)
Year of ART start					
2004-2008	2,026 (30.1)	1,604 (32.0)	422 (24.5)	353 (27.0)	69 (16.8)
2009-2013	1,852 (27.5)	1,410 (28.2)	442 (25.7)	393 (30.0)	49 (12.0)
2014-2019	1,400 (20.8)	998 (19.9)	402 (23.4)	295 (22.5)	107 (26.1)
2013-2015	838 (12.5)	553 (11.0)	285 (16.6)	181 (13.8)	104 (25.4)
2016-2019	612 (9.1)	443 (8.9)	169 (9.8)	88 (6.7)	81 (19.8)
Duration on ART at last visit, months					
0-<6	1,156 (17.2)	988 (19.7)	168 (9.8)	90 (6.9)	78 (19.0)
6-<12	1,565 (23.3)	1,328 (26.5)	237 (13.8)	145 (11.1)	92 (22.4)
≥12	4,007 (59.6)	2,692 (53.8)	1,315 (76.1)	1,075 (82.1)	240 (58.5)
Site					
Site 1	747 (11.1)	344 (6.9)	403 (23.4)	216 (16.5)	187 (45.6)
Site 2	1,961 (29.2)	1,296 (25.9)	665 (38.7)	645 (49.2)	20 (4.9)
Site 3	2,378 (35.3)	2,033 (40.6)	345 (20.1)	146 (11.2)	199 (48.5)
Site 4	1,642 (24.4)	1,335 (26.7)	307 (17.9)	303 (23.1)	4 (1.0)

LTFU: Loss to follow-up, IQR: Interquartile range, *Based on WHO 2006 definition of immune-suppression

Vital status confirmed (alive/dead) vs. not confirmed (true LTFU) in linkage data

Of 1,720 patients reported as LTFU, 1,310 (76%) were successfully linked and 410 (24%) were truly lost with no further records in the WCPHDC (Table 7.4). Among successfully linked patients, 45/1,310 (3.4%) had died, and 1,265/1,310 (97%) were receiving care within the WC, having self-transferred (802/1,265 (63%)) or been hospitalised and were alive at discharge (463/1,265 (37%)).

Compared to patients without linkable records, linkable patients were older (median age 2.1 (IQR: 0.6, 6.6) vs. 1.5 (IQR: 0.4, 5.0) years) and less likely immune-suppressed (37% vs. 57%) at ART start and last visit (median age 12.9 (IQR: 6.1, 18.2) vs. 5.5 (IQR: 2.5, 11.2) years; 24% vs. 33% immune-suppressed). More linkable than unlinkable patients were on ART for ≥12 months at last visit (82% vs. 59%). Mortality was higher among patients retained than those with vital status ascertained through linkage (9.4% vs. 3.4%) (Table 7.5).

Table 7.5: Summary of the data used in the linkage-informed study among children and adolescents living with HIV (CAHIV)

COHORT	CAHIV	LTFU/ LINKED (N (%))	NON-LTFU DIED	LINKABLE LTFU DIED
SITE 1	747	403 (54.0)	5.8%	1.2%
SITE 2	1,961	665 (33.9)	2.0%	3.9%
SITE 3	2,378	345 (14.5)	14.2%	1.2%
SITE 4	1,642	307 (18.7)	10.0%	3.3%
TOTAL	6,728	1,720 (25.6)	9.4%	3.4%

LTFU: Loss to follow-up

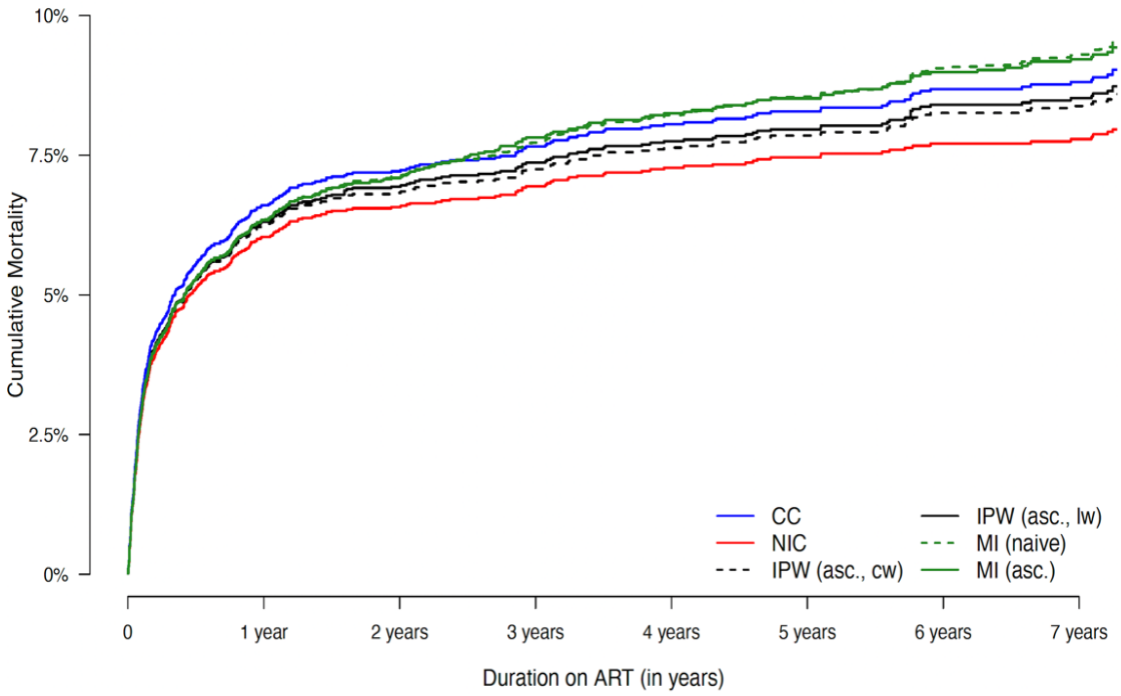
Table 7.6: Multivariable Cox regression models of mortality after correcting for LTFU among those who were linked and found using different weighting methods

	CC	NIC	MI (naive)	IPW (asc., cw)	IPW (asc., lw)	MI (asc)
Patient characteristics	**aHR£ (95% CI*)**	**aHR£ (95% CI*)**	**aHR£ (95% CI*)**	**aHR£ (95% CI*)**	**aHR£ (95% CI*)**	**aHR£ (95% CI*)**
Sex						
Male	Ref	Ref	Ref	Ref	Ref	Ref
Female	1.06 (0.88, 1.28)	1.08 (0.90, 1.31)	1.06 (0.85, 1.32)	1.10 (0.93, 1.31)	1.10 (0.93, 1.31)	1.10 (0.93, 1.31)
Age at last visit, years						
0-<2	Ref	Ref	Ref	Ref	Ref	Ref
2-<10	0.21(0.16, 0.28)	0.20 (0.15, 0.26)	0.20 (0.16, 0.25)	0.17 (0.11, 0.19)	0.15 (0.11, 0.19)	0.15 (0.11, 0.19)
10-<15	0.10 (0.07, 0.17)	0.09 (0.06, 0.14)	0.06 (0.03, 0.10)	0.05 (0.03, 0.06)	0.04 (0.03, 0.06)	0.04 (0.03, 0.06)
≥15	0.05 (0.03, 1.00)	0.03 (0.02, 0.06)	0.03 (0.02, 0.05)	0.03 (0.01, 0.03)	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)
Immune-suppression at last visit*						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	12.19 (9.30, 15.96)	11.40 (8.72, 14.90)	6.34 (4.92, 8.18)	7.89 (6.54, 10.32)	8.22 (6.54, 10.32)	8.22 (6.54, 10.32)
Year of ART start						
2004-2006	Ref	Ref	Ref	Ref	Ref	Ref
2007-2009	0.68 (0.55, 0.83)	0.65 (0.53, 0.80)	0.74 (0.58, 0.95)	0.66 (0.55, 0.82)	0.67 (0.55, 0.82)	0.67 (0.55, 0.82)
2010-2012	0.45 (0.33, 0.62)	0.40 (0.29, 54)	0.61 (0.47, 0.78)	0.44 (0.35, 0.64)	0.47 (0.35, 0.64)	0.47 (0.35, 0.64)
2013-2015	0.44 (0.29, 0.68)	0.38 (0.25, 0.58)	0.68 (0.47, 0.97)	0.40 (0.27, 0.61)	0.40 (0.27, 0.61)	0.40 (0.27, 0.61)
2016-2019	0.15 (0.07, 0.31)	0.15 (0.07, 0.31)	0.41 (0.25, 0.65)	0.21 (0.16, 0.46)	0.27 (0.16, 0.46)	0.27 (0.16, 0.46)

*CI: confidence interval, £Adjusted for site where patient initiated ART, ART: antiretroviral therapy, CC: Complete Case, NIC: Non-informative censoring, IPW (asc.,cw): Inverse Probability Weighting with constant weights, IPW (asc.,lw): Inverse Probability Weighting with logistic weights, MI (naïve): Multiple imputation before ascertainment, MI(asc): Multiple imputation with ascertainment, *Based on WHO 2006 definition of immune-suppression

Comparison of K-M curves and Cox model parameter estimates using uncorrected and corrected statistical methods for mortality ascertainment.

The NIC method consistently yielded the lowest estimates, despite low mortality in those reported as LTFU and linked (Figure 7-2). Due to high early mortality in facilities and few deaths ascertained through linkage, the CC method yielded higher estimates than corrected methods in the first two years. The MI (naïve) method yielded the highest mortality estimates at longer ART durations among all uncorrected methods.



ART: Antiretroviral therapy

Figure 7-2: Comparison of Kaplan-Meier survival curves using naïve methods: complete case (CC), non-informative censoring (NIC), inverse probability weighting (constant weights, IPW(asc.,cw)), inverse probability weighting (regression weights, IPW(asc.,lw)), multiple imputation, MI(naïve) and corrected methods: multiple imputation with ascertainment (MI(asc)) in Western Cape data. Additional outcome ascertainment of those lost to follow-up was obtained through linkage to the Western Cape Provincial Health Data Centre.

Overall, associations with mortality from corrected methods were similar to uncorrected methods (Table 7.6), as few extra deaths were identified from linkage. Nonetheless, the association of immune-suppression with mortality was attenuated in corrected vs. uncorrected methods because mortality was relatively higher among patients immune-suppressed and retained vs. linked patients than those non-immune-suppressed (Supplementary Table 7.1).

7.5 Discussion

We believe this is the first multi-country study comprehensively examining outcomes among CAYHIV reported as LTFU using tracing and linkage. Correcting for true outcomes (death or self-transfer) impacted mortality and retention estimates, with substantial variation between the tracing and linkage approaches. Ascertained mortality was higher among lost and traceable CAYHIV and lower among lost and linkable CAYHIV than those retained in care. Younger age, immune-suppression at last visit, and recent calendar years of ART initiation were associated with mortality in tracing and linkage approaches, although these associations were attenuated using corrected methods in the tracing approach.

Our study confirms previous findings that reported LTFU is non-ignorable, as patients reported as lost were identified as deceased or self-transferred, and demonstrates the complementarity of tracing and linkage in outcome ascertainment [52, 71, 128, 155, 249]. In addition, the reasons for reported LTFU among CAYHIV may be different from those of adults. CAYHIV reported as LTFU and traced were more likely to have died and less likely to have self-transferred than those who were linked (mortality: tracing vs. linkage: 13% vs. 3%; self-transfer: tracing vs. linkage: 21% vs. 47%). The resource-intensive nature of tracing, employing text messages, phone calls and home visits, may have allowed for a more thorough investigation and identification of deaths than linkage. However, while tracers can ascertain community deaths that are not reported to health facilities, they may not get accurate confirmation about a child's health visits compared to using electronic health records. In contrast, the WCPHDC links unique patient identifiers to health service data [68] and is more likely to find live patients accessing care within the health system, but unlikely to identify out-of-facility deaths, explaining the low mortality. Nevertheless, one site, a referral hospital where very sick and/or young children initiate ART, with high mortality, had more deaths among lost and linkable CAYHIV than those retained. Unlike with adults, we could not link CAYHIV data to the National Population Register (NPR) to ascertain missing out-of-facility deaths as few children have national identity numbers recorded in the WCPHDC [128]. Also, linkage was only possible for health visits in the WC, and we missed CAYHIV who migrated outside the WC [128]. While linkage likely under-ascertained deaths in those LTFU,

there may also be lower mortality in the WC due to better healthcare access and nutrition with less poverty than other countries.

While mortality was higher among CAYHIV reported as LTFU and traced compared to those retained [52, 66, 155, 249, 253, 254], previous studies have reported even higher mortality estimates in those LTFU [54, 69, 140]. In rural Tanzania, 40% of adults living with HIV who were reported LTFU and traced, had died [253]. Nonetheless, there was considerable observed variation between countries in our study suggesting that it may not be appropriate to apply mortality corrections for non-ignorable reported LTFU from one region, population or period to another, highlighting the need for updated context-specific estimates.

Results from comparison of six statistical methods also varied between tracing and linkage approaches because some methods are inappropriate as their strict assumptions May not be met. Using tracing, corrected mortality estimates were higher than uncorrected, particularly after two years on ART, whereas the reverse was true using linkage due to low mortality in linked patients. The uncorrected NIC method yielded the lowest estimates for tracing and linkage, implying that without additional outcome ascertainment among those reported as LTFU (irrespective of the proportion ascertained), programme-level mortality estimates will be underestimated, as has been found by other studies [53, 71, 130]. Whereas the CC method yielded higher mortality in the first two years of ART for tracing and linkage, this method is biased, especially with non-ignorable reported LTFU, due to excluding observations from patients reported as LTFU [255, 256]. Similarly, the MI(naïve) method, which yielded the highest mortality in both approaches, is biased because it does not incorporate information about missingness or the tracing and linkage processes [71]. The high estimated mortality may be driven by the imputation of deaths in those LTFU who are young and severely ill, as those retained with similar characteristics have the highest mortality. If the missingness process doesn't depend on the outcome, and we can model mortality among those lost using data from those retained in care, then MI(naïve) may provide correct results.

IPW methods yielded varying results. Logistic weights (IPW(asc.,lw)) produced lower mortality estimates in the tracing, while constant weights (IPW(asc.,cw)) did in the

linkage approach. IPW(asc.,cw) has been widely employed in other studies with consistent estimates [53, 54, 127]. However, if patient characteristics of those included in the tracing sample differ from those not included, or patients found by the tracer differ from those not found, as was the case in our study (Table 1), results may be biased [257]. Two-stage IPW(asc.,lw) is then more appropriate but relies on correctly-specified models to derive weights [71, 130]. Overall, estimates between the uncorrected and corrected methods were only slightly improved in the linkage approach because we could only ascertain additional deaths if they occurred in health facilities in the province, where a small proportion of all child deaths occur [258]. Given the low number of additionally ascertained deaths in the linkage data, the IPW(asc.,lw) may yield inconsistent estimates because only a small number of outcome covariate combinations was used to construct the weights (i.e., weights are based only on the few covariate values available among those identified as deceased). Schomaker et al. showed that MI(asc) was the most stable and appropriate method for low levels of ascertainment in their analysis of adult data [71], and is thus likely the most robust method for updating mortality estimates using the linkage approach in our study, given the low level of mortality ascertainment, while the most robust method using tracing data would be MI(asc.) or IPW(asc.,lw).

Risk factors for mortality were consistent in tracing and linkage approaches but with some differences between uncorrected and corrected methods due to relative differences in the proportion deceased among the retained and traced/linked CAYHIV with different characteristics. The finding of relatively fewer unreported deaths in traced younger CAYHIV vs. older CAYHIV compared to those remaining in care may partly be because health services may ascertain and confirm deaths through caregivers as part of routinely collected data among younger children, which is less feasible for older children and young adults who are less reliant on caregivers [187, 259]. Attenuation of the protective effect of recent calendar years of ART initiation in corrected methods suggests that while mortality in recent years may have declined because of programme and treatment improvements, part of the decline may be due to higher rates of reported LTFU masking under-ascertained mortality.

This is the first large multi-country study comparing tracing and linkage approaches to ascertain outcomes among CAYHIV reported as LTFU and using these data to

compare statistical methods for estimating programme-level mortality among CAYHIV. However, there are several limitations. The tracing exercise included adults and children so the number of CAYHIV reported as LTFU in the tracing sample was limited. Nonetheless, these CAYHIV were selected to represent all lost patients in the relevant age groups of the respective cohorts [52]. Outcomes could only be ascertained among 68% of those traced and their outcomes may differ from those not successfully traced. Linkage was limited to health service encounters within the WC, potentially resulting in an underestimation of outcomes, although the corrected methods accounted for this potential under-ascertainment by weighting patients successfully linked to represent all who were not linked.

Conclusions

In conclusion, this study highlights the importance and complementarity of tracing and linkage approaches to ascertain outcomes among CAYHIV reported as LTFU and confirms that LTFU is non-ignorable. Among those reported as LTFU, tracing identified substantial mortality while linkage showed that a large proportion were self-transfers but was unable to identify out-of-facility deaths. Incorporating additional data on mortality in those reported as LTFU is context-specific and it may not be appropriate to generalize correction of outcome estimates from one region or cohort to another.

7.6 Supplementary materials

Supplementary Table 7.1: Relative differences in mortality between traced/linked patients and retained patients for different patient characteristics.

Patient characteristics	Percent deceased			Percent deceased	
	Retained (%)	Traced (%)		Retained (%)	Linked (%)
Sex					
Male	7.1	12.1	Male	8.9	2.7
Female	4.5	7.1	Female	9.8	2.5
Age at last visit, years					
0-<2	20.4	23.6	0-<2	24.5	4.5
2-<10	6.1	13.0	2-<10	4.6	1.3
10-<20	4.4	6.9	10-≤15	3.1	1.9
≥20	4.3	4.4	>15	3.2	4.1
Immune-suppression at last visit					
No	7.8	4.9	No	3.1	1.4
Yes	6.4	9.0	Yes	28.0	5.7
Year of ART start					
2004-2013	8.1	12.6	2004-2006	13.3	2.6
2014-2015	2.4	7.3	2007-2009	11.4	4.5
2016-2017	0.9	10.5	2010-2012	5.9	1.7
			2013-2015	4.9	1.1
			2016-2019	1.6	2.4
Duration on ART, months					
0-5	8.0	10.6	0-5	33.0	4.2
6-24	5.3	19.1	6-24	6.1	2.5
≥24	3.6	13.6	≥24	2.3	2.4

Supplementary documentation on imputation models

In all of our imputation models, we applied the Amelia II method for imputation, utilizing five imputation models and then combined the results using Rubin's rules.

Our imputation process:

Uncorrected non-informative censoring (NIC) model:

We imputed missing data relating to immune-suppression at the last visit. The imputation model included complete variables of age at the last visit, sex, year of ART initiation, the country where the ART programme was located, censored mortality and survival time outcomes, and the partially observed immune-suppression variable.

Multiple imputation (MI(naïve)) model:

We imputed missing immune-suppression data for all CAYHIV, as well as mortality and time-to-event data for those reported as LTFU. The imputation model included complete variables of age at the last visit, sex, year of ART initiation, the country where the ART programme was situated, the incomplete immune-suppression variable, and the partially observed mortality and survival time outcomes.

Inverse probability weighting (IPW) and multiple imputation with ascertainment (MI(asc)):

We conducted imputation for missing immune-suppression data among all CAYHIV, incorporating information obtained from tracing and linkage. The imputation model included complete variables of age at the last visit, sex, year of ART initiation, the country where the ART programme was located, mortality and survival time outcomes, indicators for missing data, and indicators for ascertainment.

CHAPTER 8 Discussion and Recommendations

8.1 Introduction

The thesis sought to describe the characteristics and outcomes of CAYHIV in SSA while incorporating additional data among those reported as LTFU ascertained from tracing and linkage studies (i.e. two different approaches to obtaining additional data on outcomes). The papers included in this thesis utilise data from CAYHIV who initiated ART between 2004-2019 in six Southern African countries of Lesotho, Malawi, Mozambique, South Africa, Zambia, and Zimbabwe. These countries contribute data to IeDEA-SA and represent one of the largest pediatric HIV collaborative cohorts globally [72]. Together with data from other IeDEA regions, the IeDEA-SA cohort is used by UNAIDS to inform their AIDS impact module in the Spectrum software, including updating global pediatric HIV mortality estimates [140].

We analysed data among adolescents who had initiated ART, looking at virologic responses and early reported LTFU. Through tracing and linkage approaches, we then assessed outcomes among all CAYHIV initially reported as LTFU. We incorporated the outcomes of CAYHIV, initially reported as LTFU, and either traced and found or successfully linked to other health information exchanges, in corrected programme-level mortality estimates. The discussion will be a synopsis of the key findings of the thesis as a combined body of work. The primary focus of the discussion will be on persistently observed poorer outcomes among CAYHIV despite universal ART guidelines and the ambitious, fast-track 95-95-95 targets. The discussion will also cover strategies and alternative approaches to improve virologic and retention outcomes in this population.

The thesis includes five papers reporting the results (chapters 3-7): three have been published, one has been accepted for publication and one is under review. Collectively, the results reported in these papers emphasise the persistent challenges and negative outcomes experienced by CAYHIV despite the introduction of universal ART. The studies also highlight the challenge in assessing these outcomes due to the high rates of reported LTFU in this population. Chapters 3 and 4 (Papers 1 and 2) focused on evaluating virologic outcomes among adolescents

aged 10-14 years who initiated ART below ten years as they progressed into early adolescence (Chapter 3, Paper 1), and older adolescents aged 15-19 years with a sub-analysis among those initiating ART during pregnancy (Chapter 4, Paper 2). The analysis among the older adolescents was a competing risks regression analysis with virologic non-suppression (VNS) analysed alongside early reported LTFU. VNS is concerning among adolescents, given the multiple transitions at this stage of life associated with physiological changes, possible substance use, poor mental health, and initiating sexual activity [11, 74]. Chapters 5 and 6 examined outcomes among CAYHIV who were reported as LTFU and either traced through phone calls, text messages and home visits (Chapter 5, Paper 3) or linked to the WCPHDC [68] (Chapter 6, Paper 4, submitted to PIDJ). Chapter 7 (Paper 5, submitted to TMIH) focuses on correcting mortality estimates by incorporating the ascertained mortality from those who were successfully traced (Chapter 5) or linked (Chapter 6).

8.2 Virologic responses among adolescents (10-19 years)

As reported in the literature, there has been significant improvement in the survival of children living with HIV beyond their second birthday into adolescence and adulthood following earlier diagnosis and ART start as well as improved pediatric ART regimens and formulations [11]. ART is an important intervention for CAYHIV at the individual and public health levels. At the individual level, ART aims to achieve virologic suppression (VS) and prevent HIV disease progression, thereby improving health outcomes and reducing the risk of opportunistic infections and mortality. This further improves the quality of life by enabling CAYHIV to lead healthy, active lives [260]. At the public health level, the goal of ART for CAYHIV is to reduce the burden of HIV on individuals, families and communities as well as prevent new infections. ART, through VS, significantly reduces HIV transmission both vertically and to sexual partners or through the sharing of needles, thereby reducing HIV incidence in the population and reducing the HIV care burden on public health programmes [82].

We reported deteriorating 75th quantile viral loads (VLs) among adolescents with perinatally acquired HIV (APHIV) as they progressed through early adolescence (10-14 years), especially if on any second-line or a protease inhibitor (PI)-based first-line regimen. However, there was no particular age when VLs sharply increased and no

difference by sex [261]. This analysis used quantile regression, allowing for a more granular understanding of the factors that cause higher VLs in the most clinically relevant upper end of the range where transmission and poor health are most likely to occur, rather than just focusing on whether adolescents are suppressed or not. Other studies have also found deteriorating virologic outcomes among APHIV, suggesting adherence challenges as they transition from paediatric care [162, 228, 262, 263].

Our study among older adolescents aged 15-19 years found that about 15% experienced VNS in the first 24 months on ART, including among those initiating treatment during pregnancy [264], which is lower VNS than has been reported by other studies [84, 168, 195, 210, 264]. However, the results concur with a South African study [195], which found similar rates of VNS for adolescents attending an adolescent-friendly clinic. On the other hand, we found a very high rate of early reported LTFU in this population shortly after ART initiation, so our results should be interpreted cautiously, as the proportion with VNS may have been substantially higher if some or all of those reported as LTFU had VNS. Since CAYHIV will require treatment for many years more than adults, reported LTFU with treatment interruption, poor adherence, treatment failure and drug resistance can have serious consequences [265, 266].

8.3 Loss to follow-up among children and youth living with HIV

One of the biggest barriers to achieving VS among CAYHIV is the high rate of reported LTFU, as shown in our study among older adolescents (with the highest being among pregnant individuals) where more than 50% were reported as LTFU by 24 months on ART [264]. This study confirmed that AYHIV are a vulnerable population with high rates of reported LTFU, especially in the first 24 months after ART initiation [18, 136, 220-222]. Several other studies have reported AYHIV (10-24 years) to have worse HIV outcomes in terms of reported LTFU, VS, retention and mortality compared to either children (0-9 years) or adults (above 25 years) [32, 74, 122, 198]. For example, in East Africa, the cumulative incidence of reported LTFU at five years among young adolescents, older adolescents and young adults was 26.6%, 44.1% and 29.3%, respectively [136].

Reported LTFU makes it difficult to assess programme effectiveness because some patients reported as LTFU may have self-transferred (and may be virologically suppressed), some may have died [52, 71, 130, 237, 249, 267], and others may have been truly lost [57, 70, 155, 238, 249, 268]. ART programmes with substantial reported LTFU need to incorporate the true or inferred outcomes of those reported as LTFU in order to avoid biased estimates of retention, mortality, and the risk of being truly lost to the programme. Therefore, we used two approaches (tracing and linkage) to find out the true outcomes of those reported as LTFU and corrected the programme-level estimates of outcomes incorporating these outcomes.

8.4 Outcomes from tracing and linkage approaches among children and youth reported as LTFU

We found a disparity in true outcomes between CAYHIV initially reported as LTFU and traced or linked to a health information exchange [249]. The tracing approach revealed a high unreported mortality rate, while the linkage approach showed a low mortality rate [249]. The rate of self-transfers also varied in the two approaches, with nearly a quarter in the tracing approach found to have self-transferred vs. nearly half in the linkage approach. For both approaches, ascertained mortality among those reported as LTFU varied greatly between countries and sites. Furthermore, four in ten CAYHIV reported as LTFU who were attempted to be traced could not be found, while for a quarter of CAHIV who were reported as LTFU in whom linkage was attempted, there were no subsequent records in the WCPHDC. These CAYHIV are deemed to be truly lost. Reported predictors of mortality also differed in the two approaches and these effects were attenuated in the corrected methods in the tracing approach because of differences by patient characteristics in the relative proportion deceased among those retained and those reported as LTFU and traced. There was minimal impact on associations with mortality in the linkage approach as we did not find that many extra deaths in those LTFU with linkage. Due to incomplete data on transfers in the tracing study, we did not assess the predictors of self-transfers, however, the likelihood of transfers in the linkage increased with increasing duration on ART at the last visit (≥24 months vs. <6 months).

Mortality

The higher unreported mortality observed in the tracing approach could be attributed to the comprehensive tracing methods including phone calls, text messages and home visits. This may have facilitated the identification of deaths that occurred within the community but were not reported to any health facilities. The low mortality in the linkage approach may be because we could only link to health service data and not to the national population register (NPR) as we have previously done for adults [71, 128] since very few children in the WC had national identification numbers recorded by their HIV care service. The deaths in those reported as LTFU were thus hospital deaths in the WC that the original clinic of registration did not know of, and there may be substantial under-ascertainment of out-of-facility or out-of-province deaths [269]. The disparity in mortality in the two approaches may also be attributed to differences in resource availability and healthcare settings. The WC in South Africa is generally more well-resourced than other southern African countries, with fewer health care challenges like malaria and malnutrition. The differences in mortality between countries and sites suggests that reported LTFU and mortality estimates are context-specific and that studies estimating these outcomes may not always be generalisable.

Our findings are consistent with those reported in some other studies [55, 140]. However, overall mortality rates in our studies were lower than those reported in Malawi (11%) [116] and Zambia (26%) [124], compared to 3% in the WC and 9% in the other southern African countries. Mortality rates among adults reported as LTFU and traced also vary considerably across settings, from about 6% in Mozambique [237] to 30% in Malawi [238]. The high unreported mortality among traced patients could be attributed to patients being too ill to return to care and dying before their next appointment while still on ART. Alternatively, traced patients may have run out of ART after missing an appointment leading to VNS, disease progression, and mortality [71]. In both the tracing and linkage approaches, on average, CAYHIV who died did so within one year of being reported as LTFU (median time to death from LTFU: five months in the tracing study and nine months in the linkage study). In both approaches (tracing and linkage), 44% (27/62 and 20/45, respectively) of the deaths occurred within the first six months after the last clinic visit. The average time between appointments in both approaches was 3-6 months, indicating that at least

some of these individuals were likely too ill to return to care even before their next visit would have been scheduled.

Our study only identified younger age and immune-suppression at the last clinic visit as predictors of mortality among CAYHIV initially reported as LTFU. This is consistent with what has been found in other studies, although some studies report additional predictors including both programme and patient-related factors such as younger age (infancy), adolescence, shorter duration on ART, immune suppression and initiating ART with advanced disease [119, 140, 154, 270, 271]. Delayed diagnosis of HIV and subsequent initiation of ART among CAYHIV has been shown to double the mortality risk with very few surviving into adulthood [252]. CAYHIV are often diagnosed during hospitalisation with advanced disease, increasing their mortality risk [136, 147].

Self-transfers

Our findings also indicate that a substantial proportion of CAYHIV initially reported as LTFU had self-transferred to other health facilities. This result is consistent with what has been found in adult studies. In a systematic review examining outcomes of adults reported as LTFU in LMIC, Wilkinson et al. found that one in five ART patients initially reported as LTFU had self-transferred and was retained in care elsewhere [272]. Similarly, in Zambia, 13% of the children were found to have self-transferred [124]. Notably, on average, self-transfers occurred within the first year of being reported as LTFU in both the tracing and linkage approaches. This implies that at least for some CAYHIV there might not have been a substantial or even any gap in care and it is possible that these CAYHIV may have chosen to access care from facilities closer to them rather than the original facility of ART initiation [249]. This is encouraging, as it suggests that these patients have actively sought care in alternative facilities rather than disengaging from care completely.

Self-transfer may therefore not necessarily be a bad outcome, particularly among those with a fairly short gap (<270 days) between the last clinic visit at the original facility and the subsequent visit to a new facility. Nonetheless, longer gaps between last visit at the original site and the first visit at a new facility may indicate potential treatment interruptions for these patients, although it is possible that some received

treatment in another province in the interim. Caregiver-related issues may impact on where CAYHIV access care, with some transferring care to clinics closest to their homes, schools, or caregivers' workplaces [244]. In recent years, the scale-up of ART coverage and increasing decentralisation of the HIV care health system has contributed to a rise in self-transfers. ART scale-up has led to an increase in the number of patients seeking care and decentralisation has made services more accessible to the clients, consequently leading to high rates of self-transfers [273].

Tracing identified fewer self-transfers compared to linkage to WCPHDC. One plausible explanation for this is that the unique patient identifier allows a comprehensive tracking of a patient's engagement with the healthcare system in the WC. Thus, we were easily able to identify self-transfers compared to countries where no such linkage exists, and self-transfers are solely identified through physical tracing. Our results suggest that when the documentation of transfers is not fully captured at the initial healthcare facility, it may appear that there are high rates of reported LTFU when, in reality, many children who initiated ART are still receiving care at another facility. This implies that retention in care may be underestimated due to unknown self-transfers among patients reported as LTFU and programmes with high rates of LTFU can expect higher self-transfer rates with substantial retention underestimation.

Hospitalisation is an important indicator that may not necessarily confirm a patient's retention in care but does indicate that the patient remains in the healthcare system by indicating that the patient is alive and accessing health care. A quarter of the CAYHIV who were LTFU at their HIV care facility in the WC had been hospitalised. When estimating mortality, CAYHIV who died during hospitalisation were included in the overall mortality, while those who did not die during the study period were treated as alive and retained in care.

There is a need for HIV programmes to adapt to patient preferences for self-transferring to facilities closer to them, and to ensure that the patients can navigate the system seamlessly without experiencing treatment interruptions. Integrated health exchange systems like the WCPHDC are a promising tool to support such transfers and facilitate patient monitoring between sites, providing more accurate

estimates of retention in care and limiting the burden on health facilities of capturing all transfer information.

True LTFU

Among the traced and linked patients, 40% and 25% could not be found and linked respectively and were thus deemed "truly" lost [249] and methods are needed to estimate their likely mortality to fully correct programme mortality estimates accounting for deaths in all those reported as LTFU.

8.5 Correcting estimates of mortality for LTFU

Deaths or transfers among those reported as LTFU and determined through tracing or linkage to health information exchanges cannot simply be pooled with outcomes routinely captured. Appropriate statistical methods are needed to adjust mortality and retention estimates to account for patients who were reported as LTFU and not traced/linked or who remained LTFU despite tracing/linkage efforts ("truly lost") [53, 59, 253]. Ignoring deaths and self-transfers among CAYHIV recorded as LTFU can lead to an underestimation of overall programme-level mortality and retention estimates [56, 57, 140, 237]. This has been demonstrated in various studies including our previous global analysis of HIV mortality trends among children, where simulating mortality during the period of 180 days since last clinic visit among those initially reported as LTFU using data from children aged <15 years in our tracing study increased mortality and reduced the temporal trend of survival improvements [140]. Similarly, correction of estimates for reported LTFU among adults in two rural ART clinics in Mozambique doubled both mortality and survival estimates at four years from ART start among PLWH on ART [237]. In a national laboratory cohort study from South Africa, retention was grossly underestimated at six years compared to the national estimates which accounted for movement between ART sites nationwide [268].

Several approaches have been used to account for mortality or transfers among those who are reported as LTFU, although the majority have only been applied to adult cohorts [53, 54, 63, 69, 71, 128, 129, 132, 274, 275]. Outcomes of those whose vital status has been ascertained are used to represent those who are reported as

LTFU and not included in tracing/linkage or truly LTFU through weighting. Individuals who were not traced/linked or not successfully found during tracing/linkage are subsequently excluded from the analysis by assigning them a weight of zero.

For the tracing and linkage approaches, we conducted a comparative analysis of the existing statistical methods of correction for the two approaches, separately divided into uncorrected and corrected methods described in Chapter 7. Uncorrected methods do not incorporate additionally ascertained data and include the complete case (CC) method (the lost are dropped from the analysis), non-informative censoring (NIC) (the lost are censored at their last clinic visit) and imputation without ascertained data (MI(naïve)). We then incorporated the additionally ascertained data in corrected methods, which included IPW with constant weights (IPW(asc.,cw)), IPW with logistic regression weights (IPW(asc.,lw)) and imputation with ascertained data (MI(asc)).

In this comparative analysis, we found a disparity of results for the tracing and linkage approaches and that some methods were incorrect as their strict assumption requirements were not met. The conventional uncorrected NIC method provided the lowest estimates for both approaches, indicating the presence of inherent bias without additional outcome ascertainment. Similar findings have been reported in other studies that have explored alternative methods to correct mortality estimates for reported LTFU [53, 71, 130].

Among the corrected methods, the IPW methods yielded varying results, with logistic weights yielding lower estimates in the tracing approach and constant weights yielding lower estimates in the linkage approach. The MI(asc) method estimates were closer to the two-stage IPW method for up to five years in the tracing study, after which it yielded the highest results of all corrected methods. Conversely, in the linkage approach, the MI(asc) yielded consistently higher estimates compared to other corrected methods. Schomaker et al. demonstrated that the MI(asc) approach was the most stable and reliable when analysing adult data with low levels of ascertainment. We believe that with more data and perfectly specified imputation and ascertainment models, the MI(asc) and two-stage IPW(asc.,lw) method may yield similar results for the tracing approach and may be used interchangeably.

However, due to the low levels of ascertainment in the linkage approach for our data, the most robust method for correcting mortality estimates would be MI(asc). Given that our study is the first to compare these methods among CAYHIV, we recommend further investigation of these methods in different settings of CAYHIV to better understand their applicability and performance in different contexts.

Overall, corrected methods yielded higher estimates of mortality compared to uncorrected methods in the tracing approach, while with the linkage approach, the difference in estimates between uncorrected and corrected methods was smaller. We found that uncorrected methods were highly susceptible to bias in the presence of non-ignorable LTFU because they did not incorporate ascertained data among those traced/linked and found. If patient characteristics differ between those remaining in care and those reported as LTFU, these methods are incorrect even with high levels of ascertainment. The increase in mortality estimates after correction highlights the need to trace and ascertain outcomes among patients reported as LTFU and incorporate these outcomes in the calculation of mortality and retention estimates [71].

Repeated updates of retention and mortality estimates incorporating outcomes from those who are reported as LTFU are necessary to avoid bias and under-ascertainment of these estimates. Given that few countries in SSA have unique identifiers and/or good health information exchanges to identify transfers, we recommend the use of tracing combined with the methods that incorporate ascertained outcome data from those initially reported as LTFU. Where both tracing and linkage are possible, they should be used together to reduce the number of patients required to trace. Strengthening vital registration systems and other health information exchanges will allow linkage across the health sector for better ongoing estimates of programme outcomes. Tracing is then only required in patients where there are no subsequent linkable records so that out-of-hospital mortality and mortality not reported to death registers, and -self-transfers to services not included in the health information exchange can be identified.

8.6 Strategies and alternative approaches for improving treatment outcomes among children and youth living with HIV in ART programmes

Virologic outcomes

Use of Dolutegravir among CAYHIV

In July 2019, the WHO recommended using dolutegravir (DTG) as the preferred first- and second-line treatment for all populations including pregnant women and those of childbearing age [81]. However, South Africa has only recently revised its guidelines to roll out DTG for all people initiating ART and treatment-experienced patients [104]. In 2020 in South Africa, DTG was only used by patients newly initiating ART, those experiencing side effects on EFV and those who preferred to use it [276]. All our data on virologic outcomes are thus from the pre-DTG era.

While our studies of virologic outcomes among younger and older adolescents showed lower rates of poorer virologic outcomes than has been previously reported [261, 264], it is concerning that VLs increase as CAHIV progress through adolescence, requiring approaches tailored for CAYHIV. DTG is more effective and easier to take than other ARVs, with fewer side effects and a higher genetic barrier to development of drug resistance. It has hence been considered a game-changer in terms of VS, given the rising trend of resistance to EFV and NVP-based regimens [81]. As DTG becomes more widely available and utilised in HIV treatment including from earlier ages, we anticipate that the reduced pill burden, lower cost, fewer side effects, and high genetic barrier to resistance will result in improved VS for all PLWH, including adolescents. A systematic review done by Townsend et al. to assess the effectiveness and safety of DTG and raltegravir for treating CAHIV found that DTG was safe and effective in infants, children and adolescents, with all DTG studies reporting high efficacy and effectiveness [277]. An observational study of nearly 63,500 CAHIV aged 1 to 19 years in Tanzania, reported a proportion of 92% of the CAHIV achieving virologic suppression, with 66% who were previously unsuppressed becoming suppressed and 89% who were suppressed remaining suppressed [278]. These findings support the rollout of DTG among CAHIV. HIV programmes should however continue with virologic monitoring and continue to

provide adherence support especially among patients with high pre-transition VL, adherence challenges and possible pre-existing drug resistance, as these factors may be associated with DTG resistance [108].

Long-acting agents

Although the introduction of once-daily DTG addresses some adherence barriers, the daily oral medication still raises concerns about stigma and privacy [279, 280]. The use of long-acting (LA) agents has the potential to address some of these concerns [281]. The daily administration of ART to toddlers and school-aged CAHIV presents a significant challenge which may be alleviated by the use of LA agents to significantly improve VS. Additionally, the sexual behaviour of many adolescents and youth and their potential for transmission to their partners makes the use of LA agents particularly promising in this population both for treatment of those with HIV, and for prevention in those without. Enhancing suppression and retention among CAYHIV is crucial. However, drugs and delivery models must be simplified to facilitate suppression and retention without imposing unnecessary burdens on patients or healthcare providers like taking multiple pills sometimes more than once a day, having to find places to hide or keep medication securely without disclosing one's status inadvertently, more frequent visits to the health facilities for medication refills. Additionally, LA may require visits to be exactly on schedule, necessitate administration by a qualified healthcare worker for regular injections and may not be adaptable for administration outside of the healthcare facilities. Suboptimal dosing could also lead to an increased risk of drug resistance posing additional challenges. There is thus a pressing need for more studies to assess the optimal dosing, efficacy, and tolerability of LA agents in this population.

Virologic monitoring using point of care viral load testing

Although we found lower VNS among older adolescents than has been reported by other studies, adolescents in our study were still far off the 95% VS target. Standard of care virologic monitoring involves testing for VL at health facilities and sending samples to central laboratories for results. This frequently results in delays in receiving results, lost or misplaced samples and multiple patient visits [282, 283]. Diagnostic point-of-care (POC) testing technologies have expanded in recent years and more are expected to emerge [284, 285]. These technologies can potentially

expand VL testing coverage and improve efficiency in health care services, improving VS. POC testing simplifies and reduces clinic turnaround times for test results, improving HIV management. A study conducted in seven countries in SSA found that POC testing reduced the median time from sample collection to return of results to patients from 68 to six days [286]. Drain et al. found that POC testing combined with task shifting significantly improved VS and retention in care six months after ART initiation in a public clinic in Durban, South Africa [287]. PLWH assigned to POC testing had a 10% higher rate of VS and an 8% higher rate of retention compared to the standard of care laboratory VL testing [287]. Receiving results the same day has also been shown to reduce patient attrition [284, 285]. The high genetic barrier to resistance of DTG means that detecting VNS is less critical as most patients failing on DTG regimens are not taking their drugs rather than having resistance and will need adherence support but not a regimen change. Nonetheless, POC testing remains important to identify non-adherence and to rapidly identify the small number of patients who are at risk of DTG resistance. However, POC testing results may be hard to link to digitised health records. We recommend that POC testing is digitised, and results received in real-time, not only at the point of testing but also in the facility health records or information exchanges.

Retention in care

Rates of attrition from HIV care were alarmingly high, partly due to the lack of coordination and documentation of self-transfers across the health system. High rates of attrition suggest that our current models of care do not cater to the unique needs of CAYHIV, necessitating alternative and innovative care models addressing the underlying factors contributing to attrition.

Youth-friendly services

Youth living with HIV face various barriers in accessing treatment including long wait times at clinics, inconvenient clinic hours conflicting with school schedules, unaffordable out-of-pocket costs, long distances to travel to the clinics, fears around confidentiality and unfriendly attitudes of healthcare workers [288]. To improve outcomes among young people, HIV programmes need to be tailored towards their individual needs and preferences with a focus on youth-friendly services.

Differentiated service delivery models, including community-based ART delivery, multi-month prescriptions and dispensing of ART for those who are stable on ART or who are in school for long periods, have been successful in increasing retention rates among pediatric and adult clients and can be adapted for children and youth [289-294]. In addition, school-based mobile health services offering sexual and reproductive health services to young people including pregnant adolescents, and adapting clinic hours to make them convenient for young people along with engaging young people in the development and oversight of programmes, have demonstrated significant success in increasing the number of newly diagnosed adolescents in Kenya [295]. Over six months, these strategies resulted in an increase in retention from 62% to 94% [295]. They have been particularly effective when implemented in school settings, colleges or easily accessible places, and have proven to work for young people [296-299]. A study evaluating the effectiveness of community-based support (CBS) for improving treatment outcomes among adolescents receiving ART demonstrated significant reductions in attrition (reported LTFU and mortality) over a five-year period from approximately 42% in the first year to 36% in the fifth year [300]. Additionally, CBS was identified as a low-cost intervention with favorable cost-effectiveness indicating its potential to contribute towards achieving improved health targets in this population.

Increased peer support

Involving peers in HIV services for young people has been proven to make HIV programme services youth-friendly. Some ways of involving peers include teen expert clients, peer educators, mentors or ambassadors who can share their experiences and encourage fellow young people to adhere to ART and keep up to date with their clinic visits [299, 301]. A programme implemented by the Ministry of Health and Childcare carried out in 24 purposively selected districts in Zimbabwe between October 2017 to September 2018 demonstrated the effectiveness of a peer-led implementation programme for CAYHIV aged 0-24 years [302]. Peer supporters were trained and mentored to provide support throughout the HIV care continuum using methods such as phone call reminders, home visits and messages. A total of 15,223 household contacts and sexual partners with unknown HIV status were identified and referred for HIV testing. The programme achieved impressive outcomes, with 97% of CAYHIV being initiated on ART, 99% of them initiating on the

same day. Of those on ART, 99.8% remained alive on ART at 6 months with only a 2% mortality rate, and 99% achieved VS at six months. These results provide compelling evidence for the effectiveness of peer-led support services and highlight the importance of further exploration and implementation of such programmes in this population. It is however important to note that this programme did not collect data on costs and as a result could not provide a cost-effectiveness analysis of the programme. Consequently, it is difficult to ascertain the extent to which these findings could be generalizable to other settings. Creating peer support groups can also help provide a sense of community and encourage retention in care. Youth-friendly services unrelated to the client's main health condition like providing pamper packages for young mothers and hosting fun days in which health sessions are integrated with recreational opportunities can also increase youth uptake of HIV services [299, 301].

Integrating mental health services

Adolescents and young adults have been reported to experience disproportionate mental health challenges compared to adults or children [303]. In their systematic review of psychosocial interventions for improving engagement in care and health and behavioural outcomes for adolescents and young people living with HIV, Laurenzi et al. reported important small to moderate increases in ART adherence and reductions in VL [303]. Integrating mental health services into care can help address the emotional and psychological impact of living with HIV and improve engagement in care. These interventions may be in-person or virtual and should include peer support. Additionally, open and supportive caregiver-adolescent communication and good caregiver supervision were reported to guard against mental health problems among adolescents living in South Africa, highlighting the need for programmes to improve these relationships and provide support for caregivers [304].

Regular contact and active tracing of all CAYHIV using an integrated health information exchange

Where resources are available, pediatric ART programmes should support all CAYHIV and actively trace those who have missed at least one clinic visit. They should remind them of their appointments, and, for those who have missed a visit,

explore why they have not returned, assist them in returning to care at the most convenient location and keep track of their retention. In countries with good electronic medical records (EMR) and national registers, complementary methods of linkage and tracing should be used. In countries with poor EMR or national registers, policymakers should direct resources towards improving EMR. Integrated health information exchanges such as the WCPHDC [68] support data collection and management on all CAYHIV in a centralised health system and allow efficient sharing of health information between health providers and organisations, which improves the ability to follow-up on lost patients and improves continuity of care. This is in line with patient-centred care that accounts for patient preferences in how and where they seek care [305] and how this may change across the life course without requiring onerous record keeping of transfers at each site. Looking at the long treatment trajectory of these CAYHIV, it would be unrealistic to assume that they would be at the clinic of ART initiation throughout their lives. Ehrenkranz et al. suggested revising the service delivery cascade to a revolving door continuum of care, which accounts for the reality of patients engaging, disengaging, having treatment disruption and re-engaging in care throughout the entire period of HIV treatment [245]. CAYHIV cycling in and out of care should be expected, and health information exchanges can optimise continuity of care in this context. To minimize periods out of care, interventions that reduce provider and patient fatigue with clinic visits and taking daily medications should be considered.

Use of telemedicine or mobile health (telehealth) interventions

Telemedicine interventions have rapidly increased in recent years, providing convenient access to information and services for HIV prevention, treatment and care [306, 307]. Telehealth has been shown to improve adherence to ART [308] and patient retention [309], especially among youth living with HIV who are highly mobile. In SSA, internet use among the youth is increasing and ranges from 47% among Ugandan youth [310] to about 90% among youth in Cape Town, South Africa [311], making telehealth interventions increasingly viable. Telehealth interventions such as SMS/texting, social media or smartphone apps and other web-based platforms have been found acceptable among CAYHIV [312-315]. Jennings et al. found that two in three Kenyan youth were willing to use their devices to increase the uptake of HIV-related services across the care continuum [316]. Having access to other youth living

with HIV can provide adherence support and reduce feelings of isolation [317, 318]. Telehealth use among CAYHIV has been associated with more privacy and convenience compared to in-person healthcare, as reported by a recent pilot study among African-American youth in the San Francisco Bay [319]. However, the acceptability and feasibility of telehealth in an African setting may differ from that in the San Francisco Bay area due to sociocultural, economic and infrastructural factors. An exploratory randomised control trial evaluating the acceptability of a mobile phone support tool among Ugandan youth reported high acceptability and feasibility for promoting adherence and retention [320].

To date, most telehealth interventions have focused on the first (HIV testing or preventing primary acquisition of HIV) and last stages (ART adherence leading to VS) of the HIV care cascade, with limited focus on the critical middle stages (linkage, retention, and ART initiation). In their systematic review, Muessing et al. reported that only 4/23 of published studies and 5/32 studies in development for telehealth focused on linkage or retention or ART initiation [321]. There is a need for more research on the implementation of telehealth interventions among CAYHIV, particularly in linkage, retention and ART initiation.

8.7 Strengths and limitations

All the data analysed in this thesis were from the pre-DTG era preventing us from evaluating the impact of DTG on VS in this population. However, our findings provide valuable insight into the potential challenges faced by adolescents which may persist even in the DTG era. Due to limited VL monitoring in other Southern African countries, we were only able to assess virologic outcomes in South Africa. We were also only able to do linkage to a health information exchange in the WC as it is currently the only province in South Africa with such a system in place. It is worth noting that all our data is also from the pre-COVID-19 era, and we anticipate that there may have been an increase in treatment interruptions and reported LTFU during and after the COVID-19 pandemic. Additionally, we examined only CAYHIV on ART and thus excluded CAYHIV who had not initiated ART. Future research should consider all CAYHIV and it should consider a temporal trend analysis that

compares outcomes among CAYHIV before, during and after the COVID-19 pandemic.

Our research provides a comprehensive assessment of longitudinal HIV care outcomes for CAYHIV including virologic outcomes, reported and true LTFU, hospitalisations, mortality and self-transfers. Furthermore, the study is done in six high HIV-burden Southern African countries enhancing the robustness of our findings and their potential impact on shaping policies and guidelines for CAYHIV. The use of linkage to assess outcomes of CAYHIV initially reported as LTFU is a novel approach to HIV care management which has the potential to enhance healthcare for this population and optimize the allocation of resources. Furthermore, our study underscores the importance of not only accurately ascertaining the outcomes of CAYHIV reported as LTFU but also analysing their outcomes alongside the outcomes of those CAYHIV retained in care.

8.8 Conclusion

This thesis has reviewed the characteristics of CAYHIV in six Southern African countries and outcomes after incorporating ascertained outcomes from those previously reported as LTFU who were successfully traced or linked to provincial health records.

The first major contribution of this research is that we showed that adolescents with perinatally acquired HIV experience declining virologic outcomes as they transition from pediatric care from 10-14 years of age, particularly if receiving a PI-based first-line regimen or any second-line ART, with no differences by sex. With the majority of patients now transitioning to DTG regimens, virologic outcomes in this age group may improve. We also showed that older adolescents who initiated ART aged 15-19 years were at a heightened risk of reported LTFU shortly after ART start but a lower risk of VNS in those retained in care, especially those who initiated treatment during pregnancy. This analysis should be updated to examine virologic outcomes in the DTG era. We also recommend increased governmental and donor support and funding to expand VL monitoring services in other Southern African countries.

A second major contribution is that this is the first study that has looked at outcomes among CAYHIV who were initially reported as LTFU but subsequently traced or linked and had their outcomes ascertained using tracing and linkage approaches. We demonstrated the importance of using integrated health information exchanges and employing both tracing and linkage to optimally identify true outcomes in those reported as LTFU. Specifically, we observed that tracing was useful in identifying deaths that occurred outside of the healthcare facilities and were not reported, while linkage was highly effective in identifying self-transfers and hence reducing the number of individuals who needed to be traced to ascertain their outcomes. Our study highlights the need for supporting retention of all CAYHIV and emphasises the potential benefits of using integrated health information exchange systems to facilitate follow-up, improve coordination and documentation of self-transfers, and support these patients in receiving care. We, therefore, recommend the implementation of integrated health information exchanges and improved vital registry recording and linkage of health information exchanges to vital registries where feasible. We also recommend linking the WCPHDC to the national population register, as this may allow for ascertainment and understanding the burden and causes of mortality in all people accessing public sector health care in the province and enhance the province's ability to collect children's identity numbers more effectively. Furthermore, we recommend an ongoing assessment of true outcomes among CAYHIV reported as LTFU through a combination of linkage and tracing approaches.

Thirdly, this is the first study among CAYHIV to compare methods of analysis for incorporating outcomes among CAYHIV initially reported as LTFU, and provide corrected programme-level estimates of mortality of CAYHIV in Southern Africa. We also demonstrated new methods of correcting mortality for LTFU using two-stage IPW and MI(asc). We recommend ongoing correction of programme-level mortality and retention estimates in this group.

Finally, we believe it is important to implement youth-friendly interventions and use innovative technologies like telehealth and POC testing. Given the heterogeneity in treatment outcomes across these age bands, age-disaggregated outcomes among children (0-<2 vs. 2-9), adolescents (10-14 vs. 15-19) and young adults (20-24)

should be reported. Taking a comprehensive and innovative approach can help improve the health and quality of life of all CAYHIV.

In conclusion, substantial advancements have been made in improving the continuum of HIV care for CAYHIV. These improvements include the adoption of better treatment regimens, particularly the recent shift towards DTG-based therapies for this age group, as well as the increased number of youth friendly services. However, it is important to acknowledge that these achievements could be jeopardized by the persistent high rate of reported LTFU. To safeguard the progress made, it is imperative to implement comprehensive interventions that cover the entire spectrum of care from initial diagnosis to achieving virologic suppression. Furthermore, these interventions must adapt to the evolving needs of these CAYHIV as they grow and manage their chronic condition. In cases where individuals are reported as LTFU, it is essential to promptly initiate efforts to locate and reengage them to healthcare services, either through tracing or utilizing available health information exchanges, when possible, to reduce the risk of mortality.

References

1. Joint United Nations Programme on HIV/AIDS. UNAIDS data 2020 [7th July 2023]. Available from: [https://www.unaids.org/en/resources/documents/2020/unaids-data].
2. United Nations International Children's Emergency Fund (UNICEF). UNICEF Data: Monitoring the situation of children and women. 2020 [7th July 2023]. Available from: <https://data.unicef.org/topic/hivaids>.
3. AIDSinfo. Global data on HIV epidemiology and response 2023 [7th August 2023]. Available from: <https://aidsinfo.unaids.org>.
4. Joint United Nations Programme on HIV/AIDS. UNAIDS fact sheet 2022 [8th July 2023]. Available from: <https://www.unaids.org/en/resources/fact-sheet>.
5. Joint United Nations Programme on HIV/AIDS. In danger: UNAIDS global AIDS update.; 2022 27th July 2022. Report No.: 9210019792.
6. Dellar RC, Dlamini S, Karim QA. Adolescent girls and young women: key populations for HIV epidemic control. Journal of the International AIDS Society. 2015;18:19408.
7. United Nations International Children's Emergency Fund (UNICEF). Treatment in children living with HIV. UNICEF; 2022 6th July 2023.
8. Zanoni BC, Archary M, Buchan S, Katz IT, Haberer JE. Systematic review and meta-analysis of the adolescent HIV continuum of care in South Africa: the Cresting Wave. BMJ global health. 2016;1(3):e000004.
9. Joint United Nations Programme on HIV/AIDS. The path that ends AIDS: UNAIDS Global AIDS Update. 2023.
10. Johnson L. Thembisa 2017 [Available from: <www.thembisa.org>.
11. Slogrove AL, Schomaker M, Davies M-A, Williams P, Balkan S, Ben-Farhat J, et al. The epidemiology of adolescents living with perinatally acquired HIV: A cross-region global cohort analysis. PLoS medicine. 2018;15(3):e1002514.
12. Joint United Nations Programme on HIV/AIDS. Fast-track: ending the AIDS epidemic by 2030.; 2014 28th August 2019.
13. Joint United Nations Programme on HIV/AIDS. 90-90-90: An ambitious treatment target to help end the AIDS epidemic. 2014 October 2014.
14. Joint United Nations Programme on HIV/AIDS. Prevailing against pandemics by putting people at the centre—World AIDS Day Report 2020. UNAIDS; 2020.

15. Davies M-A, Pinto J. Targeting 90–90–90–don't leave children and adolescents behind. Journal of the International AIDS Society. 2015;18(7Suppl 6).
16. Joint United Nations Programme on HIV/AIDS. Ending AIDS: Progress towards the 90-90-90 targets. 2017 20th July 2017.
17. Ferrand RA, Munaiwa L, Matsekete J, Bandason T, Nathoo K, Ndhlovu CE, et al. Undiagnosed HIV infection among adolescents seeking primary health care in Zimbabwe. Clinical infectious diseases. 2010;51(7):844-851.
18. Evans D, Menezes C, Mahomed K, Macdonald P, Untiedt S, Levin L, et al. Treatment outcomes of HIV-infected adolescents attending public-sector HIV clinics across Gauteng and Mpumalanga, South Africa. AIDS research and human retroviruses. 2013;29(6):892-900.
19. Joint United Nations Programme on HIV/AIDS. UNAIDS data 2021 [27th April 2022]. Available from: https://www.unaids.org/sites/default/files/media_asset/JC3032_AIDS_Data_book_2021_En.pdf.
20. Khalifa A, Stover J, Mahy M, Idele P, Porth T, Lwamba C. Demographic change and HIV epidemic projections to 2050 for adolescents and young people aged 15-24. Global Health Action. 2019;12(1):1662685.
21. Joint United Nations Programme on HIV/AIDS. HIV prevention among adolescent girls and young women. UNAIDS Geneva; 2016 19th July 2016.
22. United Nations International Children's Emergency Fund. Adolescent HIV prevention. 2020 18 September 2020.
23. Zuma K, Simbayi L, Zungu N, Moyo S, Marinda E, Jooste S, et al. The HIV epidemic in South Africa: Key findings from 2017 national population-based survey. International Journal of Environmental Research and Public Health. 2022;19(13):8125.
24. Nabukeera-Barungi N, Elyanu P, Asire B, Katureebe C, Lukabwe I, Namusoke E, et al. Adherence to antiretroviral therapy and retention in care for adolescents living with HIV from 10 districts in Uganda. BMC infectious diseases. 2015;15(1):1-10.
25. Umar E, Levy JA, Bailey RC, Donenberg G, Hershow RC, Mackesy-Amiti ME. Virological non-suppression and its correlates among adolescents and young people living with HIV in Southern Malawi. AIDS and behavior. 2019;23:513-522.

26. Purchase S, Cunningham J, Esser M, Skinner D. Keeping kids in care: virological failure in a paediatric antiretroviral clinic and suggestions for improving treatment outcomes. African Journal of AIDS Research. 2016;15(3):301-309.
27. Nachega JB, Hislop M, Nguyen H, Dowdy DW, Chaisson RE, Regensberg L, et al. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents compared with adults in southern Africa. Journal of Acquired Immune Deficiency Syndromes. 2009;51(1):65.
28. Nglazi MD, Kranzer K, Holele P, Kaplan R, Mark D, Jaspan H, et al. Treatment outcomes in HIV-infected adolescents attending a community-based antiretroviral therapy clinic in South Africa. BMC infectious diseases. 2012;12:21.
29. CIPHER Global Cohort Collaboration, Slogrove AL, Botswana B, Anabwani G, Lesotho B, Mohapi E, et al. Inequality in outcomes for adolescents living with perinatally acquired HIV in sub-Saharan Africa: a Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Cohort Collaboration analysis. Journal of the International AIDS Society. 2018;21:e25044.
30. Dick B, Ferguson BJ. Health for the world's adolescents: a second chance in the second decade. Journal of Adolescent Health. 2015;56(1):3-6.
31. Flynn PM, Abrams EJ. Growing up with perinatal HIV. Aids. 2019;33(4):597-603.
32. Lowenthal ED, Bakeera-Kitaka S, Marukutira T, Chapman J, Goldrath K, Ferrand RA. Perinatally acquired HIV infection in adolescents from sub-Saharan Africa: a review of emerging challenges. The Lancet Infectious Diseases. 2014;14(7):627-639.
33. Folayan MO, Odetoyinbo M, Brown B, Harrison A. Addressing the socio-development needs of adolescents living with HIV/AIDS in Nigeria: a call for action. African Journal of Reproductive Health. 2014;18(3):93-101.
34. Slogrove AL, Mahy M, Armstrong A, Davies MA. Living and dying to be counted: what we know about the epidemiology of the global adolescent HIV epidemic. Journal of the International AIDS Society. 2017;20(S3).
35. Davies M-A, Pinto J, Bras M. Getting to 90-90-90 in paediatric HIV: What is needed? Journal of the International AIDS Society. 2015;18(7Suppl 6).
36. Kranzer K, Meghji J, Bandason T, Dauya E, Mungofa S, Busza J, et al. Barriers to provider-initiated testing and counselling for children in a high HIV prevalence setting: a mixed methods study. PLoS medicine. 2014;11(5):e1001649.

37. Callahan T, Modi S, Swanson J, Ng'eno B, Broyles LN. Pregnant adolescents living with HIV: what we know, what we need to know, where we need to go. Journal of the International AIDS Society. 2017;20(1):21858.
38. Davies MA, Gibb D, Turkova A. Survival of HIV-1 vertically infected children. Current Opinion in HIV and AIDS. 2016;11(5):455-464.
39. Bamford A, Lyall H. Paediatric HIV grows up: recent advances in perinatally acquired HIV. Archives of Disease in Childhood. 2015;100(2):183-188.
40. World Health Organization. Global update on the health sector response to HIV, 2014. 2014.
41. Enane LA, Davies M-A, Leroy V, Edmonds A, Apondi E, Adedimeji A, et al. Traversing the cascade: urgent research priorities for implementing the 'treat all'strategy for children and adolescents living with HIV in sub-Saharan Africa. Journal of virus eradication. 2018;4(Suppl 2):40.
42. World Health Organization. Adolescents: health risks and solutions. Fact sheet. 2018, (345).
43. United Nations International Children's Emergency Fund. Global and regional trends. 2019.
44. Gesesew HA, Ward P, Woldemichael K, Mwanri L. Early mortality among children and adults in antiretroviral therapy programs in Southwest Ethiopia, 2003–15. PloS one. 2018;13(6):e0198815.
45. Hudelson C, Cluver L. Factors associated with adherence to antiretroviral therapy among adolescents living with HIV/AIDS in low-and middle-income countries: a systematic review. AIDS care. 2015;27(7):805-816.
46. Kariminia A, Law M, Davies MA, Vinikoor M, Wools-Kaloustian K, Leroy V, et al. Mortality and losses to follow-up among adolescents living with HIV in the Ie DEA global cohort collaboration. Journal of the International AIDS Society. 2018;21(12):e25215.
47. Davies MA, Tsondai P, Tiffin N, Eley B, Rabie H, Euvrard J, et al. Where do HIV-infected adolescents go after transfer? - Tracking transition/transfer of HIV-infected adolescents using linkage of cohort data to a health information system platform. Journal of the International AIDS Society. 2017;20(Suppl 3):21668.
48. Zanoni BC, Archary M, Sibaya T, Musinguzi N, Haberer JE. Transition from pediatric to adult care for adolescents living with HIV in South Africa: A natural experiment and survival analysis. PloS one. 2020;15(10):e0240918.

49. Tsondai PR, Sohn AH, Phiri S, Sikombe K, Sawry S, Chimbetete C, et al. 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.
50. Penazzato M, Davies M-A, Apollo T, Negussie E, Ford N. Task shifting for the delivery of pediatric antiretroviral treatment: a systematic review. Journal of Acquired Immune Deficiency Syndromes. 2014;65(4):414-422.
51. Bonnie RJ, Stroud C, Breiner H, Committee on Improving the Health S, Council NR. Young adults in the 21st century. Investing in the health and well-being of young adults: National Academies Press (US); 2015.
52. Ballif M, Christ B, Anderegg N, Chammartin F, Muhairwe J, Jefferys L, et al. Tracing people living with HIV who are lost to follow-up at ART programs in Southern Africa: A sampling-based cohort study in six countries. Clinical infectious diseases. 2021.
53. Kiragga AN, Castelnuovo B, Musomba R, Levin J, Kambugu A, Manabe YC, et al. Comparison of methods for correction of mortality estimates for loss to follow-up after ART initiation: a case of the Infectious Diseases Institute, Uganda. PloS one. 2013;8(12):e83524.
54. Nyakato P, Kiragga AN, Kambugu A, Bradley J, Baisley K. Correction of estimates of retention in care among a cohort of HIV-positive patients in Uganda in the period before starting ART: a sampling-based approach. BMJ Open. 2018;8(4):e017487.
55. Fox MP, Rosen S. Systematic review of retention of pediatric patients on HIV treatment in low and middle-income countries 2008–2013. Aids. 2015;29(4):493-502.
56. Chammartin F, Zürcher K, Keiser O, Weigel R, Chu K, Kiragga AN, et al. Outcomes of patients lost to follow-up in African antiretroviral therapy programs: individual patient data meta-analysis. Clinical infectious diseases. 2018;67(11):1643-1652.
57. Zürcher K, Mooser A, Anderegg N, Tymejczyk O, Couvillon MJ, Nash D, et al. Outcomes of HIV-positive patients lost to follow-up in African treatment programmes. Tropical Medicine & International Health. 2017;22(4):375-387.
58. Egger M, Spycher BD, Sidle J, Weigel R, Geng EH, Fox MP, et al. Correcting mortality for loss to follow-up: a nomogram applied to antiretroviral treatment programmes in sub-Saharan Africa. PLoS Medicine. 2011;8(1):e1000390.

59. Geng EH, Bangsberg DR, Musinguzi N, Emenyonu N, Bwana MB, Yiannoutsos CT, et al. Understanding reasons for and outcomes of patients lost to follow-up in antiretroviral therapy programs in Africa through a sampling-based approach. Journal of Acquired Immune Deficiency Syndromes. 2010;53(3):405.
60. World Health Organization. HIV strategic information: accelerating progress on HIV testing and treatment for children and adolescents through improved strategic information. 2020.
61. Agwu AL, Lee L, Fleishman JA, Voss C, Yehia BR, Althoff KN, et al. Aging and loss to follow-up among youth living with human immunodeficiency virus in the HIV Research Network. Journal of Adolescent Health. 2015;56(3):345-351.
62. Sengayi M, Dwane N, Marinda E, Sipambo N, Fairlie L, Moultrie H. Predictors of loss to follow-up among children in the first and second years of antiretroviral treatment in Johannesburg, South Africa. Global health action. 2013;6(1):19248.
63. Anderegg N, Johnson LF, Zaniewski E, Althoff KN, Balestre E, Law M, et al. All-cause mortality in HIV-positive adults starting combination antiretroviral therapy: correcting for loss to follow-up. Aids. 2017;31 Suppl 1:S31-S40.
64. Brinkhof MW, Spycher BD, Yiannoutsos C, Weigel R, Wood R, Messou E, et al. Adjusting mortality for loss to follow-up: analysis of five ART programmes in sub-Saharan Africa. PloS one. 2010;5(11):e14149.
65. Schomaker M, Gsponer T, Estill J, Fox M, Boulle A. Non-ignorable loss to follow-up: correcting mortality estimates based on additional outcome ascertainment. Statistics in Medicine. 2014;33(1):129-142.
66. Christ B, Ballif M, Anderegg N, Chammartin F, Zürcher K, Michel J, et al. Tracing people living with HIV who are lost to follow-up at ART programs in Southern Africa: Study protocol. 2020.
67. Abuogi LL, Smith C, McFarland EJ. Retention of HIV-infected children in the first 12 months of anti-retroviral therapy and predictors of attrition in resource limited settings: a systematic review. PloS one. 2016;11(6):e0156506.
68. Boulle A, Heekes A, Tiffin N, Smith M, Mutemaringa T, Zinyakatira N, et al. Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. International Journal of Population Data Science. 2019;4.
69. Geng EH, Odeny TA, Lyamuya RE, Nakiwogga-Muwanga A, Diero L, Bwana M, et al. Estimation of mortality among HIV-infected people on antiretroviral

treatment in East Africa: a sampling based approach in an observational, multisite, cohort study. The Lancet HIV. 2015;2(3):e107-e116.
70. Geng EH, Odeny TA, Lyamuya R, Nakiwogga-Muwanga A, Diero L, Bwana M, et al. Retention in care and patient-reported reasons for undocumented transfer or stopping care among HIV-infected patients on antiretroviral therapy in Eastern Africa: application of a sampling-based approach. Clinical infectious diseases. 2015;62(7):935-944.
71. Schomaker M, Gsponer T, Estill J, Fox M, Boulle A. Non-ignorable loss to follow-up: correcting mortality estimates based on additional outcome ascertainment. Statistics in medicine. 2014;33(1):129-142.
72. International epidemiological Database to Evaluate AIDS-Southern Africa (IeDEA-SA). International epidemiological Database to Evaluate AIDS-Southern Africa collaboration 2020 [7th July 2021]. Available from: <https://www.iedea-sa.org>.
73. Institute of Social and Preventive Medicine (ISPM). IeDeA International epidemiology Database to Evaluate AIDS 2020 [7th July 2021]. Available from: <https://www.iedea.org>.
74. Slogrove AL, Mahy M, Armstrong A, Davies MA. Living and dying to be counted: What we know about the epidemiology of the global adolescent HIV epidemic. Journal of the International AIDS Society. 2017;20:21520.
75. Joint United Nations Programme on HIV/AIDS. All In# EndAdolescentAIDS. 2015.
76. He E, Tolmay J, Zhou S, Saal W, Toska E. Mode of HIV acquisition among adolescents living with HIV in resource-limited settings: A data-driven approach from South Africa. PloS one. 2023;18(2):e0281298.
77. Slogrove AL, Sohn AH. The global epidemiology of adolescents living with HIV: time for more granular data to improve adolescent health outcomes. Current Opinion in HIV and AIDS. 2018;13(3):170.
78. Sohn AH, Hazra R. The changing epidemiology of the global paediatric HIV epidemic: keeping track of perinatally HIV-infected adolescents. Journal of the International AIDS Society. 2013;16(1).
79. Fields EL, Bogart LM, Thurston IB, Hu CH, Skeer MR, Safren SA, et al. Qualitative comparison of barriers to antiretroviral medication adherence among

perinatally and behaviorally HIV-infected youth. Qualitative health research. 2017;27(8):1177-1189.
80. Teasdale CA, Abrams EJ, Coovadia A, Strehlau R, Martens L, Kuhn L. Adherence and viral suppression among infants and young children initiating protease inhibitor-based antiretroviral therapy. The Pediatric infectious disease journal. 2013;32(5):489.
81. World Health Organization. Policy brief: update of recommendations on first- and second-line antiretroviral regimens. World Health Organization; 2019.
82. World Health Organization. Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030. 2022.
83. Adejumo OA, Malee KM, Ryscavage P, Hunter SJ, Taiwo BO. Contemporary issues on the epidemiology and antiretroviral adherence of HIV-infected adolescents in sub-Saharan Africa: a narrative review. Journal of the International AIDS Society. 2015;18(1):20049.
84. Ferrand RA, Briggs D, Ferguson J, Penazzato M, Armstrong A, MacPherson P, et al. Viral suppression in adolescents on antiretroviral treatment: review of the literature and critical appraisal of methodological challenges. Tropical Medicine & International Health. 2016;21(3):325-333.
85. Han WM, Law MG, Egger M, Wools-Kaloustian K, Moore R, McGowan C, et al. Global estimates of viral suppression in children and adolescents and adults on antiretroviral therapy adjusted for missing viral load measurements: a multiregional, retrospective cohort study in 31 countries. The Lancet HIV. 2021;8(12):e766-e775.
86. Haghighat R, Toska E, Bungane N, Cluver L. The HIV care cascade for adolescents initiated on antiretroviral therapy in a health district of South Africa: a retrospective cohort study. BMC infectious diseases. 2021;21(1):1-9.
87. Fokam J, Sosso SM, Yagai B, Billong SC, Mbadie RED, Simo RK, et al. Viral suppression in adults, adolescents and children receiving antiretroviral therapy in Cameroon: adolescents at high risk of virological failure in the era of “test and treat”. AIDS research and therapy. 2019;16(1):1-8.
88. Djiyou AB, Penda CI, Madec Y, Ngondi GD, Moukoko A, Varloteaux M, et al. Viral load suppression in HIV-infected adolescents in cameroon: towards achieving the UNAIDS 95% viral suppression target. BMC pediatrics. 2023;23(1):119.

89. Maena J, Banke-Thomas A, Mukiza N, Kuteesa CN, Kakumba RM, Kataike H, et al. Determinants of viral load non-suppression among adolescents in Mbale District, Eastern Rural Uganda. AIDS research and therapy. 2021;18:1-9.
90. Jobanputra K, Parker LA, Azih C, Okello V, Maphalala G, Kershberger B, et al. Factors associated with virological failure and suppression after enhanced adherence counselling, in children, adolescents and adults on antiretroviral therapy for HIV in Swaziland. PloS one. 2015;10(2):e0116144.
91. Anderson K, Muloiwa R, Davies M. Treatment outcomes in perinatally infected HIVpositive adolescents and young adults after≥ 10 years on antiretroviral therapy. South African Medical Journal. 2019;109(1):27-34.
92. Makadzange A, Higgins-Biddle M, Chimukangara B, Birri R, Gordon M, Mahlanza T, et al. Clinical, Virologic, Immunologic Outcomes and Emerging HIV Drug Resistance Patterns in Children and Adolescents in Public ART Care in Zimbabwe. PloS one. 2015;10(12):e0144057.
93. Fokam J, Billong SC, Jogue F, Ndiang SMT, Motaze ACN, Paul KN, et al. Immuno-virological response and associated factors amongst HIV-1 vertically infected adolescents in Yaoundé-Cameroon. PloS one. 2017;12(11):e0187566.
94. Salou M, Dagnra AY, Butel C, Vidal N, Serrano L, Takassi E, et al. High rates of virological failure and drug resistance in perinatally HIV-1-infected children and adolescents receiving lifelong antiretroviral therapy in routine clinics in Togo. Journal of the International AIDS Society. 2016;19(1):20683.
95. Mwangi A, van Wyk B. Factors associated with viral suppression among adolescents on antiretroviral therapy in Homa Bay County, Kenya: a retrospective cross-sectional study. HIV/AIDS-Research and Palliative Care. 2021:1111-1118.
96. Desta AA, Woldearegay TW, Futwi N, Gebrehiwot GT, Gebru GG, Berhe AA, et al. HIV virological non-suppression and factors associated with non-suppression among adolescents and adults on antiretroviral therapy in northern Ethiopia: a retrospective study. BMC infectious diseases. 2020;20(1):1-10.
97. Weijsenfeld AM, Smit C, Wit FW, Mudrikova T, Nellen JF, van der Valk M, et al., editors. Long-term virological treatment outcomes in adolescents and young adults with perinatally and non-perinatally acquired human immunodeficiency virus. Open Forum Infectious Diseases; 2022: Oxford University Press US.
98. Collaboration CGC, Slogrove AL, Botswana B, Anabwani G, Lesotho B, Mohapi E, et al. Inequality in outcomes for adolescents living with perinatally

acquired HIV in sub-Saharan Africa: a Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Cohort Collaboration analysis. Journal of the International AIDS Society. 2018;21:e25044.
99. Wood SM, Lowenthal E, Lee S, Ratcliffe SJ, Dowshen N. Longitudinal viral suppression among a cohort of adolescents and young adults with behaviorally acquired human immunodeficiency virus. AIDS patient care and STDs. 2017;31(9):377-383.
100. World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. World Health Organization; 2018.
101. Kanters S, Vitoria M, Zoratti M, Doherty M, Penazzato M, Rangaraj A, et al. Comparative efficacy, tolerability and safety of dolutegravir and efavirenz 400mg among antiretroviral therapies for first-line HIV treatment: a systematic literature review and network meta-analysis. EClinicalMedicine. 2020;28:100573.
102. Brown JA, Nsakala BL, Mokhele K, Rakuoane I, Muhairwe J, Urda L, et al. Viral suppression after transition from nonnucleoside reverse transcriptase inhibitor-to dolutegravir-based antiretroviral therapy: A prospective cohort study in Lesotho (DO-REAL study). HIV medicine. 2022;23(3):287-293.
103. Esber A, Dear N, Shah N, Kibuuka H, Maswai J, Owuoth J, et al. Brief Report: Virologic Impact of the Dolutegravir Transition: Prospective Results From the Multinational African Cohort Study. Journal of Acquired Immune Deficiency Syndromes. 2022;91(3):285.
104. National Department of Health Republic of South Africa. 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. In: National Department of Health Republic of South Africa, editor.: National Department of Health Republic of South Africa,; 2023.
105. McCluskey SM, Pepperrell T, Hill A, Venter WD, Gupta RK, Siedner MJ. Adherence, resistance, and viral suppression on dolutegravir in sub-Saharan Africa: implications for the TLD era. Aids. 2021;35(Supplement 2):S127-S135.

106. Siedner MJ, Moorhouse MA, Simmons B, de Oliveira T, Lessells R, Giandhari J, et al. Reduced efficacy of HIV-1 integrase inhibitors in patients with drug resistance mutations in reverse transcriptase. Nature communications. 2020;11(1):5922.
107. Buju RT, Akilimali PZ, Kamangu EN, Mesia GK, Kayembe JMN, Situakibanza HN. Predictors of Viral Non-Suppression among Patients Living with HIV under Dolutegravir in Bunia, Democratic Republic of Congo: A Prospective Cohort Study. International Journal of Environmental Research and Public Health. 2022;19(3):1085.
108. Schramm B, Temfack E, Descamps D, Nicholas S, Peytavin G, Bitilinyu-Bangoh JE, et al. Viral suppression and HIV-1 drug resistance 1 year after pragmatic transitioning to dolutegravir first-line therapy in Malawi: a prospective cohort study. The Lancet HIV. 2022;9(8):e544-e553.
109. Chhim K, Mburu G, Tuot S, Sopha R, Khol V, Chhoun P, et al. Factors associated with viral non-suppression among adolescents living with HIV in Cambodia: a cross-sectional study. AIDS research and therapy. 2018;15(1):1-10.
110. Okonji EF, Van Wyk B, Mukumbang FC, Hughes GD. Determinants of viral suppression among adolescents on antiretroviral treatment in Ehlanzeni district, South Africa: a cross-sectional analysis. AIDS research and therapy. 2021;18:1-9.
111. Desta AA, Woldearegay TW, Futwi N, Gebrehiwot GT, Gebru GG, Berhe AA, et al. HIV virological non-suppression and factors associated with non-suppression among adolescents and adults on antiretroviral therapy in northern Ethiopia: a retrospective study. BMC infectious diseases. 2020;20:1-10.
112. Tymejczyk O, Brazier E, Wools-Kaloustian K, Davies M-A, Dilorenzo M, Edmonds A, et al. Impact of universal antiretroviral treatment eligibility on rapid treatment initiation among young adolescents with human immunodeficiency virus in Sub-Saharan Africa. The Journal of infectious diseases. 2020;222(5):755-764.
113. Chihana ML, Huerga H, Van Cutsem G, Ellman T, Wanjala S, Masiku C, et al. Impact of" test and treat" recommendations on eligibility for antiretroviral treatment: Cross sectional population survey data from three high HIV prevalence countries. PloS one. 2018;13(11):e0207656.
114. Joint United Nations Programme on HIV/AIDS. The Gap Report. Geneva: UNAIDS. 2014.

115. Leshargie CT, Demant D, Burrowes S, Frawley J. The proportion of loss to follow-up from antiretroviral therapy (art) and its association with age among adolescents living with HIV in sub-Saharan Africa: a systematic review and meta-analysis. PloS one. 2022;17(8):e0272906.
116. Ardura-Garcia C, Feldacker C, Tweya H, Chaweza T, Kalulu M, Phiri S, et al. Implementation and operational research: early tracing of children lost to follow-up from antiretroviral treatment: true outcomes and future risks. Journal of Acquired Immune Deficiency Syndromes. 2015;70(5):e160.
117. Saumu WM, Maleche-Obimbo E, Irimu G, Kumar R, Gichuhi C, Karau B. Predictors of loss to follow-up among children attending HIV clinic in a hospital in rural Kenya. Pan African Medical Journal. 2019;32(1).
118. KIDS-ART-LINC Collaboration. Low risk of death, but substantial program attrition, in pediatric HIV treatment cohorts in Sub-Saharan Africa. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2008;49(5):523-531.
119. Leroy V, Malateste K, Rabie H, Lumbiganon P, Ayaya S, Dicko F, et al. Outcomes of antiretroviral therapy in children in Asia and Africa: a comparative analysis of the IeDEA pediatric multiregional collaboration. Journal of Acquired Immune Deficiency Syndromes. 2013;62(2):208.
120. Jerene D, Abebe W, Taye K, Ruff A, Hallstrom I. Adolescents living with HIV are at higher risk of death and loss to follow up from care: Analysis of cohort data from eight health facilities in Ethiopia. PloS one. 2019;14(10).
121. Chandiwana N, Sawry S, Chersich M, Kachingwe E, Makhathini B, Fairlie L. High loss to follow-up of children on antiretroviral treatment in a primary care HIV clinic in Johannesburg, South Africa. Medicine. 2018;97(29).
122. Kranzer K, Bradley J, Musaazi J, Nyathi M, Gunguwo H, Ndebele W, et al. Loss to follow-up among children and adolescents growing up with HIV infection: age really matters. Journal of the International AIDS Society. 2017;20(1):21737.
123. Ahonkhai AA, Banigbe B, Adeola J, Adegoke AB, Regan S, Bassett IV, et al. Age matters: increased risk of inconsistent HIV care and viremia among adolescents and young adults on antiretroviral therapy in Nigeria. Journal of Adolescent Health. 2016;59(3):298-304.
124. Mutanga JN, Mutembo S, Ezeamama AE, Song X, Fubisha RC, Mutesu-Kapembwa K, et al. Predictors of loss to follow-up among children on long-term antiretroviral therapy in Zambia (2003–2015). BMC public health. 2019;19(1):1120.

125. Rachlis B, Ochieng D, Geng E, Rotich E, Ochieng V, Maritim B, et al. Implementation and operational research: evaluating outcomes of patients lost to follow-up in a large comprehensive care treatment program in western Kenya. Journal of Acquired Immune Deficiency Syndromes. 2015;68(4):e46-e55.
126. World Health Organization, Joint United Nations Programme on HIV/AIDS, United Nations International Children's Emergency Fund. Global report: UNAIDS report on the global AIDS epidemic 2013.
127. Geng EH, Emenyonu N, Bwana MB, Glidden DV, Martin JN. Sampling-based approach to determining outcomes of patients lost to follow-up in antiretroviral therapy scale-up programs in Africa. Journal of American Medical Association. 2008;300(5):506-507.
128. Johnson LF, Dorrington RE, Laubscher R, Hoffmann CJ, Wood R, Fox MP, et al. A comparison of death recording by health centres and civil registration in South Africans receiving antiretroviral treatment. Journal of International AIDS Society. 2015;18:20628.
129. Boulle A, Schomaker M, May MT, Hogg RS, Shepherd BE, Monge S, et al. Mortality in patients with HIV-1 infection starting antiretroviral therapy in South Africa, Europe, or North America: a collaborative analysis of prospective studies. PLoS medicine. 2014;11(9):e1001718.
130. Vanobberghen F, Weisser M, Kasuga B, Katende A, Battegay M, Tanner M, et al. Mortality in a Cohort of People Living with HIV in Rural Tanzania, Accounting for Unseen Mortality Among Those Lost to Follow-up. American Journal of Epidemiology. 2020.
131. Egger M, Spycher BD, Sidle J, Weigel R, Geng EH, Fox MP, et al. Correcting mortality for loss to follow-up: a nomogram applied to antiretroviral treatment programmes in sub-Saharan Africa. PLoS medicine. 2011;8(1):e1000390.
132. Frangakis CE, Rubin DB. Addressing an idiosyncrasy in estimating survival curves using double sampling in the presence of self-selected right censoring. Biometrics. 2001;57(2):333-342.
133. da Silva GAP, da Cruz Gouveia PA. Predictors of loss to follow-up among children registered in an HIV prevention mother-to-child transmission cohort study in Pernambuco, Brazil. 2014.

134. Phelps BR, Ahmed S, Amzel A, Diallo MO, Jacobs T, Kellerman SE, et al. Linkage, initiation and retention of children in the antiretroviral therapy cascade: an overview. AIDS 2013;27(0 2):S207.
135. Dellar RC, Dlamini S, Karim QA. Adolescent girls and young women: key populations for HIV epidemic control. J Int AIDS Soc. 2015;18(2 Suppl 1):19408.
136. Nuwagaba-Biribonwoha H, Kiragga AN, Yiannoutsos CT, Musick BS, Wools-Kaloustian KK, Ayaya S, et al. Adolescent pregnancy at antiretroviral therapy (ART) initiation: a critical barrier to retention on ART. Journal of the International AIDS Society. 2018;21(9):e25178.
137. Lilian R, Mutasa B, Railton J, Mongwe W, McIntyre J, Struthers H, et al. A 10-year cohort analysis of routine paediatric ART data in a rural South African setting. Epidemiology & Infection. 2017;145(1):170-180.
138. Tsondai PR, Davies M-A, Singtoroj T, Maxwell N, McGowan CC, Songtaweesin WN, et al. Improving methods to classify perinatal versus nonperinatal HIV acquisition in young adolescents 10–14 years of age. The Pediatric infectious disease journal. 2021;40(5):453-456.
139. Hassan AS, Sakwa EM, Nabwera HM, Taegtmeyer MM, Kimutai RM, Sanders EJ, et al. Dynamics and constraints of early infant diagnosis of HIV infection in Rural Kenya. AIDS Behavior. 2012;16(1):5-12.
140. Kassanjee R, Johnson LF, Zaniewski E, Ballif M, Christ B, Yiannoutsos CT, et al. Global HIV mortality trends among children on antiretroviral treatment corrected for under-reported deaths: an updated analysis of the International epidemiology Databases to Evaluate AIDS collaboration. Journal of the International AIDS Society. 2021;24:e25780.
141. Iyun V, Technau KG, Vinikoor M, Yotebieng M, Vreeman R, Abuogi L, et al. Variations in the characteristics and outcomes of children living with HIV following universal ART in sub-Saharan Africa (2006-17): a retrospective cohort study. The Lancet HIV. 2021;8(6):e353-e362.
142. HIV prevention and treatment progress for children, adolescents, and pregnant women nearly flat over past few years [press release]. United Nations International Children's Emergency Fund (UNICEF)2022.
143. Grimsrud A, Lesosky M, Kalombo C, Bekker L-G, Myer L. Community-based Adherence Clubs for the management of stable antiretroviral therapy patients in

Cape Town, South Africa: a cohort study. Journal of Acquired Immune Deficiency Syndromes. 2016;71(1):e16-23.
144. Bilinski A, Birru E, Peckarsky M, Herce M, Kalanga N, Neumann C, et al. Distance to care, enrollment and loss to follow-up of HIV patients during decentralization of antiretroviral therapy in Neno District, Malawi: A retrospective cohort study. PloS one. 2017;12(10):e0185699.
145. Fayorsey RN, Saito S, Carter RJ, Gusmao E, Frederix K, Koech-Keter E, et al. Decentralization of pediatric HIV care and treatment in five sub-Saharan African countries. Journal of Acquired Immune Deficiency Syndromes 2013;62(5):e124.
146. Nimkar S, Valvi C, Kadam D, Rewari B, Kinikar A, Gupte N, et al. Loss to follow-up and mortality among HIV-infected adolescents receiving antiretroviral therapy in Pune, India. HIV medicine. 2018;19(6):395-402.
147. Abrams EJ, Woldesenbet S, Silva JS, Coovadia A, Paed F, Black V, et al. Despite access to antiretrovirals for prevention and treatment high rates of mortality persist among HIV-infected infants and young children. The Pediatric infectious disease journal. 2017;36(6):595.
148. Gesesew HA, Gebremedhin AT, Demissie TD, Kerie MW, Sudhakar M, Mwanri L. Significant association between perceived HIV related stigma and late presentation for HIV/AIDS care in low and middle-income countries: A systematic review and meta-analysis. PloS one. 2017;12(3):e0173928.
149. Arrivé E, Dicko F, Amghar H, Aka AE, Dior H, Bouah B, et al. HIV status disclosure and retention in care in HIV-infected adolescents on antiretroviral therapy (ART) in West Africa. PloS one. 2012;7(3):e33690.
150. Beima-Sofie KM, Brandt L, Hamunime N, Shepard M, Uusiku J, John-Stewart GC, et al. Pediatric HIV disclosure intervention improves knowledge and clinical outcomes in HIV-infected children in Namibia. Journal of Acquired Immune Deficiency Syndromes. 2017;75(1):18.
151. Judd A, Davies M-A. Adolescent transition among young people with perinatal HIV in high and low income settings. Current Opinion in HIV and AIDS. 2018;13(3):236.
152. Righetti A, Prinapori R, Nulvesu L, Fornoni L, Viscoli C, Di Biagio A. Transitioning HIV-infected children and adolescents into adult care: an Italian real-life experience. Journal of the Association of Nurses in AIDS Care. 2015;26(5):652-659.

153. Kakkar F, Van der Linden D, Valois S, Maurice F, Onnorouille M, Lapointe N, et al. Health outcomes and the transition experience of HIV-infected adolescents after transfer to adult care in Quebec, Canada. BMC pediatrics. 2016;16:109.
154. Dahourou DL, Gautier-Lafaye C, Teasdale CA, Renner L, Yotebieng M, Desmonde S, et al. Transition from paediatric to adult care of adolescents living with HIV in sub-Saharan Africa: challenges, youth-friendly models, and outcomes. Journal of International AIDS Society. 2017;20(Suppl 3):21528.
155. Johnson LF, Estill J, Keiser O, Cornell M, Moolla H, Schomaker M, et al. Do increasing rates of loss to follow-up in antiretroviral treatment programs imply deteriorating patient retention? American Journal of Epidemiology. 2014;180(12):1208-1212.
156. Grimsrud AT, Cornell M, Egger M, Boulle A, Myer L. Impact of definitions of loss to follow-up (LTFU) in antiretroviral therapy program evaluation: variation in the definition can have an appreciable impact on estimated proportions of LTFU. Journal of clinical epidemiology. 2013;66(9):1006-1013.
157. Nakiwogga-Muwanga A, Musaazi J, Katabira E, Worodria W, Talisuna SA, Colebunders R. Patients who return to care after tracking remain at high risk of attrition: experience from a large HIV clinic, Uganda. International journal of STD & AIDS. 2015;26(1):42-47.
158. Mofenson LM, Cotton MF. The challenges of success: adolescents with perinatal HIV infection. Journal of the International AIDS Society. 2013;16(1):18650.
159. Joint United Nations Programme on HIV/AIDS. UNAIDS 2016 Estimates. 2017.
160. UNICEF. Turning the tide against AIDS will require more concentrated focus on adolescents and young people. data unicef org/topic/hivaids/adolescents-young-people. 2016.
161. Judd A, Sohn AH, Collins IJ. Interventions to improve treatment, retention and survival outcomes for adolescents with perinatal HIV-1 transitioning to adult care: moving on up. Current Opinion in HIV and AIDS. 2016;11(5):477-486.
162. Judd A, Lodwick R, Noguera-Julian A, Gibb DM, Butler K, Costagliola D, et al. Higher rates of triple-class virological failure in perinatally HIV-infected teenagers compared with heterosexually infected young adults in Europe. HIV medicine. 2017;18(3):171-180.

163. Agwu AL, Fairlie L. Antiretroviral treatment, management challenges and outcomes in perinatally HIV-infected adolescents. Journal of the International AIDS Society. 2013;16(1).
164. Lamb MR, Fayorsey R, Nuwagaba-Biribonwoha H, Viola V, Mutabazi V, Alwar T, et al. High attrition before and after ART initiation among youth (15–24 years of age) enrolled in HIV care. AIDS. 2014;28(4):559.
165. Fish R, Judd A, Jungmann E, O'leary C, Foster C, Network HYP. Mortality in perinatally HIV-infected young people in England following transition to adult care: an HIV Young Persons Network (HYPNet) audit. HIV medicine. 2014;15(4):239-244.
166. Kadima J, Patterson E, Mburu M, Blat C, Nyanduko M, Bukusi EA, et al. Correction: Adoption of routine virologic testing and predictors of virologic failure among HIV-infected children on antiretroviral treatment in western Kenya. PloS one. 2019;14(1):e0210908.
167. Boerma RS, Bunupuradah T, Dow D, Fokam J, Kariminia A, Lehman D, et al. Multicentre analysis of second-line antiretroviral treatment in HIV-infected children: adolescents at high risk of failure. Journal of the International AIDS Society. 2017;20(1):21930.
168. Umar E, Levy JA, Bailey RC, Donenberg G, Hershow RC, Mackesy-Amiti ME. Virological Non-suppression and Its Correlates Among Adolescents and Young People Living with HIV in Southern Malawi. AIDS and Behavior. 2018:1-10.
169. Idele P, Gillespie A, Porth T, Suzuki C, Mahy M, Kasedde S, et al. Epidemiology of HIV and AIDS among adolescents: current status, inequities, and data gaps. Journal of Acquired Immune Deficiency Syndromes. 2014;66:S144-S153.
170. Weijsenfeld AM, Blokhuis C, Stuiver MM, Wit FW, Pajkrt D. Longitudinal virological outcomes and factors associated with virological failure in behaviorally HIV-infected young adults on combination antiretroviral treatment in the Netherlands, 2000 to 2015. Medicine. 2019;98(32).
171. Li X, Chu H, Gallant JE, Hoover DR, Mack WJ, Chmiel JS, et al. Bimodal virological response to antiretroviral therapy for HIV infection: an application using a mixture model with left censoring. Journal of Epidemiology & Community Health. 2006;60(9):811-818.
172. Egger M, Ekouevi DK, Williams C, Lyamuya RE, Mukumbi H, Braitstein P, et al. Cohort Profile: The international epidemiological databases to evaluate AIDS

(IeDEA) in sub-Saharan Africa. International Journal of Epidemiology. 2012;41(5):1256-1264.
173. Africa health research institute. 2021 [30th June 2021]. Available from: <www.ahri.org>.
174. Western Cape government. 2020 [9th June 2020]. Available from: <www.westerncape.gov.za>.
175. Aid for Aids (AfA). 2020 [9th June 2020]. Available from: <www.aidforaids.co.za>.
176. Desmond Tutu HIV Foundation. 2019 [Available from: <https://desmondtutuhivfoundation.org.za>.
177. Wits RHI. University of the Witwatersrand 2020 [9th June 2020]. Available from: <http://www.wrhi.ac.za>.
178. Kheth'Impilo. Kheth'Impilo AIDS Free Living 2020 [9th June 2020]. Available from: <http://www.khethimpilo.org>.
179. Wits RHI. University of Witwatersrand 2019 [9th June 2020]. Available from: <www.wits.ac.za>.
180. The Children's Hospital Trust. 2020 [9th June 2020]. Available from: <www.childrenshospitaltrust.org.za>.
181. Heumann C, Schomaker M. Introduction to Statistics and Data Analysis: Springer; 2016.
182. Geraci M. Linear quantile mixed models: the lqmm package for Laplace quantile regression. Journal of Statistical Software. 2014;57(13):1-29.
183. Geraci M, Bottai M. Linear quantile mixed models. Statistics and computing. 2014;24(3):461-479.
184. Honaker J, King G, Blackwell M. Amelia II: A program for missing data. Journal of Statistical Software. 2011;45(7):1-47.
185. Rubin DB. Multiple imputation after 18+ years. Journal of the American Statistical Association. 1996;91(434):473-489.
186. Xu L, Munir K, Kanabkaew C, Le Coeur S. Factors influencing antiretroviral treatment suboptimal adherence among perinatally HIV-infected adolescents in Thailand. PloS one. 2017;12(2):e0172392.
187. Denison JA, Banda H, Dennis AC, Packer C, Nyambe N, Stalter RM, et al. "The sky is the limit": adhering to antiretroviral therapy and HIV self-management

from the perspectives of adolescents living with HIV and their adult caregivers. Journal of the International AIDS Society. 2015;18(1):19358.
188. Kahana SY, Fernandez MI, Wilson PA, Bauermeister JA, Lee S, Wilson CM, et al. Rates and correlates of antiretroviral therapy use and virologic suppression among perinatally and behaviorally HIV-infected youth linked to care in the United States. Journal of Acquired Immune Deficiency Syndromes. 2015;68(2):169-177.
189. Sudjaritruk T, Aurpibul L, Ly PS, Le TPK, Bunupuradah T, Hansudewechakul R, et al. Incidence of postsuppression virologic rebound in perinatally HIV-infected Asian adolescents on stable combination antiretroviral therapy. Journal of Adolescent Health. 2017;61(1):91-98.
190. Muri L, Gamell A, Ntamatungiro AJ, Glass TR, Luwanda LB, Battegay M, et al. Development of HIV drug resistance and therapeutic failure in children and adolescents in rural Tanzania: an emerging public health concern. Aids. 2017;31(1):61-70.
191. Ramadhani HO, Bartlett JA, Thielman NM, Pence BW, Kimani SM, Maro VP, et al., editors. Association of first-line and second-line antiretroviral therapy adherence. Open forum infectious diseases; 2014: Oxford University Press.
192. Mocroft A, Ruiz L, Reiss P, Ledergerber B, Katlama C, Lazzarin A, et al. Virological rebound after suppression on highly active antiretroviral therapy. Aids. 2003;17(12):1741-1751.
193. Kim MJ, Kim S-W, Chang H-H, Kim Y, Jin S, Jung H, et al. Comparison of antiretroviral regimens: adverse effects and tolerability failure that cause regimen switching. Infection & chemotherapy. 2015;47(4):231-238.
194. Duong T, Judd A, Collins IJ, Doerholt K, Lyall H, Foster C, et al. Long-term virological outcome in children on antiretroviral therapy in the UK and Ireland. Aids. 2014;28(16):2395.
195. Zanoni BC, Sibaya T, Cairns C, Lammert S, Haberer JE. Higher retention and viral suppression with adolescent-focused HIV clinic in South Africa. PloS one. 2017;12(12):e0190260.
196. Eaton JW, Garnett GP, Takavarasha FR, Mason PR, Robertson L, Schumacher CM, et al. Increasing adolescent HIV prevalence in Eastern Zimbabwe–evidence of long-term survivors of mother-to-child transmission? PloS one. 2013;8(8):e70447.

197. World Health Organization. HIV and adolescents: guidance for HIV testing and counselling and care for adolescents living with HIV: recommendations for a public health approach and considerations for policy-makers and managers. 2013.
198. Denison JA, Packer C, Stalter RM, Banda H, Mercer S, Nyambe N, et al. Factors related to incomplete adherence to antiretroviral therapy among adolescents attending three HIV clinics in the copperbelt, Zambia. AIDS and behavior. 2018;22(3):996-1005.
199. Kakkar F, Van der Linden D, Valois S, Maurice F, Onnorouille M, Lapointe N, et al. Health outcomes and the transition experience of HIV-infected adolescents after transfer to adult care in Québec, Canada. BMC pediatrics. 2016;16(1):109.
200. Dzangare J, Takarinda KC, Harries AD, Tayler-Smith K, Mhangara M, Apollo TM, et al. HIV testing uptake and retention in care of HIV-infected pregnant and breastfeeding women initiated on 'Option B+'in rural Zimbabwe. Tropical Medicine & International Health. 2016;21(2):202-209.
201. Tweya H, Gugsa S, Hosseinipour M, Speight C, Ng'ambi W, Bokosi M, et al. Understanding factors, outcomes and reasons for loss to follow-up among women in Option B+ PMTCT programme in Lilongwe, Malawi. Tropical Medicine & International Health. 2014;19(11):1360-1366.
202. Laughton B, Cornell M, Boivin M, Van Rie A. Neurodevelopment in perinatally HIV-infected children: a concern for adolescence. Journal of the International AIDS Society. 2013;16(1).
203. Health economics and epidemiology in South Africa (HE2RO). Health economics and epidemiology in South Africa [cited 2021 11 October 2021]. Available from: <https://www.heroza.org>.
204. Harriet Shezi Children's clinic. WRHI [cited 2021 11 October 2021]. Available from: <http://www.wrhi.ac.za>.
205. Heumann C, Schomaker M, Shalabh. Introduction to Statistics and Data Analysis - With Exercises, Solutions and Applications in R. Heidelberg: Springer; 2016
206. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American statistical association. 1999;94(446):496-509.

207. National Department of Health. National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults. Africa2014.
208. White IR, Royston P, Wood AM. Multiple imputation using chained equations. Statistics in medicine. 2011;30:377-399.
209. Joint United Nations Programme on HIV/AIDS. Fast-track: ending the AIDS epidemic by 2030. 2014.
210. Chhim K, Mburu G, Tuot S, Sopha R, Khol V, Chhoun P, et al. Factors associated with viral non-suppression among adolescents living with HIV in Cambodia: a cross-sectional study. AIDS Research and Therapy. 2018;15(1):20.
211. Cheng Y, Sauer B, Zhang Y, Nickman NA, Jamjian C, Stevens V, et al. Adherence and virologic outcomes among treatment-naïve veteran patients with human immunodeficiency virus type 1 infection. Medicine. 2018;97(2).
212. Scott Sutton S, Magagnoli J, Hardin JW. Impact of pill burden on adherence, risk of hospitalization, and viral suppression in patients with HIV infection and AIDS receiving antiretroviral therapy. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2016;36(4):385-401.
213. Nachega JB, Sam-Agudu NA, Mofenson LM, Schechter M, Mellors JW. Achieving Viral Suppression in 90% of People Living With Human Immunodeficiency Virus on Antiretroviral Therapy in Low-and Middle-Income Countries: Progress, Challenges, and Opportunities. Clinical infectious diseases. 2018;66(10):1487-1491.
214. World Health Organization. Adolescent friendly health services for adolescents living with HIV: from theory to practice, December 2019: technical brief. World Health Organization; 2019.
215. MacPherson P, Munthali C, Ferguson J, Armstrong A, Kranzer K, Ferrand RA, et al. Service delivery interventions to improve adolescents' linkage, retention and adherence to antiretroviral therapy and HIV care. Tropical Medicine & International Health. 2015;20(8):1015-1032.
216. Neal S, Channon AA, Chintsanya J. The impact of young maternal age at birth on neonatal mortality: Evidence from 45 low and middle income countries. PloS one. 2018;13(5):e0195731.
217. Jiamsakul A, Kariminia A, Althoff KN, Cesar C, Cortes CP, Davies M-A, et al. HIV viral load suppression in adults and children receiving antiretroviral therapy–

results from the IeDEA collaboration. Journal of Acquired Immune Deficiency Syndromes. 2017;76(3):319.
218. Brown K, Williams DB, Kinchen S, Saito S, Radin E, Patel H, et al. Status of HIV epidemic control among adolescent girls and young women aged 15–24 years—seven African countries, 2015–2017. Morbidity and Mortality Weekly Report. 2018;67(1):29.
219. Keiser O, Chi BH, Gsponer T, Boulle A, Orrell C, Phiri S, et al. Outcomes of antiretroviral treatment in programmes with and without routine viral load monitoring in Southern Africa. Aids. 2011;25(14):1761.
220. van Wyk B, Kriel E, Mukumbang F. Retention in care for adolescents who were newly initiated on antiretroviral therapy in the Cape Metropole in South Africa. Southern African Journal of HIV Medicine. 2020;21(1):1-8.
221. Kranzer K, Bradley J, Musaazi J, Nyathi M, Gunguwo H, Ndebele W, et al. Loss to follow-up among children and adolescents growing up with HIV infection: age really matters. Journal of International AIDS Society. 2017;20(1):21737.
222. Zanoni BC, Mayer KH. The adolescent and young adult HIV cascade of care in the United States: exaggerated health disparities. AIDS Patient Care STDS. 2014;28(3):128-135.
223. Atuyambe LM, Kibira SP, Bukenya J, Muhumuza C, Apolot RR, Mulogo E. Understanding sexual and reproductive health needs of adolescents: evidence from a formative evaluation in Wakiso district, Uganda. Reproductive health. 2015;12(1):35.
224. Kadam DD, Saurabha U, Tiwari SC. Health needs of adolescent girls living in an urban slum of a metropolitan city-A mixed method approach. Journal of Family Medicine and Primary Care. 2019;8(8):2661.
225. Luseno WK, Iritani BJ, Maman S, Mbai I, Ongili B, Otieno FA, et al. “If the mother does not know, there is no way she can tell the adolescent to go for drugs”: Challenges in promoting health and preventing transmission among pregnant and parenting Kenyan adolescents living with HIV. Children and Youth Services Review. 2019.
226. Horwood C, Butler LM, Haskins L, Phakathi S, Rollins N. HIV-infected adolescent mothers and their infants: low coverage of HIV services and high risk of HIV transmission in KwaZulu-Natal, South Africa. PloS one. 2013;8(9):e74568.

227. Phillips T, Thebus E, Bekker LG, Mcintyre J, Abrams EJ, Myer L. Disengagement of HIV-positive pregnant and postpartum women from antiretroviral therapy services: a cohort study. Journal of the International AIDS Society. 2014;17(1):19242.
228. Agwu AL, Fleishman JA, Rutstein R, Korthuis PT, Gebo K. Changes in Advanced Immunosuppression and Detectable HIV Viremia Among Perinatally HIV-Infected Youth in the Multisite United States HIV Research Network. Journal Pediatric Infectious Diseases Society. 2013;2(3):215-223.
229. Tsondai PR, Wilkinson LS, Grimsrud A, Mdlalo PT, Ullauri A, Boulle A. High rates of retention and viral suppression in the scale-up of antiretroviral therapy adherence clubs in Cape Town, South Africa. Journal of the International AIDS Society. 2017;20(S4).
230. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach: World Health Organization; 2016.
231. Kredo T, Adeniyi FB, Bateganya M, Pienaar ED. Task shifting from doctors to non-doctors for initiation and maintenance of antiretroviral therapy. Cochrane Database of Systematic Reviews. 2014, (7).
232. Tene G, Lahuerta M, Teasdale C, Mugisha V, Kayonde L, Muhayimpundu R, et al. High retention among HIV-infected children in Rwanda during scale-up and decentralization of HIV care and treatment programs, 2004 to 2010. Pediatric Infectious Disease Journal. 2013;32(8):e341.
233. Kumar P. Long term non-progressor (LTNP) HIV infection. The Indian journal of medical research. 2013;138(3):291.
234. Chammartin F, Ostinelli CHD, Anastos K, Jaquet A, Brazier E, Brown S, et al. Cohort profile: the international epidemiology databases to evaluate AIDS (IeDEA) in sub-Saharan Africa, 2012–2019. BMJ Open. 2012;10:e035246.
235. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Statistics in medicine. 2011;30(4):377-399.
236. Rubin DB. Inference and missing data. Biometrika. 1976;63(3):581-592.
237. Anderegg N, Hector J, Jefferys LF, Burgos-Soto J, Hobbins MA, Ehmer J, et al. Loss to follow-up correction increased mortality estimates in HIV–positive people

on antiretroviral therapy in Mozambique. Journal of clinical epidemiology. 2020;128:83-92.
238. Tweya H, Feldacker C, Estill J, Jahn A, Ng'ambi W, Ben-Smith A, et al. Are they really lost?"True" status and reasons for treatment discontinuation among HIV infected patients on antiretroviral therapy considered lost to follow up in urban Malawi. PloS one. 2013;8(9):e75761.
239. Newell M-L, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. The Lancet. 2004;364(9441):1236-1243.
240. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early antiretroviral therapy and mortality among HIV-infected infants. New England Journal of Medicine. 2008;359(21):2233-2244.
241. Howe CJ, Cole SR, Lau B, Napravnik S, Eron JJ, Jr. Selection Bias Due to Loss to Follow Up in Cohort Studies. Epidemiology. 2016;27(1):91-97.
242. Braitstein P, Songok J, Vreeman R, Wools-Kaloustian K, Koskei P, Walusuna L, et al. 'Wamepotea'(They have become lost): Outcomes of HIV-positive and HIV-exposed children lost to follow-up from a large HIV treatment program in western Kenya. Journal of Acquired Immune Deficiency Syndromes. 2011;57(3):e40.
243. World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children: World Health Organization; 2007.
244. De Schacht C, Lucas C, Mboa C, Gill M, Macasse E, Dimande SA, et al. Access to HIV prevention and care for HIV-exposed and HIV-infected children: a qualitative study in rural and urban Mozambique. BMC public health. 2014;14(1):1240.
245. Ehrenkranz P, Rosen S, Boulle A, Eaton JW, Ford N, Fox MP, et al. The revolving door of HIV care: Revising the service delivery cascade to achieve the UNAIDS 95-95-95 goals. PLoS medicine. 2021;18(5):e1003651.
246. Dicko F, Desmonde S, Koumakpai S, Dior-Mbodj H, Koueta F, Baeta N, et al. Reasons for hospitalization in HIV-infected children in West Africa. Journal of the International AIDS Society. 2014;17(1):18818.
247. Frigati L, Brown K, Cotton MF, Myer L, Zar H. Hospitalization in South African Adolescents with Perinatally-acquired HIV on Antiretroviral Therapy. Pediatric Infectious Disease Journal. 2020;39(11):1035.

248. Sui X, Massar K, Kessels LT, Reddy PS, Ruiter RA, Sanders-Phillips K. Violence exposure in South African adolescents: Differential and cumulative effects on psychological functioning. Journal of interpersonal violence. 2021;36(9-10):4084-4110.
249. Nyakato P, Christ B, Anderegg N, Muhairwe J, Jefferys L, van Dijk J, et al. High Unreported Mortality in Children and Youth (< 25 Years) Living With HIV Who Were Lost to Care From Antiretroviral Therapy Programs in Southern Africa: Results From a Multicountry Tracing Study. Journal of Acquired Immune Deficiency Syndromes. 2022;91(5):429-433.
250. Rachlis B, Bakoyannis G, Easterbrook P, Genberg B, Braithwaite RS, Cohen CR, et al. Facility-level factors influencing retention of patients in HIV care in East Africa. PloS one. 2016;11(8):e0159994.
251. European Pregnancy Paediatric HIV Cohort Collaboration study group in EuroCoord, Judd A, Chappell E, Turkova A, Le Coeur S, Noguera-Julian A, et al. Long-term trends in mortality and AIDS-defining events after combination ART initiation among children and adolescents with perinatal HIV infection in 17 middle- and high-income countries in Europe and Thailand: a cohort study. PLoS medicine. 2018;15(1):e1002491.
252. Kuhn L, Paximadis M, Da Costa Dias B, Loubser S, Strehlau R, Patel F, et al. Age at antiretroviral therapy initiation and cell-associated HIV-1 DNA levels in HIV-1-infected children. PloS one. 2018;13(4):e0195514.
253. Vanobberghen F, Weisser M, Kasuga B, Katende A, Battegay M, Tanner M, et al. Mortality Rate in a Cohort of People Living With HIV in Rural Tanzania After Accounting for Unseen Deaths Among Those Lost to Follow-up. American Journal of Epidemiology. 2020;190(2):251-264.
254. Phillips TK, Clouse K, Zerbe A, Orrell C, Abrams EJ, Myer L. Linkage to care, mobility and retention of HIV-positive postpartum women in antiretroviral therapy services in South Africa. Journal of the International AIDS Society. 2018;21:e25114.
255. Knol MJ, Janssen KJ, Donders ART, Egberts AC, Heerdink ER, Grobbee DE, et al. Unpredictable bias when using the missing indicator method or complete case analysis for missing confounder values: an empirical example. Journal of clinical epidemiology. 2010;63(7):728-736.

256. White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. Statistics in medicine. 2010;29(28):2920-2931.
257. Kristman V, Manno M, Côté P. Loss to follow-up in cohort studies: how much is too much? European journal of epidemiology. 2004;19:751-760.
258. Mathews S, Martin LJ, Coetzee D, Scott C, Naidoo T, Brijmohun Y, et al. The South African child death review pilot: A multiagency approach to strengthen healthcare and protection for children. South African Medical Journal. 2016;106(9):895-899.
259. World Health Organization. Nurturing care for children affected by HIV: early childhood development and children affected by HIV. 2020.
260. Davis K, Pickles M, Gregson S, Hargreaves J, Ayles H, Bock P, et al. The effect of universal testing and treatment for HIV on health-related quality of life-data from the HPTN 071 (PopART) cluster randomised trial in Zambia and South Africa. 2022.
261. Nyakato P, Schomaker M, Sipambo N, Technau K-G, Fatti G, Rabie H, et al. Virologic response of adolescents living with perinatally acquired HIV receiving antiretroviral therapy in the period of early adolescence (10-14 years) in South Africa. 'AIDS'. 2021;35(6):971.
262. Judd A, Collins IJ, Parrott F, Hill T, Jose S, Ford D, et al. Growing up with perinatal HIV: changes in clinical outcomes before and after transfer to adult care in the UK. Journal of the International AIDS Society. 2017;20:21577.
263. Neilan AM, Karalius B, Patel K, Van Dyke RB, Abzug MJ, Agwu AL, et al. Association of Risk of Viremia, Immunosuppression, Serious Clinical Events, and Mortality With Increasing Age in Perinatally Human Immunodeficiency Virus-Infected Youth. Journal of American Medical Association Pediatrics. 2017;171(5):450-460.
264. Nyakato P, Schomaker M, Fatti G, Tanser F, Euvrard J, Sipambo N, et al. Virologic non-suppression and early loss to follow up among pregnant and non-pregnant adolescents aged 15–19 years initiating antiretroviral therapy in South Africa: a retrospective cohort study. Journal of the International AIDS Society. 2022;25(1):e25870.
265. Schwartz SR, Kavanagh MM, Sugarman J, Solomon SS, Njindam IM, Rebe K, et al. HIV viral load monitoring among key populations in low-and middle-income

countries: challenges and opportunities. Journal of the International AIDS Society. 2017;20:e25003.
266. Marcus R, Ferrand RA, Kranzer K, Bekker LG. The case for viral load testing in adolescents in resource-limited settings. Journal of the International AIDS Society. 2017;20:e25002.
267. Brinkhof MW, Pujades-Rodriguez M, Egger M. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. PloS one. 2009;4(6):e5790.
268. Fox MP, Bor J, Brennan AT, MacLeod WB, Maskew M, Stevens WS, et al. Estimating retention in HIV care accounting for patient transfers: A national laboratory cohort study in South Africa. PLoS medicine. 2018;15(6):e1002589.
269. Kehoe K, Morden E, Jacobs T, Zinyakatira N, Smith M, Heekes A, et al. Comparison of paediatric infectious disease deaths in public sector health facilities using different data sources in the Western Cape, South Africa (2007–2021). BMC infectious diseases. 2023;23(1):1-11.
270. Davies M-A, Gibb D, Turkova A. Survival of HIV-1 vertically infected children. Current Opinion in HIV and AIDS. 2016;11(5):455.
271. Teasdale CA, Alwar T, Chege D, Fayorsey R, Hawken MP, Abrams EJ. Impact of youth and adolescent friendly services on retention of 10–24-year-olds in HIV care and treatment programs in Nyanza, Kenya. Journal of Acquired Immune Deficiency Syndromes. 2016;71(2):e56.
272. Wilkinson LS, Skordis-Worrall J, Ajose O, Ford N. Self-transfer and mortality amongst adults lost to follow-up in ART programmes in low-and middle-income countries: systematic review and meta-analysis. Tropical Medicine & International Health. 2015;20(3):365-379.
273. Grimsrud A, Bygrave H, Doherty M, Ehrenkranz P, Ellman T, Ferris R, et al. Reimagining HIV service delivery: the role of differentiated care from prevention to suppression. Journal of the International AIDS Society. 2016;19(1).
274. Geng EH, Glidden DV, Bangsberg DR, Bwana MB, Musinguzi N, Nash D, et al. A causal framework for understanding the effect of losses to follow-up on epidemiologic analyses in clinic-based cohorts: the case of HIV-infected patients on antiretroviral therapy in Africa. American Journal of Epidemiology. 2012;175(10):1080-1087.

275. Holmes CB, Sikazwe I, Sikombe K, Eshun-Wilson I, Czaicki N, Beres LK, et al. Estimated mortality on HIV treatment among active patients and patients lost to follow-up in 4 provinces of Zambia: findings from a multistage sampling-based survey. PLoS medicine. 2018;15(1):e1002489.
276. National Department of Health Republic of South Africa. 2019 ART clinical guidelines for the management of HIV in adults, pregnancy, adolescents, children, infants and neonates. Republic of South Africa National Department of Health,; 2019.
277. Townsend CL, O'Rourke J, Milanzi E, Collins IJ, Judd A, Castro H, et al. Effectiveness and safety of dolutegravir and raltegravir for treating children and adolescents living with HIV: a systematic review. Journal of the International AIDS Society. 2022;25(11):e25970.
278. Maghembe AA, de Boer MS, Marikias G, Amour C, Mahande MJ. HIV viral suppression and associated factors among children and adolescents on a dolutegravir (DTG) based antiretroviral regimen in Tanzania mainland. medRxiv. 2023.
279. Turkova A, White E, Mujuru HA, Kekitiinwa AR, Kityo CM, Violari A, et al. Dolutegravir as first-or second-line treatment for HIV-1 infection in children. New England Journal of Medicine. 2021;385(27):2531-2543.
280. Ruel TD, Acosta EP, Liu JP, Gray KP, George K, Montañez N, et al. Pharmacokinetics, safety, tolerability, and antiviral activity of dolutegravir dispersible tablets in infants and children with HIV-1 (IMPAACT P1093): results of an open-label, phase 1–2 trial. The Lancet HIV. 2022;9(5):e332-e340.
281. Abrams EJ, Capparelli E, Ruel T, Mirochnick M. Potential of Long-Acting Products to Transform the Treatment and Prevention of Human Immunodeficiency Virus (HIV) in Infants, Children, and Adolescents. Clinical infectious diseases. 2022;75(Supplement_4):S562-S570.
282. Calmy A, Ford N, Hirschel B, Reynolds SJ, Lynen L, Goemaere E, et al. HIV viral load monitoring in resource-limited regions: optional or necessary? Clinical infectious diseases. 2007;44(1):128-134.
283. Nicholas S, Poulet E, Wolters L, Wapling J, Rakesh A, Amoros I, et al. Point-of-care viral load monitoring: outcomes from a decentralized HIV programme in Malawi. Journal of the International AIDS Society. 2019;22(8):e25387.

284. Drain PK, Dorward J, Bender A, Lillis L, Marinucci F, Sacks J, et al. Point-of-care HIV viral load testing: an essential tool for a sustainable global HIV/AIDS response. Clinical microbiology reviews. 2019;32(3):e00097-00018.
285. Drain PK, Hyle EP, Noubary F, Freedberg KA, Wilson D, Bishai WR, et al. Diagnostic point-of-care tests in resource-limited settings. The Lancet Infectious Diseases. 2014;14(3):239-249.
286. Boeke CE, Joseph J, Atem C, Banda C, Coulibaly KD, Doi N, et al. Evaluation of near point-of-care viral load implementation in public health facilities across seven countries in sub-Saharan Africa. Journal of the International AIDS Society. 2021;24(1):e25663.
287. Drain PK, Dorward J, Violette LR, Quame-Amaglo J, Thomas KK, Samsunder N, et al. Point-of-care HIV viral load testing combined with task shifting to improve treatment outcomes (STREAM): findings from an open-label, non-inferiority, randomised controlled trial. The Lancet HIV. 2020;7(4):e229-e237.
288. St Clair-Sullivan N, Mwamba C, Whetham J, Moore CB, Darking M, Vera J. Barriers to HIV care and adherence for young people living with HIV in Zambia and mHealth. Mhealth. 2019;5.
289. Srivastava M, Amzel A, Golin R, Grimsrud A, Sullivan D, Wilkinson L, et al. Families matter: differentiated service delivery for HIV. The Lancet HIV. 2019;6(10):e646-e648.
290. Jaffar S, Amuron B, Foster S, Birungi J, Levin J, Namara G, et al. Rates of virological failure in patients treated in a home-based versus a facility-based HIV-care model in Jinja, southeast Uganda: a cluster-randomised equivalence trial. The Lancet. 2009;374(9707):2080-2089.
291. Mukherjee JS, Barry D, Weatherford RD, Desai IK, Farmer PE. Community-based ART programs: sustaining adherence and follow-up. Current HIV/AIDS Reports. 2016;13(6):359-366.
292. World Health Organization. Key considerations for differentiated antiretroviral therapy delivery for specific populations: children, adolescents, pregnant and breastfeeding women and key populations. World Health Organization; 2017.
293. Amadhila JN. Evaluation of the implementation of the Baby and Mother Friendly Initative in Namibia 2017.

294. Wilkinson L, Grimsrud A. The time is now: expedited HIV differentiated service delivery during the COVID-19 pandemic. Journal of the International AIDS Society. 2020;23(5).
295. Ruria EC, Masaba R, Kose J, Woelk G, Mwangi E, Matu L, et al. Optimizing linkage to care and initiation and retention on treatment of adolescents with newly diagnosed HIV infection. Aids. 2017;31(Suppl 3):S253.
296. World Health Organization. Making health services adolescent friendly. Developing national quality standards for adolescent-friendly health services. Geneva: WHO. World Health Organization. 2012.
297. World Health Organization. Making health services adolescent friendly. Developing national quality standards for adolescent-friendly health services Geneva: WHO. 2012.
298. Elizabeth Glaser Pediatric AIDS Foundation. 2004 [press release]. 2004.
299. Elizabeth Glaser Pediatric AIDS Foundation. ADOLESCENTS AND HIV.
300. Fatti G, Jackson D, Goga AE, Shaikh N, Eley B, Nachega JB, et al. The effectiveness and cost-effectiveness of community-based support for adolescents receiving antiretroviral treatment: an operational research study in South Africa. Journal of the International AIDS Society. 2018;21:e25041.
301. Siberry GK, Amzel A, Watts DH, Ahmed S. Supplement Introduction: Accelerating Children's HIV/AIDS Treatment (ACT) Initiative: Using What We Learned to Maintain the Pace to Close the Pediatric HIV Treatment Gap. Journal of Acquired Immune Deficiency Syndromes. 2018;78:S63-S64.
302. Tapera T, Willis N, Madzeke K, Napei T, Mawodzeke M, Chamoko S, et al. Effects of a peer-led intervention on HIV care continuum outcomes among contacts of children, adolescents, and young adults living with HIV in Zimbabwe. Global Health: Science and Practice. 2019;7(4):575-584.
303. Laurenzi CA, du Toit S, Ameyan W, Melendez-Torres G, Kara T, Brand A, et al. Psychosocial interventions for improving engagement in care and health and behavioural outcomes for adolescents and young people living with HIV: a systematic review and meta-analysis. Journal of the International AIDS Society. 2021;24(8):e25741.
304. Shenderovich Y, Boyes M, Esposti MD, Casale M, Toska E, Roberts KJ, et al. Relationships with caregivers and mental health outcomes among adolescents living

with HIV: a prospective cohort study in South Africa. BMC public health. 2021;21(1):1-11.
305. Boyd CM, Lucas GM. Patient-centered care for people living with multimorbidity. Current Opinion in HIV and AIDS. 2014;9(4):419.
306. Memiah P, Lathan-Dye M, Opanga Y, Muhula S, Gitahi-Kamau N, Kamau A, et al. Highlighting a Digital Platform to Assess Young People Needs: Reaching and Engaging Adolescents and Young Adults for Care Continuum in Health Project (REACH). Adolescents. 2022;2(2):150-163.
307. Ybarra ML, Bull SS. Current trends in Internet-and cell phone-based HIV prevention and intervention programs. Current HIV/AIDS Reports. 2007;4(4):201-207.
308. Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, De Walque D, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. Aids. 2011;25(6):825.
309. Joseph-Davey D, Ponce W, Augusto O, Traca D, Jetha E, de Palha de Sousa C, editors. Improved retention in HIV care following SMS reminders in Mozambique: a randomized controlled trial. 7th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; 2013.
310. Swahn MH, Braunstein S, Kasirye R. Demographic and psychosocial characteristics of mobile phone ownership and usage among youth living in the slums of Kampala, Uganda. Western journal of emergency medicine. 2014;15(5):600.
311. Ybarra ML, Mwaba K, Prescott TL, Roman NV, Rooi B, Bull S. Opportunities for technology-based HIV prevention programming among high school students in Cape Town, South Africa. AIDS care. 2014;26(12):1562-1567.
312. Goldstein M, Archary M, Adong J, Haberer JE, Kuhns LM, Kurth A, et al. Systematic Review of mHealth Interventions for Adolescent and Young Adult HIV Prevention and the Adolescent HIV Continuum of Care in Low to Middle Income Countries. AIDS and behavior. 2022:1-22.
313. Muessig KE, LeGrand S, Horvath KJ, Bauermeister JA, Hightow-Weidman LB. Recent mHealth interventions to support medication adherence among HIV-positive men who have sex with men. Current Opinion in HIV and AIDS. 2017;12(5):432.

314. Hightow-Weidman LB, Muessig KE, Bauermeister J, Zhang C, LeGrand S. Youth, technology, and HIV: recent advances and future directions. Current HIV/AIDS Reports. 2015;12(4):500-515.
315. Navarra A-MD, Gwadz MV, Whittemore R, Bakken SR, Cleland CM, Burleson W, et al. Health technology-enabled interventions for adherence support and retention in care among US HIV-infected adolescents and young adults: an integrative review. AIDS and behavior. 2017;21(11):3154-3171.
316. Jennings Mayo-Wilson L, Kang B-A, Mathai M, Mak'anyengo MO, Ssewamala FM. Mobile phone access, willingness, and usage for HIV-related services among young adults living in informal urban settlements in Kenya: A cross-sectional analysis. International Journal of Medical Informatics. 2022;161:104728.
317. LeGrand S, Muessig KE, McNulty T, Soni K, Knudtson K, Lemann A, et al. Epic allies: development of a gaming app to improve antiretroviral therapy adherence among young HIV-positive men who have sex with men. Journal of Medical Internat Research (JMIR) serious games. 2016;4(1):e5687.
318. Saberi P, Siedle-Khan R, Sheon N, Lightfoot M. The use of mobile health applications among youth and young adults living with HIV: focus group findings. AIDS patient care and STDs. 2016;30(6):254-260.
319. Saberi P, Yuan P, John M, Sheon N, Johnson MO. A pilot study to engage and counsel HIV-positive African American youth via telehealth technology. AIDS patient care and STDs. 2013;27(9):529-532.
320. Twimukye A, Bwanika Naggirinya A, Parkes-Ratanshi R, Kasirye R, Kiragga A, Castelnuovo B, et al. Acceptability of a mobile phone support tool (call for life Uganda) for promoting adherence to antiretroviral therapy among young adults in a randomized controlled trial: exploratory qualitative study. Journal of Medical Internat Research (JMIR) mHealth and uHealth. 2021;9(6):e17418.
321. Muessig KE, Nekkanti M, Bauermeister J, Bull S, Hightow-Weidman LB. A systematic review of recent smartphone, Internet and Web 2.0 interventions to address the HIV continuum of care. Current HIV/AIDS Reports. 2015;12(1):173-190.