ART adherence trajectories and correlates of treatment outcomes among adolescents in the Eastern Cape Province of South Africa

by

Siyanai Zhou

ZHXSIY001

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Supervisors

Assoc. Prof. Lucia Knight & Assoc. Prof. Elona Toska

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To God be the glory.

Declaration

I, Siyanai Zhou, hereby declare that this thesis is my own work, both in concept and execution, apart from the guidance received from supervisors and the contributions of those acknowledged.

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 or educational institution.

The work in this thesis is solely of the candidate, and in the case of multi-authored published chapters, the candidate was the lead author.

The thesis is presented for examination for the degree of PhD.

Signature: Signed by candidate

Name: Siyanai Zhou

Date: 29 November 2024

Preface

This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) in Public Health completed in the Division of Social & Behavioural Sciences, School of Public Health & Family Medicine, Faculty of Health Sciences at the University of Cape Town.

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

1. Zhou, S., Toska, E., Langwenya, N., Edun, O., Cluver L., Knight L. Exploring Self-reported Adherence Measures to Screen for Elevated HIV Viral Load in Adolescents: A South African Cohort Study. *AIDS Behav* **27**, 3537–3547 (2023). https://doi.org/10.1007/s10461-023-04068-2
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adolescents living with HIV in South Africa. *Manuscript is being prepared for submission.*

The candidate's contribution to each manuscript is outlined at the beginning of each chapter. The candidate was the lead and corresponding author on all manuscripts, conceptualised the analysis, prepared the data for analysis, conducted all the analyses, and drafted all the versions of the manuscripts. All co-authors provided feedback and approved the submitted manuscripts. The candidate's supervisors have confirmed to the University of Cape Town Doctoral Degrees Board that included papers all constitute the candidate's original scientific work.

Signature: Date: 29 November 2024

Student name: Siyanai Zhou Student number: ZHXSIY001

List of Abbreviations

ART	Antiretroviral therapy
AIC	Akaike Information Criterion
AIDS	Acquired immunodeficiency syndrome
ALHIV	Adolescents living with HIV
ARV	Antiretroviral
AUROC	Area under the receiver operating characteristic curve
AYNPHIV	Adolescents and Youth living with non-perinatally Acquired HIV
AYPHIV	Adolescents and Youth living with Perinatally Acquired HIV
ALPHIV	Adolescents living with Perinatally Acquired HIV
ANPHIV	Adolescents living with non-perinatally Acquired HIV
BIC	Bayesian Information Criterion
CDI	Child Depression Inventory
CSSR	Centre for Social Science Research
DMP	Data Management Plans
DOTS	Directly observed therapy
DRC	Democratic Republic of Congo
DSD	Differentiated service delivery
ELISA	Enzyme-linked immunosorbent assay
GBTM	Group-based trajectory modelling
GSEM	Generalized structural equation model
HEADSS	Home, Education, Activities, Drug use and abuse, Sexual behaviour, Suicidality and depression
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee
HSRC	Human Sciences Research Council
IQR	Inter-Quartile Range
IRR	Incidence rate ratios
LFTU	Lost-to-study-follow-up
LMIC	Low- or Middle-Income Country
MEMS	Medication event monitoring systems

MOS-SSS	Medical Outcomes Study Social Support Survey
MW	Mzantsi Wakho
NGO	Non-governmental organization
NHLS	National Health Laboratory Service
NICD	National Institute For Communicable Diseases
NPV	Negative predictive value
OCC	Odds of correct classification
PDC	Proportion of days covered
PMTCT	Prevention of mother-to-child transmission of HIV
POPIA	Protection of Personal Information Act
PPV	Positive predictive value
RCMAS	Revised Children's Manifest Anxiety Scale
RCS	Resource-constrained settings
RCT	Randomised control trials
RNA	Ribonucleic acid
ROC	Receiver operating characteristic curve
SOP	Standard operating procedures
SSA	sub-Saharan Africa
TB	Pulmonary Tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
UPLIFT	Understanding Predictors of Lifelong Initiation and Follow-up Treatment for Adolescents Living with HIV
UTT	Universal Test and Treat
VL	Viral load
VLS	Viral suppression
WHO	World Health Organisation

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Abstract

Background: Sustained adherence to antiretroviral treatment (ART) is essential for viral suppression among adolescents living with HIV. In turn, suppressed viral load reduces the risk of onward transmission, HIV-related morbidity, and mortality, optimising overall health and well-being. Yet, adherence to ART among adolescents living with HIV (ALHIV) remains suboptimal compared to children and adults. Adherence measurement varies widely with no gold standard, and composite assessments such as longitudinal self-reported adherence have not been thoroughly evaluated among ALHIV in low-resource settings. In sub-Saharan Africa, evidence on longitudinal sustained ART adherence and its impacts on subsequent HIV treatment outcomes for ALHIV remains scarce. Prior studies on ART adherence—largely cross-sectional—have relied on traditional aggregate methods, dichotomising adolescents as adherent versus non-adherent which is insufficient to capture variations in adherence over time. Longitudinal ART adherence trajectories may aid the assessment of sustained long-term adherence and its impact on HIV treatment outcomes among ALHIV. To address these gaps, this PhD examined the validity of longitudinal self-reported measures of ART adherence among ALHIV in South Africa. It used group-based trajectory models (GBTMs) to identify ART adherence trajectories and examined their association with HIV treatment outcomes—viral suppression and mortality. It further explored factors contributing to distinct adherence trajectories, and the impact of psychosocial and structural provisions on long-term HIV treatment outcomes among ALHIV in South Africa.

Methods: This PhD is an analysis of a three-wave longitudinal cohort study of 1046 ALHIV and 473 HIV-negative peers aged 10-19 years at baseline, in the Eastern Cape province of South Africa. From 2014 to 2018, participants completed questionnaires that included their socio-demographic information and self-reported adherence at all three visits. All participants and their caregivers gave informed consent to participate. In parallel, routine viral load data were extracted from physical and electronic patient files in health facilities, and the National Health Laboratory Services (NHLS) of South Africa (2014-2019). Viral load laboratory test results for 75.2% of the participants were obtained. Mortality was ascertained through community tracing and reporting from 2016 to 2022. All analyses in this thesis used the longitudinal cohort data to address the specific objectives. Statistical analyses included mixed effects logistic regression, group-based trajectory modelling, and path analysis.

Findings: The first analysis (Chapter 4) explored the validity of five longitudinal self-reported adherence measures to screen for non-adherence and identify ALHIV with elevated viral load (>1000 copies/mL). Self-report measures included any missed dose in the past 3-days, past-week, past-month, days missed in the past-month, and any past-year missed clinic appointment and were all significantly

associated with elevated viral load. The individual sensitivity of each measure varied from 79.5% to 91.6%, and positive predictive values were above 75%. Using the five self-reported adherence measures and group-based trajectory modelling, four adolescent adherence trajectories were identified (Chapter 5), namely *'consistent* (49.8%), *'low start and increasing'* (20.8%); *'gradually decreasing'* (23.5%), and *'low and decreasing* (5.9%) adherence. Compared to the consistent adherence trajectory, membership in each of the three inconsistent adherence trajectories was significantly associated with lower adjusted odds of durable viral suppression—having suppressed viral load (<1000 copies/ml) at two or more consecutive study waves. Complementary mortality analysis (Chapter 6) showed that all-cause mortality rates differ across the four adherence trajectories, and sustained adherence to ART was associated with lower rates of mortality among ALHIV. The analysis found that ALHIV experience higher all-cause mortality than their HIV-negative peers, despite ART rollout in South Africa. Guided by the socio-ecological model (Chapter 7), pathways linking barriers contributing to the distinct longitudinal adherence trajectories were established using path analysis. Experiencing mental health symptoms, medication side effects, internalised HIV stigma, food insecurity, longer clinic travel time (>1 hour), and witnessing domestic violence or conflict were associated with inconsistent adherence trajectories relative to the '*consistent adherence*' trajectory. More importantly, the pathways linking co-occurring barriers, and mental health symptoms to longitudinal adherence were unique for each trajectory or ALHIV sub-group. The final analysis (Chapter 8) revealed that access to government-provided social protection and family psychosocial support was associated with greater improvements in long-term ART adherence and viral load outcomes.

Conclusions: This PhD documents multiple ART adherence trajectories, low rates of viral suppression, and high all-cause mortality among ALHIV in South Africa. Self-reported adherence shows promise for low-cost and relatively easy-to-administer alternative measures to ensure timely identification of poor adherence to ART among adolescents, particularly in settings where virologic monitoring is limited. ALHIV displayed distinct adherence behaviour patterns over time, which provides an opportunity to identify and target specific sub-groups of ALHIV in need of adherence support interventions. The multiple barriers identified and their pathways to longitudinal adherence trajectories present another opportunity to tailor care to specific groups of ALHIV, possibly informing differentiated service delivery to different sub-groups of ALHIV. Government-provided social protection and strategies to address psychological well-being can be key add-on support provisions to enhance the effectiveness of ART treatment among ALHIV in low-resource settings. Overall, this PhD demonstrates the need to shift from a one-size-fits-all model of care to customised HIV care and combine biomedical with psychosocial and structural interventions to address the needs of distinct groups of ALHIV.

Candidate's Role and Contributions to the Mzantsi Wakho/UPLIFT Research Projects

The candidate is a quantitative co-investigator for the UPLIFT linkage project (HIV and related laboratory test results linked to a subset of the adolescents in the main Mzantsi Wakho cohort using algorithms developed by the National Health Laboratory Services). The candidate joined the research team in February 2018 during the second follow-up round of the Mzantsi Wakho data collection. As a quantitative researcher, the candidate has been directly involved with the following project components:

a. *Co-leading UPLIFT linkage project:* As part of this thesis and the wider research work, this candidate has been leading and overseeing the matching, linking, and merging of adolescents' self-reported data to their laboratory tests at the National Health Laboratory Services (NHLS) of South Africa since 2021. This role involves coordinating with the NHLS team, providing oversight on the sharing of raw data between NHLS and the research team, and supervising data cleaning and merging of matched electronic data from laboratory test results from the national database. In addition, the candidate also ensures the ethical management of data in line with Protection of Personal Information Act (POPIA) standards, in terms of storage, data access, and data sharing of de-identified data.

b. *Fieldwork:* Following the extensive involvement in data curation and management of the Mzantsi Wakho research project data, the candidate had a chance to co-lead fieldwork linked to this project in 2022. As part of Mzantsi Wakho cohort maintenance and to assess the impact of COVID-19, we set out to follow up with the male participants from the Mzantsi Wakho cohort in East London, South Africa (female participants were followed separately, and as part of a new project, in the same period). This candidate co-managed the data collection, designed, reviewed, and finalised the follow-up questionnaire for the males-only data collection. The candidate's responsibilities during this time included week-to-week oversight of fieldwork logistics and management of the field team (~10 research assistants and fieldwork coordinators). This work also involved field visits, and training staff in presenting the project to participants and the public.

c. *Data curation:* From February 2018, the candidate co-led the cleaning and merging of the first and second follow-up data from the Mzantsi Wakho project. The data

cleaning process involved the use of statistical software (Stata, SPSS, and R), liaising with the fieldwork team to resolve any data cleaning queries, and supporting the research team with answering any data-related questions. In the process, the candidate was overseeing the curation of datasets from multiple sources –that are related to the wider Mzantsi Wakho project–, such as patient files or folder reviews, and more recently electronic data from laboratory tests in the South African national database. The candidate also led the merging of the three-wave cohort data and integration with other data sources in a repository for analysis.

d. *Data management:* Since 2018, the candidate has also been directly involved in was responsible for processed data storage and safety, ensuring confidentiality, anonymity, and readiness of data for analysis. In particular, the candidate has been managing the file system and cloud storage of the micro-data produced from the research project. This also involves iterative data quality checks based on feedback from analysts and researchers, to identify and resolve data errors and inconsistencies. The candidate also managed the data access procedures and conducted end-user training annually, on how to access and use the processed data. In addition, the candidate led the documentation of metadata including the write-up of Data Management Plans (DMPs) for the wider Mzantsi Wakho project data and UPLIFT linkage data, respectively.

The data analysis and writing for all results papers presented in this thesis were conceptualised and led by the candidate with guidance from Assoc. Prof. Lucia Knight and Assoc. Prof. Elona Toska (Mzantsi Wakho co-PI) and mentorship from Prof Lucie Cluver (Mzantsi Wakho co-PI), Prof Marl Orkin, and Prof Gayle Sherman (UPLIFT co-I).

CHAPTER 1. INTRODUCTION

1.1. Background

According to the most recent UNAIDS estimates, 1.7 million adolescents aged 10-19 years were living with HIV (ALHIV) globally in 2022, 80% of whom were living in sub-Saharan Africa (SSA) [1, 2]. South Africa has the largest number of ALHIV in SSA, with an estimated 320,000 adolescents living with HIV as of 2022 [2, 3]. Due to increased and early access to antiretroviral therapy (ART), more children born with HIV survive into adolescence and new infections among 15-24 year-olds continue to rise [4, 5] contributing to the global burden of HIV [6, 7]. Moreover, despite global reductions in HIV mortality and morbidity, in South Africa, HIV-related deaths among older adolescents (aged 15-19 years) continue to increase compared to their younger (10-14 year-old) counterparts [5, 8]. Although available mortality data remain regionally variable, estimates show that adolescent mortality rates are high, ranging between 1.2 to 4.5 per 100 person-years in South Africa [9, 10] and HIV remains the leading cause of death among adolescents in SSA [11]. This increase in mortality, as well as the scale and complexity of the epidemic among adolescents, requires attention and strategies to prevent this are urgently needed.

In light of the increasing HIV burden, adolescents continue to face a set of unique challenges relating to ART uptake, linkage to and retention in HIV care, ART adherence and poor treatment outcomes [12]. Despite the relative general success in scaling up access to ART in South Africa, adherence to ART among adolescents remains sub-optimal [13], and lower compared to children and adults [13-15]. A meta-analysis of adolescents and young people found that 62% were adherent to ART [4]. Sub-optimal adherence leads to poor viral suppression rates, undesirable treatment outcomes (e.g., viral failure), and increased risk of developing opportunistic infections [16] such as tuberculosis (TB) resulting in high morbidity in this population group [17, 18]. Longitudinal studies have also estimated that adolescent viral suppression rates in SSA are low ranging from 28-78% compared to 90% in adults on similar regimens [19-21]. Thus, more efforts aimed at improving long-term adherence, and subsequent HIV treatment outcomes among adolescents in resource-constrained settings are needed [22, 23].

In the face of infrequent availability and poor accessibility of objective measures of adherence like viral load (VL) [24, 25], self-reported measures remain widely used in both research and clinic settings to identify adolescents at risk of virologic failure and poor health [24, 25]. In part, this is due to their low cost, minimal patient burden, and ease of administration [24]. However, there is limited evidence assessing the validity and consistency of these measures among ALHIV using longitudinal data.

Several studies have adopted one or more of these self-reported measures to assess ART adherence among adolescents in SSA [26-28]. However, much of the available evidence on this is qualitative or cross-sectional, which cannot appropriately reflect dynamic changes in adherence among adolescents [16]. Furthermore, most research has focused on adolescents with perinatally acquired HIV [23, 29, 30], and there is a lack of longitudinal data on ART adherence and HIV treatment outcomes, particularly for those in resource-constrained settings [29, 31-36]. In particular, no known study has utilised multiple self-reported measures to assess adolescents' longitudinal adherence trajectories in South Africa [37]. Longitudinal adherence trajectories represent clusters or groups of adolescents with similar patterns of adherence over time, critical to the understanding of long-term adherence behaviour change among ALHIV [38-40]. Understanding longitudinal and self-reported ART adherence in the context of adolescent development will aid the early identification of those at risk of long-term poor adherence and subsequent negative treatment outcomes. Longitudinal adherence trajectories among ALHIV contribute to research on sustained ART adherence, identified as critical to implementing the WHO's Universal Test and Treat (UTT) approach [41]. This is also critical to shedding light on potential malleable factors to support ALHIV in SSA to adhere to their treatment and minimise treatment failure [42].

A global research agenda priority-setting exercise focused on ALHIV emphasized identifying malleable factors influencing retention in HIV care, and adherence to improve HIV treatment outcomes including viral suppression [32, 43]. Adolescents are particularly vulnerable and face specific challenges at the individual, household, community, healthcare, and structural levels that impede sustained long-term ART adherence, distinct from those faced by children and adults [4, 19, 23]. Previous research identified numerous factors influencing ART adherence among ALHIV, particularly in SSA and South Africa [23, 28, 37, 44, 45]. For example, a recent systematic review of ART adherence found over 60 separate variables associated with ART treatment adherence that fall under different levels of the adolescents'

social environment [30, 46]. These factors may intersect across these levels and generate compounded effects, particularly in resource-constrained settings. However, there is limited longitudinal data on the impact of these intersecting factors on long-term ART adherence trajectories. Therefore, there is a need for further investigation into barriers and facilitators of ART adherence, and how they shape longitudinal adherence trajectories among ALHIV in South Africa. This is essential for designing comprehensive and timely targeted support or intervention strategies to improve adherence and retention in HIV care, and subsequent treatment outcomes.

1.2. Research aims, objectives, and hypothesis

The overall aim of this research is to:

(i) Explore the longitudinal ART adherence trajectories, their determinants, and associations with HIV treatment outcomes in a cohort of ALHIV in South Africa.

The specific objectives of this study were:

a. To evaluate the longitudinal self-reported measures of ART adherence against viral load in a cohort of ALHIV in resource-limited settings.

b. To identify and describe longitudinal trajectories of ART adherence using multiple self-reported adherence measures among ALHIV.

c. Describe sex- and age-specific all-cause mortality and their differences by mode of HIV acquisition and longitudinal adherence to ART among ALHIV.

d. Identify and describe the mechanisms linking socio-ecological barriers with distinct longitudinal ART adherence trajectories.

e. Examine the impact of psychosocial and economic support on longitudinal adherence and viral suppression among ALHIV.

1.3. Hypotheses

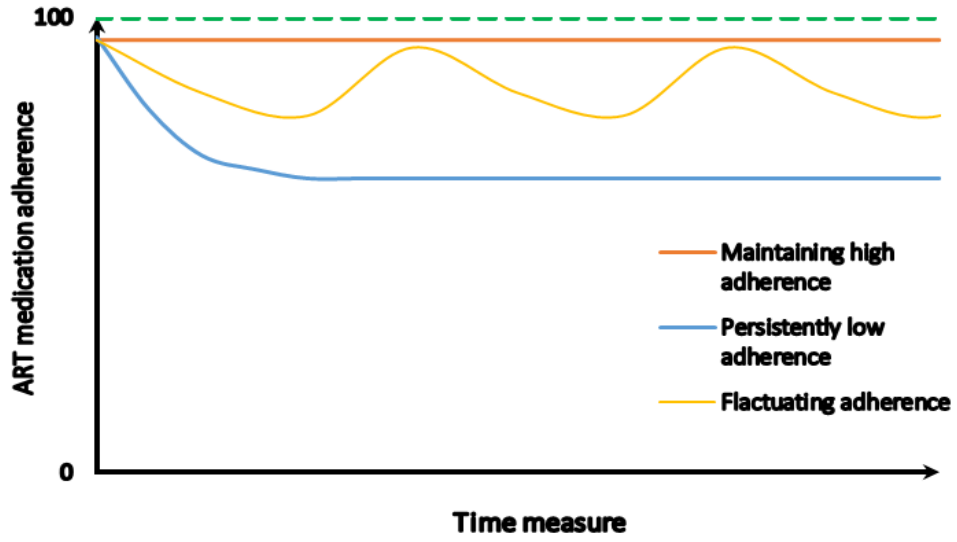
The main hypothesis for Objectives 2 and 3 is based on the heterogeneity of ART adherence trajectories over time. Specifically, we hypothesize that

a. There are at least three longitudinal patterns of adherence namely: (1) a sub-group that maintains high ART adherence, (2) a sub-group that has persistently low ART

adherence, and (3) a sub-group that has fluctuating ART adherence as illustrated in Figure 2 below.

b. Each trajectory described in Figure 1.1 may be shaped by unique factors (barriers or facilitators) of adherence leading to varying treatment outcomes.
c. These factors may be interrelated at multiple levels of the socio-ecological model contributing to different long-term adherence trajectories among ALHIV.

Figure 1.1: Hypothesized longitudinal ART adherence patterns



1.4. Structure of the thesis

This thesis consists of nine chapters namely: introduction and background, literature review, methodology, five results chapters and a discussion and recommendations chapter synthesising the overall findings of this thesis. The introduction and background chapter places the challenges of ART adherence and poor HIV treatment outcomes, specifically among ALHIV in SSA, into context, and provides the statement of the problem. The main aim(s) and specific objectives of this research are also presented in this chapter. The next chapter, the literature review, presents the review of the literature on ART adherence among adolescents living with HIV and its determinants among adolescents, self-reported adherence measurement, longitudinal trajectories of ART adherence, and HIV treatment outcomes. This chapter also presents the theoretical framework of the study. Chapter 3, the methodology, describes the data sources including the study design and data collection procedures. This chapter also presents a detailed overview of the statistical analysis methods and data analysis

steps. The five results chapters addressing the specific objectives using data from a cohort of adolescents who were recruited in the Eastern Cape province in South Africa and followed up between 2014 and 2022 are summarised in Table 1.1. Seventy percent of the adolescents in the cohort were living with HIV and had already initiated ART at baseline. All the results chapters are either published manuscripts, submitted, or being prepared for submission (Table 1.1). The findings of this research are synthesised and discussed in Chapter 9, along with a summary of key contributions, policy recommendations and opportunities for future research. References are presented at the end of each chapter, except for Chapter 1-3 and 9, which are combined and presented at the end of the discussion chapter.

Table 1.1: Summary of thesis results chapters, and data sources

Chapter	Objective	Manuscript title and status	Data source
Chapter 4	1. To evaluate the longitudinal self-reported measures of ART adherence against viral load in a cohort of ALHIV in resource-limited settings.	Zhou S, Toska E, Langwenya N, Edun O, Cluver L, Knight L. Exploring Self-reported Adherence Measures to Screen for Elevated HIV Viral Load in Adolescents: A South African Cohort Study. *AIDS Behav*. 2023 Nov;27(11):3537-3547. doi: 10.1007/s10461-023-04068-2. Epub 2023 Apr 17.	Mzantsi Wakho self-reported quantitative surveys
Chapter 5	2. To identify and describe longitudinal trajectories of ART adherence using multiple self-reported adherence measures among ALHIV.	Zhou, S., Cluver, L., Knight, L., Edun, O., Sherman, G. and Toska, E., 2024. Longitudinal Trajectories of Antiretroviral Treatment Adherence and Associations With Durable Viral Suppression Among Adolescents Living With HIV in South Africa. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *96*(2), pp.171-179. | doi: 10.1097/QAI.0000000000003408	Mzantsi Wakho self-reported quantitative surveys, and UPLIFT viral load data
Chapter 6	3. Describe sex- and age-specific all-cause mortality and their differences by mode of HIV acquisition and longitudinal adherence to ART among ALHIV.	Zhou S, Toska E, Gwampi B, Johnson L, Tolmay J, Saal W, Knight L, Cluver L. Age-specific all-cause mortality rates among adolescents and youth living with HIV in South Africa. *Submitted to the Journal of International AIDS Society.*	Mzantsi Wakho self-reported quantitative surveys
Chapter 7	4. Identify and describe the mechanisms linking socio-ecological barriers with distinct longitudinal ART adherence trajectories.	Zhou S, Toska E, Knight L, Cluver L. Pathways to Poor Longitudinal Antiretroviral Adherence Among Adolescents Living with HIV in South Africa: The role of socio-ecological barriers. *Submitted to AIDS and behaviour*.	Mzantsi Wakho self-reported quantitative surveys
Chapter 8	5. Examine the impact of psychosocial and economic support on longitudinal adherence and viral suppression among ALHIV.	Zhou S, Cluver L, Orkin M, Rudgard W, Bachman G, Knight L, Sherman G, Toska E. Impact of social-economic support on HIV treatment outcomes among adolescents living with HIV in South Africa. *Being prepared for submission.*	Mzantsi Wakho self-reported quantitative surveys, and UPLIFT viral load data

CHAPTER 2. LITERATURE REVIEW

2.1. Introduction

This chapter presents a review of the relevant literature on adherence to ART, and related HIV treatment outcomes among adolescents. It is comprised of five sections. The first section provides an overview of the ART adherence situation in adolescents regionally and in the South African context. The second section introduces the concept of adherence trajectories as a method of assessing longitudinal adherence and reviews its application in ART adherence research, including among ALHIV. The literature on viral load suppression and mortality among adolescents living with HIV is reviewed in the third section. The fourth section reviews factors affecting adherence among ALHIV in Southern Africa using a socio-ecological model. The last section of the review describes adherence measurement with a specific focus on self-reported measures which are adopted in this research.

2.2. Adherence to ART among ALHIV

With larger numbers of perinatally infected children surviving into adolescence, the global burden of adolescents living with HIV continues to increase [47]. Despite the improved access and success of ART, adherence to treatment remains a challenge among ALHIV [14, 15, 48-52]. Several studies, largely cross-sectional, have reported lower adherence rates among adolescents compared to adults and children [48, 51], which consequently, increases their risk of treatment failure. For example, a study of 519 adolescents living with perinatally acquired HIV (ALPHIV) attending two large HIV clinics in Malawi found that only 55% of all adolescents reported adherence to ART in the past month [26]. Similarly, a recent study in Tanzania, found that only 65.3% of ALPHIV reached optimal adherence (> 95%) recorded through pharmacy refills [53]. A systematic review and meta-analysis of over 50 studies globally found that only 62.3% of adolescents were adherent to ART [4]. This is similar to findings from a most recent mixed-methods systematic review and meta-analysis in SSA, which found that ART adherence remains as low as 65% (95%CI 56–74) among adolescents in the region [54]. These findings reinforce the need for continuous assessment of adherence and its determinants as well as how they change over time. Moreover, the need to maintain ALHIV on treatment for a lifetime requires a long-term perspective on adherence to ART.

Presently, scant empirical evidence exists on long-term adherence among ALHIV, particularly in resource-limited settings. A small cohort study of (N=154) adolescents living with non-perinatally acquired HIV (ANPHIV) in nine Southern African countries found that few (20.7%) adolescents achieved ≥95% adherence at 6 months and sustained adherence over time decreased to 6.6% at 24 months [55]. Another cohort study (N=250) of both ALPHIV and ANPHIV aged 12–18 years, assessing long-term adherence over 3 years, in nine sites located in Asia, found that the proportion of adherence decreased from 69% at baseline to 60% at 36 months [56]. Similarly, evidence from another cohort study of (N=179) ALPHIV in the United States, with over 5 years of follow-up, found that past-week adherence decreased from 65% at 12 months to 58% at 48 months [57]. Evidence from these cohort studies suggests that ALHIV fail to achieve and sustain adequate adherence although sustained ART adherence is critical to achieving and maintaining suppressed viral load, preventing disease progression and transmission, and reducing morbidity and mortality [58]. However, numerous gaps exist in our understanding of longitudinal ART adherence and how it influences long-term HIV treatment outcomes among adolescents in SSA.

2.2.1. ART Adherence trajectories: A life-course approach

Adherence to ART is a complex and dynamic process, and limited attention has been given to how adherence changes over time and variability in adherence patterns both between and within adolescents [59]. Most recently, trajectory analysis has been utilised to model long-term changes in health behaviours such as adherence and treatment outcomes (e.g., viral suppression) [60-62]. Trajectory analysis is premised upon the life-course perspective which suggests that an individual life course is shaped by multiple trajectories [63] and it focuses on how health behaviours and psychosocial resources influence an individual's health over time. Premised upon the life-course perspective and Moffitt's typological theory [64], Nagin and Land introduced the group-based trajectory model (GBTM) to help quantify trajectories – identify groups of individuals following similar progressions— of any health behaviour e.g., adherence to ART over time in any identifiable population. Recently adopted into clinical and health research [38], GBTM potentially helps to draw out common trajectories and make sense of repeated measures or longitudinal data. The primary objective of GBTM is to determine if there exist unobserved sub-groups of individuals who exhibit different patterns of change. GBTM facilitates distinguishing between-group and within-group trajectory changes, and/or differences over time which could be useful in identifying groups or sub-

groups of adolescents who most need adherence support or those at risk of treatment failure. Analysing health outcomes trajectories requires repeated measurements, with a minimum of three measurements allowing the description of patterns in trajectories [38].

Several studies have applied trajectory modelling to unpack the complexity and dynamics of adherence patterns related to different medications such as ART [60-62] and treatment outcomes [65-70]. One of the earliest applications of GBTM in ART adherence used the Swiss HIV cohort study (adults with a median age of 41 years) to identify longitudinal trajectories of adherence and the associated predictors using the information on self-reported missed doses of combination ART (cART) collected every six months as a measure of adherence [71]. In this study, four adherence trajectories were identified namely: good, worsening, improving, and poor adherence. Recent applications of GBTM sought to identify adherence trajectories to cART and evaluated the migration behaviour of adult patients between trajectory groups in Brazil [61]. Using the data from a retrospective cohort study, the authors used the proportion of days covered (PDC) ≥95% as a measure of adherence to cART to identify distinctive adherence trajectories pre-and-post switching from multiple to a single-pill regimen. This study identified four adherence trajectories in each period: early non-adherence, insufficient adherence, slow increase in adherence and nearly always adherent. Although this study did not identify predictors of distinctive adherence trajectories, patient characteristics varied across different adherence trajectories, female patients and those with lower levels of education were likely to belong to trajectories exhibiting the worst adherence [61].

Another study in Australia also used GBTM to examine patterns of adherence among adults (with a mean age of 48 years) on cART for 360 days from the first observed day of dispensing [60]. Using PDC calculated as the total number of days that a patient had access to all components of their cART regimen as a measure of adherence, the authors identified three distinct adherence trajectories: nearly always adherent (67.8% of the cohort), moderate (26.6%), and low adherence (5.6%). Moderate and low adherence groups were more likely to have experienced treatment interruptions. They were also likely to be on multiple regimens and to be cART experienced with longer lengths of time on treatment. A similar study used the trajectory framework to estimate ART trajectories among black Americans living with HIV over three-time points spanning six months [62]. Using combined data from two studies they identified three adherence trajectories of individuals: high-stable (40%), moderately

low-stable (35%), and low-decreasing (25%), and they also identified several factors associated with distinct adherence trajectories using the socio-ecological model. Specifically, being older was associated with higher odds of being in the high-stable adherence group, and substance use, and lower quality health care ratings were associated with higher odds of being in the sub-optimal adherence groups. A more recent application of GBTM was conducted among youth living with HIV (45% had acquired HIV perinatally) in the US to characterize patterns of ART adherence measured by electronic dose monitoring (EDM) over 24 weeks. The study identified four trajectory groups namely: worst (13%), declining (25%), good (37%), and best (consistently high adherence: 25%) groups [72].

In general, the above study findings demonstrate the utility of GBTM in summarising long-term medication adherence [73]. However, the contexts and age/groups for whom GBTM has been utilised are diverse, with limited applications to ALHIV. Furthermore, there is no evidence of longitudinal adherence trajectories for adolescents, particularly those living in resource-constrained settings, with most GBTM applications conducted in high-income settings. Classification of long-term adherence trajectories among ALHIV may provide a suitable framework to identify modifiable factors associated with better adherence and identify individuals at risk of treatment failure. The findings from this approach could reveal important opportunities for clinicians and researchers to target improvement interventions more accurately [61].

2.3. HIV treatment outcomes among ALHIV

In this section, the literature on viral load (VL) outcomes and mortality among ALHIV is summarised with a focus on data from South Africa and SSA.

2.3.1. Viral Load Suppression

Several studies have shown that HIV treatment, taken as intended and prescribed, leads to VL suppression. The main objective of ART is to reduce the replication of HIV to an acceptable level leading to the restoration of the immune system [23]. VL suppression is also essential for reducing morbidity and mortality [74]. Various VL cut-off points have been used to indicate successful viral suppression in literature, ranging from below 50 copies/ml to below 1000 copies/ml of HIV RNA in the blood [75]. Zanoni and colleagues [33] in their systematic review of South African evidence, where the majority of studies used <400 copies/mL to represent viral suppression, estimated that 80% of adolescents and young people living with

HIV were virally suppressed. Other similar studies in South Africa (using <400 copies/mL) found that VL suppression among ALHIV ranges from 28% to 78% compared to 90% for adults on similar regimens [9, 19, 44]. Similarly, a recent systematic review found that the proportion of ALHIV with virological suppression at 12 months ranged from 27% to 89%. A slightly lower estimate was observed [76] in South Africa, with only 23.2% fully virally suppressed at 12 months post-initiation. These findings demonstrate that viral suppression remains sub-optimal among adolescents compared to adults. Therefore, longitudinal data on viral suppression among adolescents in South Africa is needed to inform the development of effective interventions, and ultimately enhance the health and well-being of ALHIV.

In South Africa, routine VL monitoring was first rolled out in 2004. The South African National Consolidated guidelines in 2020 recommend a 6-month routine VL collection from ART initiation, followed by a 12-month VL [77]. If the patient is stable and adherent on ART, then a 12-month VL assessment is recommended. This is in line with the WHO recommendations on routine VL monitoring as a preferred method for ART response monitoring and treatment failure early identification [78]. Several studies have shown that VL monitoring combined with appropriate action, based on the level of VL, can lead to a reduction in mortality and morbidity as well as improve HIV treatment outcomes [79, 80]. However, access to routine VL testing among adolescents in resource-constrained settings such as South Africa is limited due to financial and logistical factors: specimen integrity and results delivery [81, 82]. The uptake of routine VL monitoring among adolescents was estimated to be approximately 57% between July 2019 and June 2020 [83] which is lower than the UNAIDS revised treatment target of 95%.

2.3.2. Mortality among adolescents

A recent systematic analysis showed a shift in the global burden of mortality in adolescents and young people aged 10-24 years to SSA, where HIV causes one-third of deaths in this age group [84, 85]. Poor retention in HIV care, ART adherence and viral suppression in South Africa and SSA at large, may explain the differences in mortality rates among adolescents compared to other age groups [36], and the continued rise in mortality rates among the older compared to younger adolescents [5]. A recent study of country estimates of HIV mortality showed that since 2012, following the prioritisation of adolescents as a key population in the HIV epidemic, HIV-related mortality has reduced in number in the population group [5]. Despite this improvement, this estimated reduction in mortality among adolescents was found

to be 8% less than that for the overall population living with HIV [5, 36]. The study also highlights that the older adolescent cohort (15-19 years) continued to experience increased mortality compared to their (10-14 years) counterparts. Another study from a cohort of adolescents living with HIV attending a community-based ART clinic in South Africa found that overall mortality rates were high in both adolescents and young adults ranging between 1.2 and 3.1 deaths per 100 person-years [9]. These rates are similar to those in the IeDEA global cohort study on adolescents which found that the four-year cumulative mortality was 3.9 versus 5.4% for adolescents with perinatally acquired infection compared to those acquired during adolescence [10]. Although available mortality data remain regionally variable, adolescents' rates range between 1.2 to 4.5 per 100 person-years in South Africa [9, 10]. More granular evidence is needed on HIV-related mortality among ALHIV to better understand its burden in resource-limited settings. Identified risk factors of adolescent mortality include low CD4 count, viremia, and advanced HIV-related disease, all of which are linked to ART adherence behaviour [36]. The observed high mortality rates among adolescents underscore the importance of understanding adherence behaviours, identifying individuals at risk of poor adherence, and intervening earlier in the cascade of care. Moreover, there is a need to estimate and understand the risk of poor HIV treatment outcomes including mortality, associated with inconsistencies in long-term adherence to ART among ALHIV.

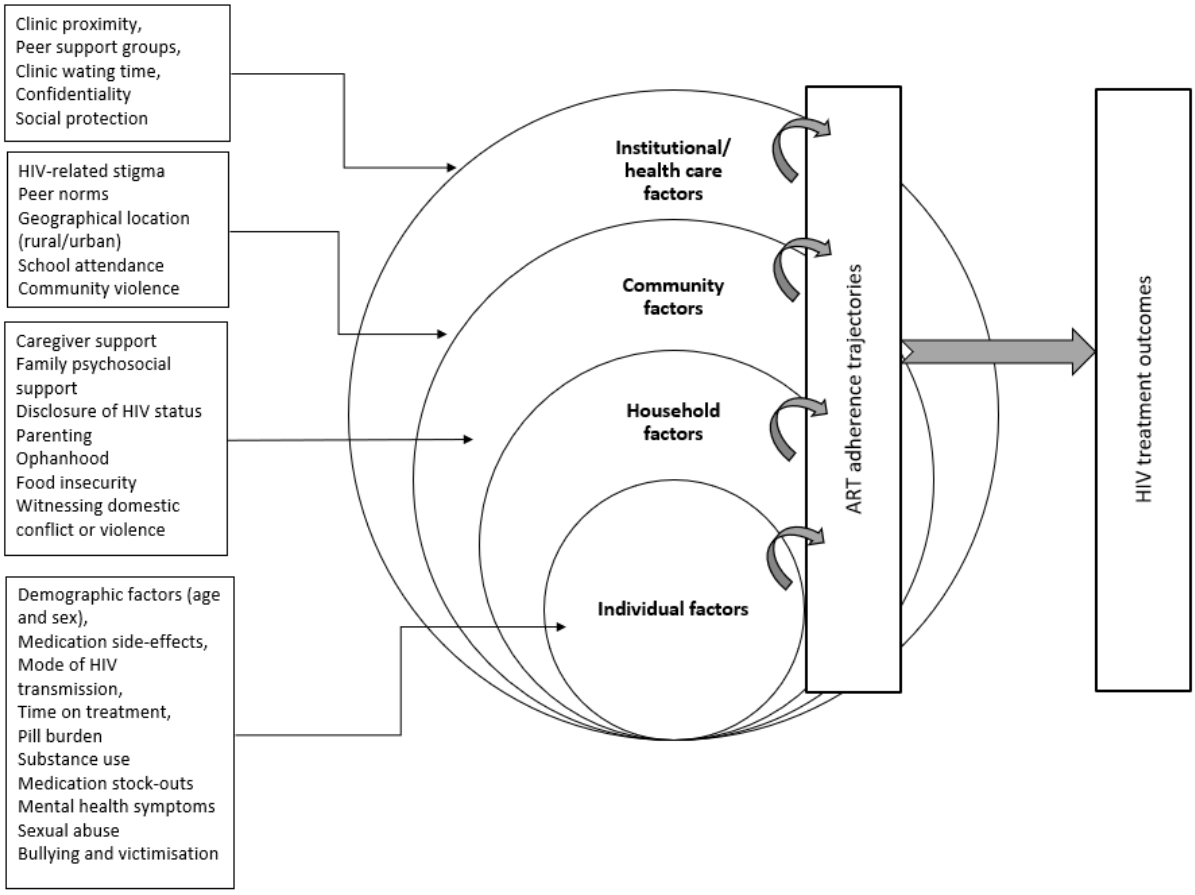
2.4. Factors affecting ART adherence among ALHIV

2.4.1. Barriers to ART adherence

Adolescence is a particularly critical stage of life, characterised by increased vulnerability as individuals experience physical, sexual, emotional, and psychological maturation [4], and is associated with accelerated behaviour changes [19]. In the context of HIV, research shows that adolescents face specific challenges at the individual, household, community, and healthcare levels—that are distinct from other population groups—which may impact their ART adherence behaviour [23]. These barriers can intersect across these different levels of the socio-ecological model, as shown in Figure 2.1**,** and generate multiplicative effects. For example, adolescents who experience a combination of the different factors at different levels may be less adherent than those facing single factors [86]. However, there is limited evidence assessing the effects of these barriers on adolescents' ability to sustain ART adherence over time and achieve good HIV treatment outcomes [87]. Therefore, one of the main objectives

of this thesis is to investigate barriers to longitudinal ART adherence, and further examine their interrelationships at multiple levels of the socio-ecological model among ALHIV contribute to distinct ART adherence trajectories among ALHIV. This sub-section provides an overview of the complex barriers to ART adherence among adolescents.

Figure 2.1: Nested relationships of the hypothesized factors –from individual to healthcare level— that impact ART adherence among adolescents (adapted from Kaufman et al. 2014)



2.4.1.1. Individual-level factors

Individual-level barriers to sustained ART adherence identify intrapersonal factors that directly influence ART adherence behaviour, these include mental health challenges (experiences of depression, anxiety, and suicidality). Adolescents and young people living with HIV face an increased burden of mental health challenges resulting from HIV disease, and adverse influences from their social environment among other recurrent and cumulative stressors [29]. Mental health challenges impact adolescents' ability to adhere to ART [30]. For example, good mental health may be associated with autonomy and better control over one's health, hence improved adherence and overall health. Several studies report a high

prevalence of mental health challenges among ALHIV. For example, a large cross-sectional study in Uganda reported a prevalence of 17% of any mental health disorder, and this was more common in ALHIV than in other age groups [88]. Similar findings were reported in a study in South Africa, with ALHIV reporting higher levels of depression, disruptive behaviour and clinically significant anger compared to their HIV-negative peers [89], which is associated with lower adherence to ART [90]. However, these findings vary widely by context and longitudinal evidence is limited. Moreover, most literature addressing the impact of mental health on ART adherence among adolescents does not explore the underlying mechanisms leading to this relationship.

Another key barrier: substance abuse has been reported to play a unique role in adolescents' ART adherence and is associated with poor adherence [30]. Patients may forget to take treatment when they have taken alcohol or drugs [91]. The drivers and effects of intoxication have been reported to involve psychosocial deficiency and psychiatric dysfunction hence this negative effect on adherence [91]. However, more evidence on the impact of substance abuse on long-term adherence to ART among adolescents is needed.

Qualitative and quantitative evidence has also demonstrated that experiences of trauma such as sexual abuse, bullying and victimization are associated with poor adherence to ART and an increased risk of poor health outcomes and mortality [92, 93]. Quantitative research in SSA shows that adolescents are exposed to some of the world's highest rates of violence which include physical, emotional, or sexual abuse [94], with sharp rises in sexual abuse recorded due to the COVID-19 pandemic [95]. Research estimates rates of sexual abuse to be as high as 17.4% (11.4%-23.3%) in SSA [96]. A recent review showed that over 50% of school-going youth in Eastern and Southern Africa experience some form of bullying and victimization [97, 98] which is associated with adverse health outcomes among adolescents [99]. These different trauma stressors have been shown to elevate mental distress which may impact adherence to ART [26, 52, 96]. Research has also elucidated the causal effects of bullying on mental health challenges [100]. However, the link between bullying (emotional or physical), mental health and ART adherence among adolescents living with HIV requires further investigation to understand the adverse effects of bullying and ways to mitigate these. There is also a need for longitudinal evidence on the impacts of trauma stressors, as well as pathways to poor long-term ART adherence among adolescents.

Medication-related barriers (i.e., medication side effects and pill burden) also present a key challenge for ALHIV in low-resource settings. The most commonly reported ART side effects are nausea, dizziness, headache, anaemia and gastrointestinal tolerance [30]. While some of these decline over time, some severe cases may lead to a change in regimens or combinations of medications taken [101]. ART side effects could also be visible, for example, body changes including hair loss and skin rashes, which could lead to low self-esteem and stigmatisation [102]. Several systematic reviews have shown that ART-related side effects are a barrier to adherence among adolescents [103-105], however, most of the available evidence comes from qualitative work. Survey data on ALHIV have found pill burden to be a barrier to adherence [106, 107]. Multiple studies have found that single-tablet regimens and their related lower pill burdens are associated with higher adherence rates compared with multiple-tablet regimens [108]. While these findings show that single-dose regimens facilitate improvement in adherence to ART, there is limited data assessing the long-term effects of pill burden and side effects on ART adherence or how they shape adolescents' adherence trajectories.

Furthermore, several studies have investigated the relationship between knowledge of HIV status and adherence [103, 109]. Recent research in South Africa [109] assessed the associations between HIV-disclosure and adherence, and found that knowledge of HIV-positive status was positively associated with adherence. Similarly, a narrative review [103] showed that disclosure rates were low in LMICs and adherence was poor among adolescents who did not know their status. A recent study in Zambia found that only 38% of adolescents knew their HIV-positive status and adherence was better among those who knew their status [110]. In general, adolescents unaware of their status and taking their ART medication for no reason have been reported to show consistently poor adherence [30]. In contrast, a systematic review of LMICs showed that some studies found no relation between knowledge of HIV status and adherence among adolescents [23]. These varied findings show the necessity for an assessment of the long-term relationship between knowledge of HIV status and adherence using longitudinal designs.

Socio-demographic factors such as age, biological sex, and place of residence are the most cited socio-demographic characteristics associated with ART adherence among adolescents. The relationship between age and adherence is complex and varies by study. A recent systematic review [23] revealed that older age was associated with poor adherence. While

mixed methods findings from Uganda showed no association between age and adherence (aOR= 0.82, 95%CI 0.60-1.13) [49] study in Malawi found otherwise [26]. Other studies have also shown varied findings, but most find that older age is associated with increasing responsibility for self-health care [103, 111]. Given the complexity of the relationship between age and ART adherence, the present study will assess the nature of the relationship between age and longitudinal adherence. It will also help to ascertain the effect of transition into older adolescent age on adherence.

The association between biological sex assigned at birth and ART adherence for ALHIV has been similarly varied. A recent systematic review [30] showed no conclusive relationship between sex and adherence. A study in Uganda [49] found no relationship between sex and adherence (aOR=1.33, 95%CI 0.84-2.13), similarly, another study in Malawi [26] also found no association with adolescents' adherence (aOR=1.06, 95%CI 0.71-1.58). Other studies have found contrasting results, for example, a study in Botswana [112] found that males (aOR=3.29, 95%CI 1.13-9.54) were more likely to adhere poorly to ART compared to females. However, a Ugandan study [113] found that males reported higher adherence than females. Given these inconsistent findings, investigating the relationship between sex and adherence over multiple waves of data collection is needed.

Several studies have also shown that place of residence, rural or urban is significantly associated with adolescent ART adherence [114, 115]. A recent systematic review [30], reported poor adherence levels among adolescents residing in rural areas compared to those in urban. This is similar to findings from an earlier study in the US [116]. Another study in Uganda [49] reported better urban adherence levels among ALHIV compared to rural (aOR=2.64, 95%CI 1.28-5.43). This evidence points to the impact of rural residence on adherence hence more evidence is needed on how the place of residence shapes longitudinal adherence.

Another major determinant that shapes adherence behaviour is the mode of HIV acquisition: perinatal or sexual transmission [117]. Adolescents with perinatally acquired HIV present with physical and cognitive development challenges, including stunting and neurocognitive defects, which may have implications for this young population, particularly for adherence to ART [118, 119]. Although, much work has been done on those ALHIV with perinatally acquired HIV, leading to improved treatment adherence and survival into adolescence [103], more evidence is needed for adolescents with sexually acquired HIV. Studies including both

ALHIV with perinatally and sexually acquired HIV find that the former are younger, have greater HIV disease severity, and have more structural support [120]. A study in the US found that both groups of adolescents had sub-optimal adherence [121]. This study also found that each group experiences unique barriers to adherence due to differences in lived and treatment experiences, duration, and contexts. A similar study in three US cities [120] found that acquiring HIV sexually (aOR=4.38, 95%CI 1.06-18.2) was associated with higher odds of non-adherence relative to acquiring HIV perinatally. These findings show the need to further explore differences between the two ALHIV groups. However, there is limited research combining these two groups, and assessing the differences in ART adherence over time to identify potential phases of support needs.

2.4.1.2. Household-level factors

Household and family-level barriers to sustained ART adherence largely involve the adolescent's close relationships, which may contribute to their perception regarding ART [122]. Several studies have investigated the relationship between double-orphanhood and ART adherence as ALHIV are likely to be orphaned and change caregivers [23]. Orphans face numerous financial, psychosocial, and caregiving stressors that present significant barriers to maintaining adherence to ART [123]. In the context of perinatally acquired HIV, for adolescents who lost both parents earlier in the HIV epidemic, having non-parental caregivers could have potentially lessened the burden of social isolation and parent-child reversed roles due to parental illness [124]. However, the changing of caregivers (i.e., living with non-parental caregivers) came with its complications (e.g., lack of adequate knowledge about HIV among non-parental caregivers), and did not reduce the psychosocial trauma caused by the loss of parents [124, 125]. Although HIV care has evolved, with ART scale-up in resource-limited settings, research shows that the role of caregivers (both parental and non-parental) in providing adherence support differs by orphanhood status, with double orphans receiving relatively less support [126]. This may be partly explained by low caregiver involvement, possibly due to a lack of understanding about the importance of adherence among non-parental caregivers [127]. More recent evidence also shows that double orphanhood is associated with the highest risk of non-adherence among adolescents in countries such as Rwanda [127] and Kenya [128]. Therefore, more evidence is needed to understand the family context of orphans living with HIV in South Africa, to support them improve their long-term ART adherence.

An increasingly recognised barrier to ART adherence is the availability of caregiver support through monitoring and supervision [127, 129]. However, the type of caregiver (parental versus non-parental) may have implications for the adolescent's ART adherence. Caregivers are important in ALHIV adherence because they may remind them to take their medications and attend their clinic appointments and support them in dealing with stigma [130]. Paternal and maternal orphans may receive better adherence support from biological mothers and grandmothers compared to double orphans who live with non-parental caregivers (mostly relatives) [126]. Non-parental caregivers have reported stress and inadequacy in providing care for the orphaned adolescent. A review of orphans living with non-parental caregivers in SSA found that they have unique lived experiences (e.g., suffer maltreatment and neglect) which impact their ART adherence [126]. A strong association between caregiver supervision and ART adherence among adolescents was found in the Democratic Republic of Congo [129]. However, this study highlighted that the impact depends on the state of the child-caregiver relationship, which is likely to be more strained for orphaned children living with non-parental caregivers. Another study in Kigali showed that parental caregiver involvement was associated with lower odds of suboptimal adherence [127]. This study found that maternal orphans (aOR=0.31, 95%CI 0.12–0.80), paternal orphans (aOR=0.35, 95%CI 0.14–0.89), and non-orphans (aOR=0.45, 95%CI 0.21–0.99) were less likely to be non-adherent to ART compared to double orphans. Adolescence, particularly in SSA, is marked by a lack of caregiver support, especially if the caregiver is HIV affected or deceased [29]. Without caregiver support, adolescents must assume responsibility for treatment, while ongoing developmental, psychological, economic, and social challenges—including the desire for peer approval—threaten the consistency of care-seeking behaviours [29, 129].

Experiencing or witnessing domestic conflict or violence, often something experienced within the household leads to psychological distress which has been shown to increase the risk of non-adherence among adolescents [131]. However, longitudinal evidence on the pathways linking witnessing domestic violence to ART adherence among adolescents is limited. Globally, adolescents are directly or indirectly (e.g., through witnessing) exposed to multiple forms of violence which include witnessing domestic violence between adults or caregivers in their homes. Both direct and indirect exposure have adverse effects on the adolescents' physical and mental well-being which may negatively impact their ability to adhere to treatment [132]. Therefore, there is a need to examine the impacts, as well as

cumulative effects of multiple forms of violence exposure on longitudinal adherence trajectories among ALHIV. Qualitative studies have underscored the lack of food at home as a reason adolescents fail to adhere to ART [133]. Food insufficiency in the household makes it difficult for adolescents to prioritize treatment adherence, particularly those experiencing adverse hunger-related medication side effects. A qualitative study in the Democratic Republic of Congo (DRC) [129], found that adolescents who lacked food in the morning or at scheduled dose time reported a burning sensation or feeling dizzy after taking ART on an empty stomach leading to missed doses. Similarly, a qualitative study in South Africa also reported a lack of food as a key barrier to adolescent adherence [30]. A quasi-experimental study in Zambia [134] and a retrospective cohort study in Niger [135] found that access to monthly food ration was positively associated with adherence.

2.4.1.3. Community-level factors

The factors at the community level that may influence ALHIV adherence to ART, include HIV-related stigma, social norms towards ART access, exposure to community violence and school attendance [136]. HIV-related stigma presents a key challenge for ALHIV in SSA, and several studies have noted that patients reporting stigma have a lower chance of adherence with adolescents often skipping doses to hide their status from friends and family [29, 30, 137]. For example, a qualitative study in Uganda also found that experiencing stigma and discrimination for ALHIV was associated with suboptimal adherence [49]. Another quantitative study conducted in Northern Tanzania revealed that patients experiencing stigma had over two times higher odds (aOR=2.16, 95% CI 1.17-4.01) of non-adherence [138]. However, other studies have reported otherwise, showing no statistically significant relationship between HIV-related stigma and adherence to ART [23].

Closely tied to HIV-related stigma is the effect of individual school attendance on adherence among adolescents. A systematic review of LMICs found that schooling was associated with poor adherence due to stigma at school and lack of support from school staff [115]. These findings are supported by recent qualitative work in Uganda [130] which found that schooling can pose specific challenges to adherence. These include the lack of privacy in boarding school spaces or schedules which complicates ART adherence. In contrast, a review in the US found that being in school was associated with better adherence [104]. These contrasting findings show the need for further evaluation of the relationship between schooling and adherence.

Peer norms have also been shown to significantly influence individuals' behaviour and attitudes [139]. In terms of adherence to ART, findings suggest that ALHIV are likely to conform to the ART adherence behaviours of their peer group. In particular, norms, or individuals' beliefs about the behaviours that their peers engage in, can alter individual behaviours [140]. Negative peer norms, particularly those related to condom use, can influence HIV-related risk behaviours, suggesting that interventions targeting peer norms may be effective in promoting adherence to ART [141]. This underscores the importance of considering peer norms in interventions aimed at improving ART adherence. However, the impact of peer norms on ART adherence among peers living with HIV is seldom assessed in studies of health and support. Furthermore, the extent to which the association between HIV stigma and ART adherence is modified by peer norms is unknown.

Furthermore, adolescents in SSA are exposed to some of the world's highest rates of violence [94, 131]. Violence against adolescents takes several forms, which frequently occur together in all settings adolescents find themselves—at home, in school, in the community or among peers [131]. About two-thirds of children were reported to have been exposed to community violence, such as seeing someone being attacked or hearing gunshots, with the figure rising in adolescence in a South African cohort study [142]. In most qualitative studies, ALHIV have cited addressing violence (including HIV-associated violence) as the most challenging unmet need [143]. However, to date, few studies have assessed the impact of exposure to community violence on ART adherence among adolescents.

2.4.1.4. Institutional or health care level factors

Institutional influences on ART adherence include the characteristics of the healthcare services available to ALHIV [144]. Healthcare-level factors include clinic proximity, clinic service waiting time, peer support groups, patient-provider relationships, lack of privacy and confidentiality, and timely medication availability are all relevant here. Clinic proximity refers to how close the clinic or treatment centre is to the adolescent which has a direct impact on the time travelled and cost incurred by the patient for clinic appointments [103]. Several studies have investigated the impact of clinic proximity on adherence with varied findings [26, 109, 145]. For example, a study in Ethiopia among adolescents receiving ART found that living close to the clinic or treatment centre (aOR=2.31, 95%CI 1.94-4.63) was associated with better ART adherence [145]. Another study in South Africa had similar findings that travel time to the clinic had an impact on adolescents' ART adherence [109].

Similarly, a study in Zimbabwe [146] found that living far from the clinic was associated with 2.5 times the risk of non-adherence. However, some studies have found no significant impact of clinic proximity on adherence. For example, a study on adherence barriers and associated factors among adolescents in Malawi did not find a significant association between adherence and clinic travel time (aOR=0.96, 95%CI 0.53-1.75) [26]. Similarly, another study in Zimbabwe [147] did not find evidence of the impact of clinic travel time on adherence.

Another clinic-level factor affecting ART adherence is the waiting time at the health facility. A systematic review for SSA reported that long waiting times at the treatment centre or clinic act as a barrier to adherence among ALHIV [30]. Recent research in Cape Town found that long waiting times were one of the major barriers to adolescent adherence [148]. This is supported by earlier findings among a cohort of adolescents in Johannesburg, who found that in addition to the cost and time associated with travelling to the clinic, the duration of time spent waiting in queues was one of the major factors impacting patient adherence [12]. However, another study in Zimbabwe [146] found no significant association between long waiting times and adherence.

The lack of privacy and confidentiality at the healthcare facility has been reported as a major barrier to adherence by adolescents [12]. Qualitative studies have reported that patients complain that healthcare workers may lack confidentiality and be perceived to sometimes gossip or discuss patients' HIV status with others [133]. In some instances, ALHIV feel uncomfortable being seen while picking up easily identified ART pill bottles from the pharmacy window or holding distinctly coloured HIV care files in the queues for appointments, compounding concerns about being identified by others. Notably, some ALHIV stop going to the clinic altogether because they do not want to be seen [30]. Therefore, insensitivity towards patients' needs and a lack of confidentiality of patient's medical records could impact ART adherence in this group.

Furthermore, enrolment into formal peer support groups linked to the health system or institutions that involve activities ranging from support groups to peer-to-peer counselling and treatment buddy programs may impact ART adherence among ALHIV [149]. A study in Uganda found that HIV peer support groups were beneficial in improving adherence [49]. Similarly, Ugandan qualitative evidence found that peer-support groups created an important network to support adherence [130]. A study in South Africa reported a lack of peer support groups negatively impacted ALHIV adherence, especially in younger adolescents [12]. A

recent exploration of interventions to promote adherence to ART in Africa found that peer support for adolescents significantly improved adherence [137]. This is further supported by a recent systematic review which reported that several studies found that HIV peer support groups facilitate adherence among adolescents [30].

2.4.2. Potential strategies to improve adherence among ALHIV

Adherence to ART among adolescents remains sub-optimal, largely due to numerous barriers, as underscored in several reviews [23]. There is, therefore, a need to improve adherence by identifying and mitigating these barriers. Improving adherence to ART among ALHIV requires a multifaceted approach addressing individual, family, community, healthcare, and structural barriers. Several support strategies and interventions have shown promise in resource-limited settings. These include individual/group counselling, mHealth interventions, community-based interventions (e.g., home visits from community health workers and community-based social network support), facility-based interventions and task shifting, e.g., from hospitals to clinics, peer-led adherence clubs or mentoring programs, social protection (e.g., conditional cash grants) and psychosocial support [31, 137, 150-153]. Individual and group counselling have emerged as evidence-based interventions to support ART adherence, addressing both psychosocial and structural barriers [154, 155]. Research highlights that individualised counselling support, such as motivational interviewing and cognitive-behavioural strategies, can significantly enhance adherence by tailoring support to the unique circumstances and challenges of individuals [154]. On the other hand, group counselling leverages the power of peer support (e.g., through adherence clubs), offering a communal platform to share experiences and receive counselling, leading to improved ART adherence [155].

mHealth interventions—the use of mobile wireless technologies for health—such as mobile phone-based reminders delivered using SMS/texting, social media, and smartphone applications [156], have shown significant promise in enhancing engagement in HIV care and adherence to ART [31]. A pilot study using clinic-based bi-directional texting in the US demonstrated the potential for enhancing engagement in HIV care [157]. Evidence from a recent meta-analysis also revealed that interactive or bidirectional SMS significantly increased antiretroviral therapy adherence [158]. A 12-week feasibility study of a mobile app providing self-care strategies to people living with HIV found significant improvements in ART adherence [159]. The interactive capabilities of these mHealth applications strengthen

adherence by addressing individual concerns in real-time and fostering a sense of connectedness [160]. A meta-analysis assessing interventions to promote adherence to ART in Africa also showed overall improved adherence and viral suppression among patients using mHealth technology [161]. A recent systematic review of mHealth interventions targeting adolescents and young adults in low- and middle-income countries found that these interventions have the potential to remedy disparities for this group [162]. Overall, mHealth offers a scalable, cost-effective solution to strengthen ART programs, and has the potential to engage adolescents in resource-limited settings but more evidence—from larger and powered studies—is needed [163].

Facility-based interventions and task shifting have also shown promise in improving ART adherence in resource-limited settings. In Uganda, facility-based interventions, including appointment systems, fast-tracking, and longer prescriptions for stable patients, significantly reduced missed appointments and medication gaps [164]. Task-shifting programs include feasibly shifting key ART tasks to lower-level facilities and identifying training gaps [165]. In Zambia, a comprehensive task-shifting program involving existing health providers and community-based workers successfully expanded ART services while maintaining the quality of care [166].

Community-based interventions such as peer support programs which involve activities ranging from widely implemented support groups to peer-to-peer counselling and treatment buddy programs, have also shown promising results in improving adherence [149]. A study in Uganda [49] found that HIV peer support groups were beneficial in improving adherence. Similarly, qualitative evidence from the same country also found that peer-support groups created an important network to support adherence hence it is a crucial facilitator [130]. Another study in South Africa reported a lack of peer support groups had an impact on adolescents' adherence and the impact was mostly seen in younger adolescents [12]. A more recent exploration of interventions to promote adherence to ART in African countries found that peer support for adolescents significantly improved adherence [137].

Research also demonstrates that a combination of strategies, including individual/group counselling, education, late clinic attendee tracing, and adherence diaries, significantly improves ART adherence [167]. However, more research is needed to address barriers and improve adherence among ALHIV. A few emerging studies—mostly randomised control trials (RCTs)—have demonstrated the effectiveness of two support mechanisms namely:

social protection [168, 169] and psychosocial support [170, 171]. Social protection which includes social grants "cash" (with high coverage in South Africa) mitigates structural deprivations by providing financial support [168, 169, 172], which may influence adolescents' HIV treatment outcomes [173]. A recent longitudinal cluster randomised trial in southern Uganda (2012-2017) [174, 175], found that family-based economic empowerment or interventions addressing economic insecurity improved ART adherence among vulnerable ALHIV in low-resource settings. Social grants, a form of social protection, are a popular social assistance program in South Africa (the largest in Africa) and are a component of structural interventions. However, there is no evidence of the effectiveness of economic empowerment (social protection) among ALHIV, when implemented within national government health, economic and social services.

Psychosocial support is defined as interpersonal activities and strategies aimed at improving an individual's mental health and wellbeing [170, 176]. Recently, NGO-led peer psychosocial support models have been shown to improve ART adherence and viral load suppression among adolescents [177]. Several reviews also underscore the potential of psychosocial interventions to support ALHIV to achieve better HIV treatment outcomes [170, 178]. For example, a recent systematic review and meta-analysis of RCTs assessing psychosocial interventions for adolescents in the US, SSA and Southeast Asia found that, overall, these interventions are effective in improving ART adherence and reducing viral load [170]. However, there is no evidence of the effectiveness of family-based psychosocial interventions, nor does any research examine whether combinations of government-provided social protection and family-based psychosocial support may be more effective than individual provisions. Overall, there is a need for multi-level interventions that combine multiple approaches to improve the health and well-being of adolescents, including research on how best we can support them [179].

2.5. ART Adherence Measurement

According to the World Health Organisation (WHO), optimal ART adherence is defined as the intake of 95% or more of the correct number of doses at the required times [26, 180, 181]. It has been shown that poor adherence leads to undesirable treatment outcomes even among adolescents [74, 182]. Therefore, accurate measurement of adherence is critical for effective monitoring as well as targeting interventions to increase adherence. However, a gold standard measure of ART adherence remains elusive [29]. There are various methods of measuring

adherence that have been reported in the literature, ranging from directly observed therapy (DOTS) to indirect methods which have their advantages and disadvantages depending on context and time [183, 184]. In SSA, especially in resource-limited settings, adherence studies among ALHIV have mostly used indirect measures [184].

Indirect measures of adherence include patient self-reporting, pill count, pharmacy pill refill, electronic monitoring devices, clinic attendance as well as caregiver and provider reporting [29, 185]. Self-reported adherence measures are the most widely employed in SSA [27], including the number of prescribed doses a patient missed in a specified period. Self-reported measures are easy to obtain during routine clinic visits and are relatively inexpensive. Several studies using these measures have demonstrated correlations with virologic outcomes [14, 186]. However, these may be prone to social desirability and recall bias, resulting in overestimation [187]. Another widely employed indirect measure, pill count is usually done during clinical appointments, and the calculation of adherence is done based on the last refill date [185]. It has also been demonstrated to be a valid measure of adherence among adolescents [188]. Unannounced home visit-based counts may improve the reliability of the measure. However, this can be easily manipulated and depends on the patient's cooperation [185]. This may also be time-consuming and inconvenient in a busy clinic. Medication event monitoring systems (MEMS) are relatively new and record the date and time the drug container is opened—providing detailed information on patterns of medication-taking [189]. It is not commonly used in routine care in resource-constrained due to cost despite clear correlations with virologic suppression [185]. Pharmacy pill refills use a similar logic as MEMS, medication is dispensed for the exact period between visit and return, and delayed returns are then taken to be indicative of missed doses [190]. This is useful in resource-limited settings as it is easy to obtain and inexpensive. However, evidence suggests this measure may not reflect ART use and the use of multiple pharmacy sources makes it unreliable [29]. Finally, patient clinic attendance monitors the timing and frequency of clinic visits and is the most common measurement method to assess retention in care but may also be unreliable [191].

In general, although there are many methods of measuring ART adherence, none of the methods are completely reliable, particularly in resource-constrained settings [24, 189]. Studies demonstrated that ART adherence varies significantly by measure [192]. Other studies have also demonstrated that self-reported measures of adherence are prone to bias and

may overestimate adherence. Therefore, there is a need for a multi-method or multi-measure approach that combines feasible self-report measures and any other objective measures to estimate adherence.

2.6. Theoretical framework

The conceptual model which guides the hypothesized pathways linking multiple factors at different levels of the adolescent's environment to longitudinal adherence is the socio-ecological model, first proposed by Bronfenbrenner in 1977 [193]. This model allows a better understanding of the dynamic relationships predicting longitudinal adherence among ALHIV. The socio-ecological model has been widely applied to understand several health issues including ART adherence. However, a limited number of studies, largely in developed nations have assessed how adolescent adherence trajectories are shaped by numerous factors across the different levels of this socio-ecological model using longitudinal data [194, 195]. A recent application of the socio-ecological model to identify groups of factors associated with distinct adherence trajectories was a study among black Americans in the US, the authors proposed factors at the structural, institutional/health system, community, interpersonal/network, and individual levels [196, 197]. The individual level includes factors comprising the micro-level such as adolescents' perceptions; the interpersonal/network level- which includes family influences such as family social support; the community level-which includes group-level influences such as social capital; the institutional level-which includes factors within the entire healthcare system, such as quality of service and confidentiality; and finally structural level- which includes the most macro-level factors affecting behaviour. Another US study applied the socio-ecological model to explore the factors associated with longitudinal adherence in youth [198]. The authors hypothesised that three levels of baseline factors: individual, family, and extra-familial systems which combined the micro and macro level factors (e.g., low social support, and less engagement with the medical team) were associated with longitudinal adherence.

There is no quantitative evidence of the socio-ecological model application in adolescents' long-term ART adherence in South Africa. Studies vary in their application of the components of the model, most studies adapt the original model to suit their specific context and choose a different set of factors based on their line of inquiry and available data. The socio-ecological model is relevant here because elsewhere, it facilitates an exploration of the factors that affect adolescents' adherence behaviour and how these are interrelated, which is

critical to their well-being. The model has the flexibility to allow us to look at the factors over time. Our conceptual framework (Figure 1) is adapted from the original and differentiates the microsystem factors into individual and household level factors and the meso- or macrosystem levels into the community and institutional factors as shown in a number of studies, structural level factors are not adequately measured in our data but are likely similar for all the ALHIV included in the data. This framework will inform the selection of variables for the analysis as well as the statistical methodology for assessing the interrelatedness of individual, household, community, and institutional factors affecting longitudinal adherence.

2.7. Summary

2.7.1. Gaps in Literature

Poor adherence to ART remains a major concern in adolescents, and research shows that adherence is generally lower among ALHIV compared to other age groups [14, 199], which leads to poor HIV treatment outcomes [28, 35, 44]. While considerable methodological challenges exist in the measurement of ART adherence, numerous gaps exist in our understanding of longitudinal ART adherence and how it influences long-term HIV treatment outcomes among ALHIV. No research has used longitudinal adherence trajectories to describe the dynamic nature of adolescents' ART adherence among this vulnerable group. Our understanding of predictors of longitudinal ART adherence among adolescents, in particular, on how they influence the dynamic changes over time is limited. This is essential to inform the designing of multi-level targeted adherence interventions and allows health providers to anticipate the future health needs of ALHIV in these settings. This thesis will address five specific gaps:

What is the potential of longitudinal self-reported adherence measures to detect the risk of elevated viral load among adolescents living with HIV?

Self-reported ART adherence measures are often the only practical and readily available method in these resource-constrained settings due to their low cost, minimal patient burden, and ease of administration but are known to be subject to bias. Assessing these self-reported adherence measures using longitudinal data and longitudinal methods has the potential to reduce this bias, contribute to the assessment of long-term adherence, and facilitate the development of adolescents' specific routine adherence measurement tools.

What are the longitudinal trajectories of ART adherence, and their impact on viral suppression among among adolescents living with HIV?

There is limited evidence examining the dynamics of ART adherence over time using longitudinal data among adolescents. No prior research has categorised longitudinal ART adherence behaviour among ALHIV as distinct ART adherence trajectories which may inform current strategies targeting high-risk adolescents and comprehensive support interventions which are critical to improving adolescents' treatment outcomes.

What are the rates of all-cause mortality among ALHIV, and do these rates differ by ART adherence over time?

We lack data disaggregated data on mortality among adolescents in resource-limited settings, which may inform the estimation of the most widely used global estimates of HIV indicators such as UNAIDS estimates. Evidence on how changes in ART adherence influence mortality among ALHIV is scarce. These data guide the adolescent-centred interventions needed to improve their health and well-being.

What are the socio-ecological factors contributing to distinct longitudinal ART adherence trajectories among adolescents?

ART adherence is a complex and dynamic process which involves a complex interplay among numerous factors, but no quantitative studies –using longitudinal data— have assessed how these different factors influence adherence over time. Moreover, there is no evidence on how these factors interact to influence distinct longitudinal ART adherence trajectories among ALHIV which may inform policy and practice by clarifying when and what to target in multilevel adherence support strategies and interventions for adolescents living with HIV.

What is the impact of psychosocial and economic support on longitudinal ART adherence and viral suppression among adolescents living with HIV?

The effectiveness of the current essential biomedical ART interventions is compromised by gaps in the HIV care continuum (i.e., high rates of disengagement from care, sub-optimal ART adherence, and linked increases in episodes of elevated viral load (VL) among ALHIV. There is an urgent need for scalable add-on support provisions that can reduce poor HIV treatment outcomes among adolescents living with HIV. Social protection and psychosocial support may be valuable provisions to reduce gaps in HIV care, but we lack longitudinal evidence.

2.7.1.1. Overview

ALHIV continue to have sub-optimal ART adherence which is influenced by many factors that fall within the multiple levels of the socio-ecological systems framework, leading to poor HIV treatment outcomes. The strengths of the existing knowledge base include a well-defined spectrum of health challenges faced by adolescents and youth in high-income settings, yet this evidence is largely weak for resource-constrained settings. Limitations include lack of longitudinal data, small sample sizes, the absence of HIV-negative peers for comparison, and mostly among adults [67]. Evidence on the collective effect, capturing the relationships between socio-ecological factors affecting long-term adherence to ART among adolescents remains unknown. Many ALHIV studies are from high-income settings where the burden of HIV is much less than in resource-constrained settings. There is no known study on longitudinal adherence trajectories among adolescents in resource-constrained settings and no evidence of how changes in adolescents' ART adherence influence subsequent HIV treatment outcomes over time [16, 35, 200]. By addressing these gaps, this thesis will improve our understanding of long-term ART uptake among adolescents, factors influencing long-term ART adherence and its impact on subsequent HIV treatment outcomes during adolescence. This work will also inform the robust measurement of ART adherence in this vulnerable group. The ultimate goal of this work is to inform the development of multiple-level tailored adolescent-centred interventions and support strategies to improve long-term ART uptake, health and well-being among adolescents and youth living with HIV.

The next chapter will present how this thesis seeks to answer the research questions above using quantitative data collected from adolescents living with HIV in the Eastern Cape Province in South Africa.

CHAPTER 3. METHODOLOGY

This chapter provides an overview of the study methodology including sample and data sources, and specific statistical and analysis methods for the respective Chapters 4-8 (PhD papers 1-5). Finally, ethical considerations, statistical methods, and analysis steps for the respective results chapters are also presented.

3.1. Data sources

Data for this thesis were drawn from two primary sources: (1) a retrospective cohort study (the Mzantsi Wakho 'Your South Africa' study), a large longitudinal, mixed-methods study of adolescents (10-19 years) living with HIV (led by Associate Professor Elona Toska at the University of Cape Town, and Professor Lucie Cluver from the University of Oxford and the University of Cape Town), and (2) the Understanding Predictors of Lifelong Initiation and Follow-up Treatment for adolescents living with HIV (UPLIFT) linkage study, consisting of laboratory data for all participants enrolled in the Mzantsi Wakho study obtained through a formal collaboration between the research team (led by Associate Professor Elona Toska) and the National Institute for Communicable Diseases (NICD) of South Africa. The laboratory test data was obtained by linking adolescents' socio-demographic characteristics to their clinical records in national data warehouse at the National Health Laboratory Services (NHLS) within NICD. As the two studies are linked, first, the Mzantsi Wakho study details are shared followed by any additional details from UPLIFT.

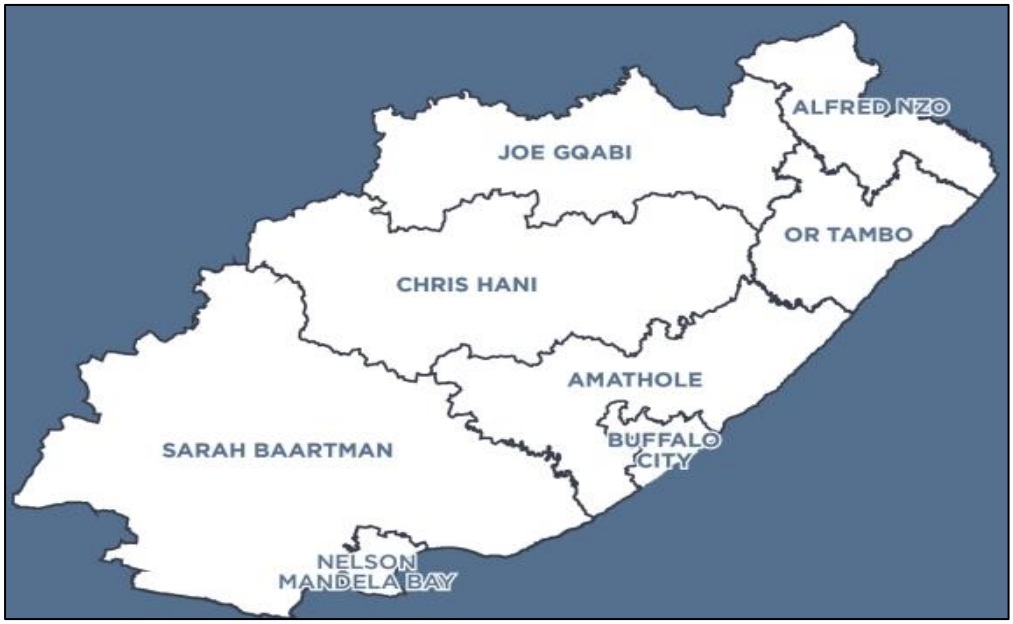
3.1.1. Mzantsi Wakho study aims and design

The Mzantsi Wakho (MW) study was designed to understand adolescents' health needs, particularly those living with HIV and growing up in resource-limited settings. The study sought to investigate how individual, household, and structural factors impact adolescent ART adherence, HIV treatment outcomes, and uptake of health services. Informed by ongoing qualitative research [109], the MW consisted of three waves of surveys conducted among 1046 ART-initiated adolescents aged 10-19 years at baseline in 2013-2014, in the Eastern Cape Province of South Africa, between 2014-2018 [109, 201, 202]. Additional follow-up was conducted between 2021 and 2023, as part of long-term cohort maintenance, including participant mortality (see Chapter 6). This thesis uses longitudinal study data consisting of both self-reported questionnaire data and clinical biomarkers from routinely collected data.

3.1.2. Mzantsi Wakho Study Setting

The study included participants from two districts in the Eastern Cape Province of South Africa: Buffalo City Municipality and Amathole Health District (Figure 3.1). The Eastern Cape Province is the second largest province in size home to 11.4% of South Africa's total population, and of these approximately 1.3 million (20%) are adolescents aged 10-19 years of age [203]. This is also the country's poorest province, with over 67% of adults living in poverty [204]. The province is severely affected by HIV, with a reported antenatal HIV prevalence of 32.9% (95% CI: 31.5 – 34.2) in 2022 [205]. The overall HIV prevalence rate was estimated at 18.8%, the third highest in South Africa in 2022 [6, 206]. HIV care delivery in this province is constrained by a lack of resources including human resources, lack of standardised staff training, lack of functional computerised clinic registers, and other competing healthcare priorities [207, 208]. In recent years, there has been an improvement in access to ART, with significant gains made in the number of people accessing treatment. However, the province must continue to make progress to reach the HIV targets for 2030, as the Eastern Cape recorded only 58% of all people living with HIV to have achieved viral suppression by 2020 [209].

Figure 3.1: Geographical map of the districts in the Eastern Cape Province, South Africa



Source: www.municicpalitites.co.za

3.1.3. Mzantsi Wakho sampling strategy and recruitment

Due to a lack of age-specific disaggregated adolescent data (10-19 years) –the national-level data presented by Statistics South Africa usually presents its population-level estimates grouped as 0-14 years and 15-49 years [203]. This made it difficult to identify national-level estimates for ALHIV or determine a representative sample in 2012-2013. Thus, the MW sampling strategy followed four critical stages. The first of these was the mapping of all ART-providing health facilities (n=81) in the study area using the Department of Health Register and annual reports. Information on facility type, the total number of adolescents enrolled in HIV care and data availability were used to select facilities for inclusion in the study. In the second stage, health facility sampling was done using information from the initial mapping above. If a facility provided care to at least five ALHIV, was a government facility and had a register with records of patients including those lost to follow-up, then it was selected. A total of 32 facilities were selected based on these criteria. At these 32 facilities, the research team found that most of the adolescents had been down-referred to other clinics in 2012-2013 as part of South Africa's national primary healthcare re-engineering [210]. Further tracing was done and an additional 20 clinics which met the criteria above were included leading to a total of 52 facilities in the Mzantsi Wakho study. These include nine hospitals, five community health centres, and 38 primary care clinics.

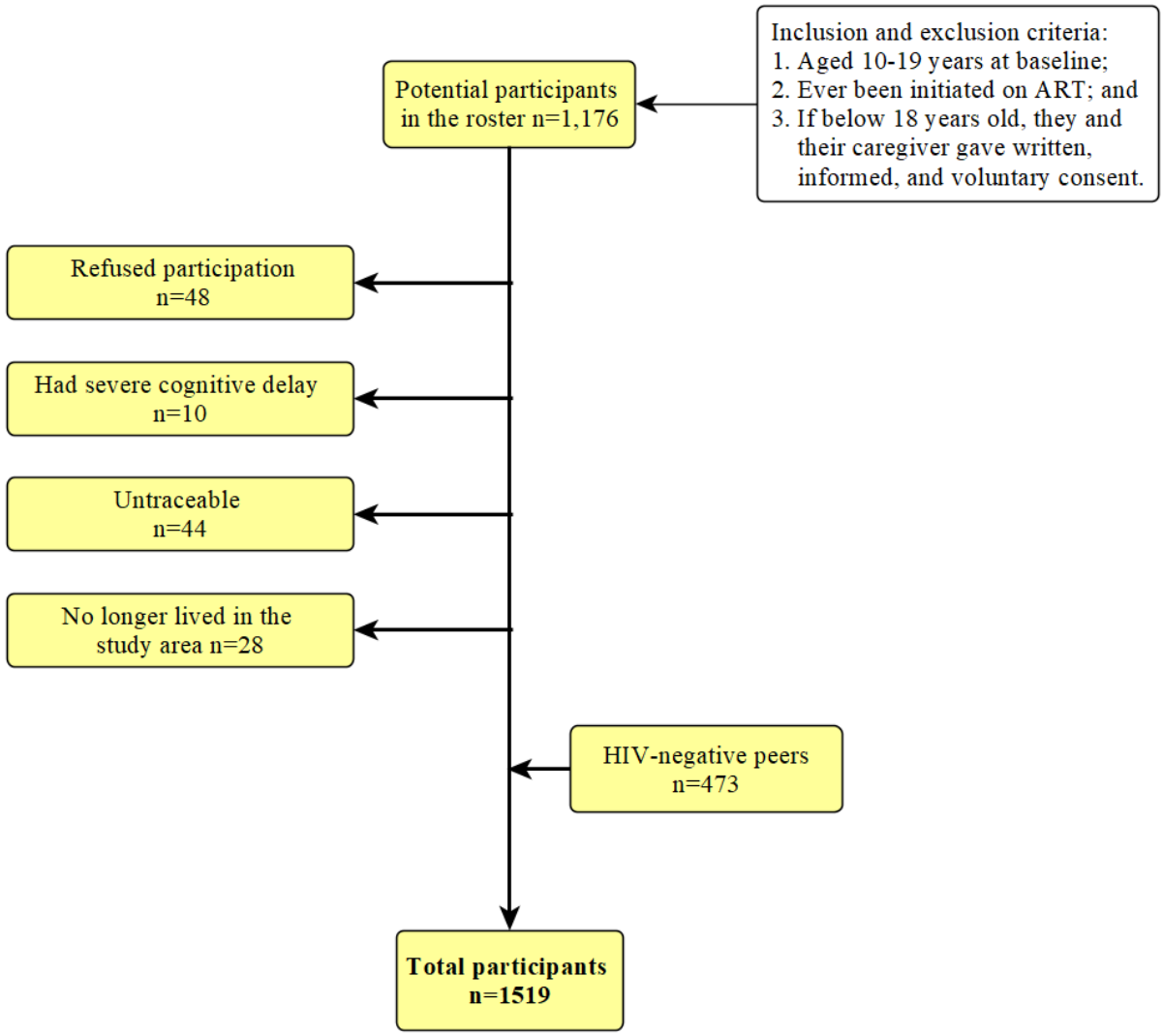
In the third stage, a roster of eligible adolescent participants from the 52 facilities was prepared. Based on clinic records not older than three years, all adolescents (10-19 years) who had ever initiated ART or had been on ART were approached to participate in the study. Adolescent patients were eligible for inclusion even if they had defaulted or were LFTU to minimise potential bias towards adolescents more engaged in care [44]. Recruitment at the facility for adolescents presenting themselves for treatment or related issues was conducted by trained research assistants. The final step was designed to avoid potential stigma for ALHIV, an additional 473 HIV-negative adolescents, co-resident with current participants or living in neighbouring communities were recruited in the baseline study.

Awareness of HIV status was assessed firstly through clinic records and healthcare worker reports, and then with primary caregivers during the consent process at baseline. In cases of discrepancies, interviewers asked adolescents if they knew what their illness was, if they had ever tested for HIV, and if they knew what their medication was [109]. Adolescents were considered to be fully aware of their status if reported both knowledge of living with HIV and

their medication as ART used to treat HIV. To avoid unintended disclosure through the research process, those unaware of their HIV-positive status were asked about "illness" and "medication" as opposed to "HIV" and "ART" in study questionnaires. Awareness of HIV-positive status was reassessed at subsequent study rounds from primary caregivers and adolescents during the consent process for those unaware at baseline.

The final sample at baseline comprised a total of 1519 adolescents, 1 046 ALHIV and 473 community controls (Figure 3.2**)**. This thesis is based on all ALHIV in the study except for Chapter 6 which includes HIV-negative peers as a comparison group for mortality analysis. After the baseline study, adolescents who had consented to the follow-up were re-interviewed at a second wave (94% retention) and a third wave with a retention rate of 97% between wave 2 and wave 3 and a 3.3% mortality by the third and final wave [201, 202, 211].

Figure 3.2. Participant flow throughout from recruitment to baseline.



3.1.4. Mzantsi Wakho Data Collection

The data collection for the Mzantsi Wakho study started in March 2014 and participants were followed up twice until September 2018. The participant-level questionnaire was developed through extensive consultation with various stakeholders including adolescents themselves to ensure validity and acceptability. This questionnaire explored adolescents' health outcomes, including ART adherence and sexual and reproductive health outcomes and individual, household, community, and structural level factors affecting HIV treatment outcomes ranging from mental health, and social protection to relationships with peers. Where applicable, some measures were adapted from validated tools and piloted prior to use. Measures and scales used to record the potential correlates of ART adherence are described in more detail in the methods section of each results chapter (Chapters 4-8). A summary, including the sources of the measures and scales used in the full questionnaire, is included in Appendix 10-1.

Questionnaires were translated from English into isiXhosa and back-translated to ensure cultural equivalence of meaning. Before the interview, trained community-based research assistants sat with the adolescents to demonstrate how to use the tablet on which the questionnaire was completed and were present to guide them when necessary. The participants completed the questionnaire on their own on the tablet in their choice of English or isiXhosa. At baseline, the questionnaire was composed of 12 sections and each of the questionnaires for the respective wave of data collection can be found here: http://www.youngcarers.org.za/youthpulse. HIV-negative peers were given a version of the questionnaire that did not contain survey items relating to HIV or ARTs.

At the 52 study healthcare facilities, the clinic-based research team recorded information for all participants with patient files. Given the high degree of inter-facility mobility among adolescents [212], searching for all participant's files at all facilities enabled the collation of a complete clinic record. This approach also enabled the inclusion of seroconverted participants during the study period. To identify available patient files, the research staff searched clinic rosters and registers of ART patients manually including alternate spellings of names, with the supervision of the facility data capturer. Staff also searched for participants on each facility's Tier.net system to identify any additional electronic records.

Data were extracted using a standardised questionnaire, according to a protocol previously applied in other studies of adolescents on ART and adapted to the patient filing system [9]. Extracted data included HIV-RNA VL, CD4 cell count, and the WHO staging where

available (see Appendix 10-2 and **Error! Reference source not found.**). Clinical records were found for 88.1% (n=951) of ALHIV, of these 92.3% (n=878) had at least one VL recorded. Data were extracted from patient files at baseline for 2014 to 2015 records and the second round of patient file extraction for 2016 to 2017 records was completed in February 2018.

3.1.4.1. MW Participant check-in in 2021-2023

Female participants were contacted—in 2021-2023—as part of the recruitment to a study on adolescent mothers: the HEY BABY study (https://www.heybaby.org.za/). To ensure follow-up across both male and female participants, a short check-in questionnaire was designed for males (n=659) to capture mortality. In the face of eased COVID-19-related restrictions and reduction in infection rates in South Africa including the Eastern Cape Province, we planned to conduct face-to-face check-ins (approx. 15 minutes) to (1) update participants' contact details since we last spoke to them in mid-2018, and (2) understand their experiences and life changes including in their families. The face-to-face check-ins were chosen to facilitate contact tracing and to ensure that the targeted participant was the respondent. During follow-up, if the participant was not found, the reason for being unavailable for the interview was recorded including the details of the person reporting. If the reason for non-participation was death, then a follow-up question to understand the circumstances leading to their death was asked to the caregiver or person reporting. Where possible, details of the deceased such as the date and cause of death were recorded.

Various research challenges and constraints were encountered during this data collection. This included mobility, crime, the COVID-19 pandemic, remote areas, and participant mental health challenges. The research team was experienced in managing these complex data collection challenges with additional COVID-19 support and training provided.

3.1.5. Understanding Predictors of Lifelong Initiation and Follow-up Treatment for adolescents living with HIV (UPLIFT) linked data

A formal collaboration with the National Institute for Communicable Diseases (NICD) of South Africa was established in 2018 to match participants' socio-demographic characteristics to their laboratory test records in the NHLS data warehouse. The data warehouse contains among other data (see Appendix 10-2), the results of all HIV tests, including VL and CD4 count and tuberculosis (TB) tests for all adolescents accessing public

sector HIV care and treatment dating back to 2004. Data are captured from each laboratory requisition form at the time a blood sample is taken and include demographic information such as name, surname, gender, and date of birth [34]. The record linkage process used by the NHLS occurs at a national level and all laboratory tests are observed for individual patients regardless of where they seek care and not just within the study area. This enables access to participant laboratory records even if they have transferred out of the study area to receive treatment.

Figure 3.3 below summarises the iterative nature of the linkage process which was repeated annually in the period 2021-2023. In Step 1, a list of all the participant details namely: first name, last name, national identification numbers, and date of birth was compiled based on the list from the main Mzantsi Wakho study. Each participant retained their unique identifier from the parent study. Additional information, such as the name of the health facility where they accessed care, and their patient folder number (where available) including HIV test results extracted from these folders was also compiled for each participant. This list or roster was compiled on a password-protected and encrypted spreadsheet.

In Step 2: The password-protected roster of participant details was sent to the NHLS team. Using a refined and adapted probabilistic record-linking algorithm [213], the participant's socio-demographic details were used to search the NHLS data warehouse and match them to their likely laboratory test results. All test episode numbers—likely belonging to the same person—are extracted using this probabilistic record-linking algorithm. Test episode numbers are generated whenever a sample is sent and registered in the data warehouse and can be used to estimate the number of different tests performed. All participants are matched based on their first name, last name and date of birth using exact linking [214]. Additional attributes such as the South African national identity number and patient folder number are utilised for exact linking, where available [215]. For records or episodes not linked by the exact linking stored procedure, fuzzy-logic linking is utilised to accommodate for differences in spelling, transcription or typographical errors in names, and date of birth.

In Step 3, following Step 2, different laboratory test information is extracted (both HIV and non-HIV related tests) and stored in a password-protected spreadsheet. The test information extracted includes the date the test was registered, the name or type of test, the facility name and the location where the participant was tested for both the exact and fuzzy-logic linking results. This also includes extracted demographics of the participant, i.e., their first and last

name, date of birth, and sex. This test information alongside test episode numbers is shared with the UPLIFT team.

In Step 4, laboratory test information and socio-demographic details of potential matches received from the NHLS were further screened by a team of researchers including the candidate to ensure the accuracy of the matched participant records. Study participants were ascertained to be a match to an NHLS record if all their details (name, surname, and date of birth) were an exact match. In cases where names and surnames were identical but not date of birth, we accepted date of birth records which were exactly one day or one month off, or when the day and month of birth were reversed. In cases of discrepancies in names and surnames, researchers with knowledge of the South African language—IsiXhosa—assessed if these were locally acceptable variations of participant names. In addition, where study participants had test results from the clinical and laboratory file data abstraction, this was used as supporting evidence to confirm matches if the same results were identified in the NHLS records. The confirmed matched episode numbers and related test information are sent back to NHLS.

In Step 5, all linked test results for each matched test episode number are extracted from the NHLS data warehouse. These include both HIV-related and non-HIV test results, for example, one test episode number may be linked to both groups of tests. All test information, demographic details and test results are sent back to the UPLIFT team in two separate sheets (HIV and non-HIV test results).

In Step 6, the test results data received is cleaned and merged into analysis-ready data. Steps 1-6 were repeated ed in three rounds (three times). The first round of data searches and extraction for ALHIV was conducted between November 2020 to July 2021, with two follow-up rounds conducted between December 2021 to June 2022 and July to November 2023, respectively.

In compliance with the POPI Act, all matched patient-level data and the associated laboratory test results obtained from NHLS were linked, cleaned, and analysed, following secure and privacy-conscious procedures to protect individual personal information. This involved assigning password-encrypting all files related to the project at every step, assigning unique study identifiers to anonymize personal information, and ensuring no direct or personal identifiers were used. All personally identifiable information was completely excluded from the final dataset. Data access was restricted to authorized personnel and monitored at every stage of the data life cycle, to safeguard sensitive information and ensure confidentiality

throughout the study process. All information is stored in a secure, encrypted storage system and no copies or versions of the files are stored on personal devices or unencrypted storage files or devices. Table 3.1 below shows the total proportions of adolescents matched to the NHLS database over time.

Figure 3.3: Summary steps of the NHLS routine data linkage and matching process

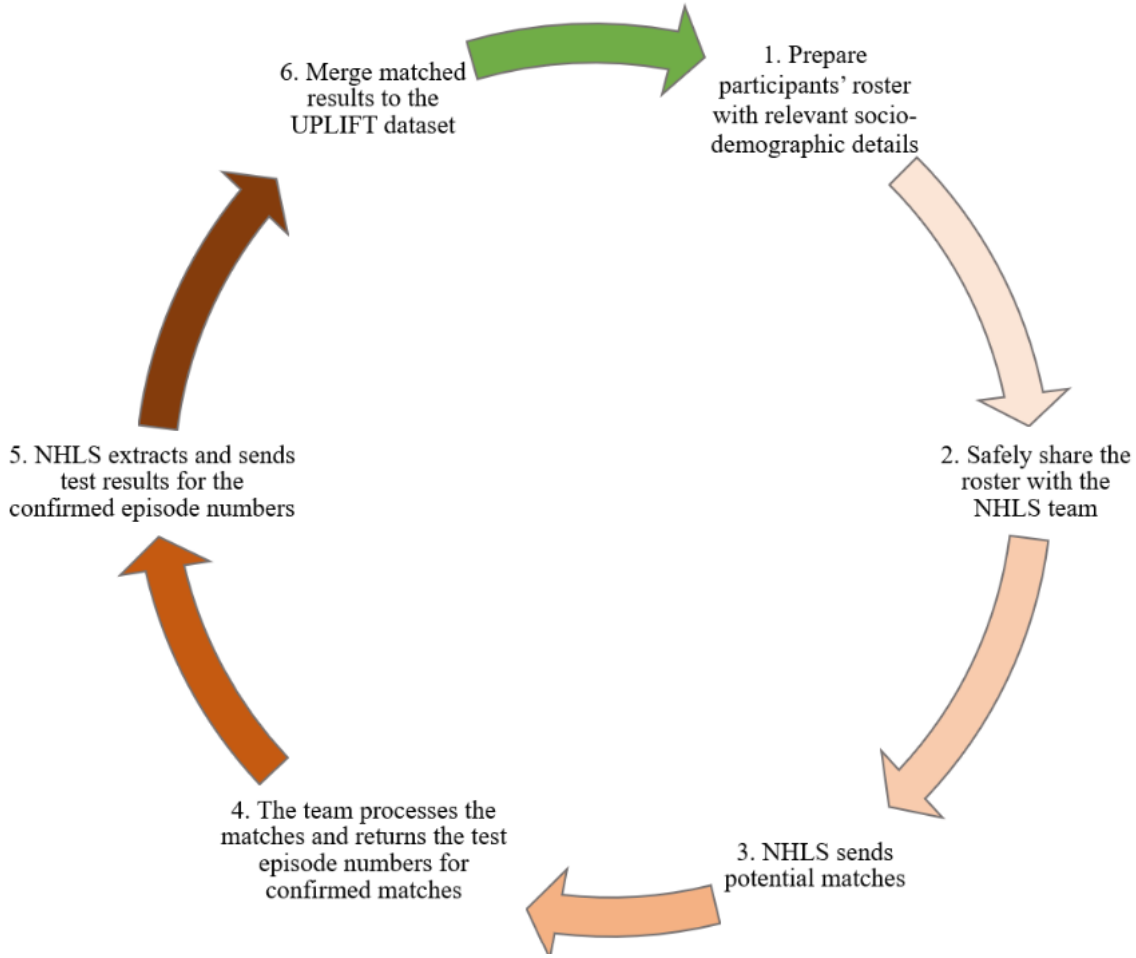


Table 3.1: Proportion of adolescents matched to the NHLS database over time: HIV-test results

Test results	MW participants only (N = 1563)		
	Round	ALHIV (n = 1107)	Not living with HIV/unknown status (456)
With any HIV-related tests (viral load, CD4, HIV rapid and TB test), n (%)	1 (2021)	814 (73.5)	46 (10.1)
	2 (2022)	845 (76.3)	72 (15.8)
	3 (2023)	846 (76.4)	78 (17.1)

3.2. Data management, storage, and access

The MW data were collected using a tablet-based electronic questionnaire for data entry that did not allow for illogical responses. Validation of responses through spot-checking was done regularly in parallel with data collection before submission to a secure server through an open-source software platform—Open Data Kit (www.opendatakit.org). Regular backups of data ensured that the database was safe, and the server was password encrypted and only accessible by the project management team. Data cleaning was done at the end of each wave of data collection led by the candidate and data was anonymised before any data analysis to preserve person-identifying information and ensure participant confidentiality. The longitudinal dataset for participant-level questionnaires (Waves 1-3) was created in Stata Software. Participants' unique identifiers were created, and all potentially individual-identifying information was removed from the resulting cohort data for use by researchers and analysts. A similar process was done for the NHLS-linked laboratory test data and MW male check-in data. This candidate-led documentation of the Data Management Plans (DMPs) for each study or sub-study data. Data access is done through requests approved by the study PIs.

3.3. Ethical Considerations

All the data used in this research has already been collected and the student was co-leading data cleaning between 2018 and 2020. Ethical approval for the Mzantsi Wakho study was granted by Research Ethics Committees at the Universities of Oxford (SSD/CUREC2/12–21/RE001) and Cape Town (UCT/CSSR/2013/4, UCT/CSSR/2019/01, UCT CSSR/2022/01). NHLS Academic Affairs and Research Management System (2019/08/07) granted access to the laboratory test data, and Eastern Cape Departments of Health and Basic Education boards allowed access to the participating facilities (Appendix 10-5). The University of Cape Town Human Research Ethics Committee (HREC-REF 121/2022, Appendix 10-6) granted ethics approval for the analyses presented in this thesis.

Written and verbal voluntary consent was obtained for each participant. In the case of young people under the age of 18, consent was obtained by their caregivers before the interview at all study waves, including for access to adolescents' clinical records. Participants/caregivers were given an information sheet explaining the research in the language of their choice, as well as the contact details of the project principal investigators and their right to refuse and

withdraw from the research. Consent to extract clinical information from participants' clinical records was also included in the consent form.

3.3.1. Potential Harms, Harm Prevention and Mitigation

This study context presented a significant power inequality which was carefully and sensitively considered since the participants were as young as 10 years of age and the interviewers (fieldwork team) were adults. Interviews were conducted by trained fieldworkers experienced in interviewing HIV-affected children and adolescents and attention was focused on unequal power relations and how to reduce the impact on adolescents. Guidelines to reduce participants becoming distressed during the interview were developed for the fieldworkers. Emphasis was placed on building trust and rapport with participants and consultation during data collection, analysis, and dissemination of findings. Participants had an opportunity to access referrals where necessary and a social worker advised on cases that required referrals to services following adolescent-reported harm or risk of significant harm.

3.3.2. Privacy/Confidentiality

The time, location, and nature of the engagement with the interviewer were chosen by the participants. Digital tablets were used in this study to increase the privacy and confidentiality of the responses given by participants as fieldworkers did not see answers unless the participant chose to share them. In the case of participants sharing contact details with researchers, this information was kept confidential. Contact information or any identifying information of participants were not included in the questionnaire. Each participant was identified by a unique identifier or participant ID, hence maintaining the confidentiality of the participant. No study clinical record included the participant's identifying information, including records that may reflect HIV test results or information about ART. The use of digital or mobile devices has been reported to allow truthful responses and greater confidentiality compared to paper-based questionnaires [216].

3.3.3. Reimbursements/Incentives, Potential Benefits

While participating in the research activities all participants, including those who withdrew, were given snacks as well as packs containing useful daily-use items, as advised by the Teen Advisory Group. Additionally, all participants received a Certificate of Participation. In case a participant chose to travel for privacy purposes, they were reimbursed for travel costs. No

financial rewards were provided to participants to avoid conflicts within the community or household and prevent coercion.

3.4. Methods Specific to this Thesis

3.4.1. Study sample

Because this thesis explores ART adherence, associated health outcomes, and experiences for ART-initiated adolescents, analyses included only participants living with HIV (n=1046) at baseline, except for the last results chapter which describes all-cause mortality for the whole cohort (all adolescents ever initiated on ART, n=1107 and their HIV-negative peers, n=456). Among those living with HIV at baseline (n=1046), 63.8% were aged 10-14 years, and 36% were aged 15-19 years. About three-quarters (74%) of the participants in this sample lived in both urban/peri-urban and 26% in rural areas. Over half (55%) of the sample were female participants, and almost all (96%) of the sample's first language was in isiXhosa.

3.4.2. Data Analysis

3.4.2.1. Objective 1: To evaluate the longitudinal self-reported measures of ART adherence in a cohort of adolescents living with HIV in resource-limited settings

The main variables of interest in this analysis were:

i. Seven self-reported adherence measures on missed doses, and clinic appointments – with varying recall timeframes adapted from the Patient Medication Adherence Questionnaire (see Appendix 10-3).
ii. Viral load (VL) measures obtained from data abstracted from participants' clinic folders and routine biomarker data from South Africa's NHLS (Appendix 10-4) were the primary outcome (defined as elevated VL: VL ≥ 1000 copies/mL).

The sample size for this analysis was restricted to ALHIV at baseline, who completed the questionnaire on all three occasions. A total of n=1046 ALHIV completed the questionnaire at baseline, and n=933 (89.2%) of these completed the questionnaire at all three waves and were included in this analysis. Sociodemographic and clinical variables from the baseline were compared between groups using t-tests, and chi-square tests as appropriate.

Cronbach's alpha and item correlation were used to assess how closely related the seven self-report ART adherence items are, as a group and random effects logistic regression models were employed to assess the association between each self-reported measure and elevated

VL. Measures of test accuracy –sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operating characteristic curve (AUROC) were computed to assess the accuracy of each of the self-reported measures in confirming elevated VL.

3.4.2.2. Objective 2: To identify and describe longitudinal trajectories of ART adherence among adolescents living with HIV.

The key indicators of the primary outcome were five self-reported ART adherence measures on missed doses –with varying recall timeframes and missed clinic appointments which showed good test accuracy against viral load in Objective 1. All adherence indicators were dichotomised and positively coded to represent adherence. Our secondary outcome, durable viral suppression was defined as having at least two viral loads <1000 copies/ml across the three study waves. The sample size for this analysis was limited to n=933 (those who completed the questionnaire at all three waves).

GBTM was used to identify longitudinal ART adherence trajectories for ALHIV using the multiple adherence indicators above. GBTM is chosen because it allows the use of multiple indicators over time or age to describe distinct patterns of adherence behaviour. It also takes into account the dynamic nature of adherence and the changes over time. Information criterion and interpretability were employed for model selection [38]. Differences between trajectory groups by sociodemographic and HIV-related characteristics were assessed using the chi-squared, Kruskal-Wallis, or Fisher's exact tests as appropriate, and multinomial logistic regression. A multivariate logistic regression model was used to assess the association between adherence trajectory membership and the secondary outcome: durable viral suppression. Multiple imputation methods were employed where necessary to account for missingness.

3.4.2.3. Objective 3: Describe sex- and age-specific all-cause mortality rates among ALHIV

The primary outcome of this analysis was all-cause mortality. All-cause mortality outcomes were ascertained through community tracing for follow-up interviews through November 2022. This included learning from community members or family members when returning for a follow-up interview, that the participant had passed away. For this analysis, data were censored when the following appeared first (1) death, (2) lost-to-study follow-up (censored at the last interview or contact date), and (3) alive (censored at the end of follow-up).

The sample size for this analysis included all adolescents (ALHIV: N=1107, and HIV-negative peers: N=456) followed up in the Mzantsi Wakho study between 2014 to 2022. Crude mortality incidence rates per 100 person-years of follow-up, stratified by age and sex across adolescent HIV acquisition groups (vertical and sexual) were estimated. Incidence rates were calculated as the number of deaths divided by the total number of person-years of follow-up for each age group and sex stratum, and Poisson regression was used to estimate adjusted incidence rate ratios (IRR) of mortality and their 95% CIs for ALHIV with vertically acquired HIV compared to those with sexually acquired HIV. Cox proportional hazards regression model to estimate the risk of death by ART adherence adjusting for age, sex, mode of HIV acquisition and time on ART treatment.

3.4.2.4. Objective 4: Identify socio-ecological barriers associated with distinct longitudinal ART adherence trajectories.

The main outcome variable in this analysis was the longitudinal ART adherence trajectory group variable obtained in Objective 2, categorized as four distinct adherence trajectories over three-time points. The key independent variables of interest were baseline individual (medication side-effects, mode of HIV transmission, time on treatment, pill burden, substance use, medication stock-outs, mental health symptoms, sexual abuse, bullying and victimization), family/household (food insecurity, witnessing domestic conflict or violence, and having no one to accompany the child to the clinic), community (HIV-related stigma, negative peer norms, and community violence), and healthcare level barriers (clinic travel time, clinic waiting time, and not enrolled in a peer support groups). Socio-demographic characteristics included as controls in the analysis included baseline age, sex, and urban/rural residence. The selection of these key factors was informed by their relevance to adherence as identified in the existing literature in Chapter 2, their alignment with the socio-ecological model, and the availability of the measures in the current study data. To achieve this objective, only factors that act as barriers to adherence were selected from those presented in the socio-ecological model in Figure 2.1. The sample size for this analysis was limited to those who completed the questionnaire at all three waves and had a valid outcome (n=933).

Univariate logistic regression models were used to assess the association between ART adherence trajectories and socio-ecological barriers. Purposeful selection with a cut-off significance level of $p < 0.20$, was used to select variables for inclusion into each subsequent path model. We further checked for multicollinearity among selected variables (variance

inflation factor>5 indicates multicollinearity). Generalized structural equation models (GSEM) were employed to fit path models to evaluate pathways and the underlying mechanisms linking barriers to ART adherence trajectory outcomes among ALHIV. Multiple imputation methods were employed where necessary to account for missingness.

3.4.2.5. Objective 5: Examine the impact of psychosocial and economic support on adherence and viral suppression among ALHIV

The primary outcomes of this analysis were:

i. ART adherence trajectories.
ii. *Elevated VL/non-adherence* was defined as having elevated VL (≥1000 copies/ml) at each wave of data collection.
iii. Self-reported ART non-adherence was defined as a binary indicator of missed doses in the past seven days (including weekdays and weekends and currently taking ART) informed by Objective 1.

Psychosocial and economic support was based on two forms of support namely: *social protection* defined as the receipt of any direct government social grants in the adolescent's household, and *psychosocial support* was measured using the Medical Outcomes Study Social Support Survey (MOS-SSS) scale's seven of the nineteen support items measured in this study data. These included items on availability of someone to *(1) listen to you; (2) give you good advice; (3) share worries with; (4) turn to for suggestions; (5) help if confined in bed; (6) take you to the doctor; and (7) prepare meals*.

N=933 participants were retained at all three study rounds which form the analytic sample for this analysis. Descriptive statistics of all measures at each study round for the analysis sample were presented using frequencies. Multinomial logistic regression was used to evaluate the relationship between baseline access to government social protection and family psychosocial support and longitudinal adherence trajectories. The mixed-effects logistic regression model was used to examine the impact of social protection and psychosocial support on elevated VL and non-adherence, given the repeated-measures nature of the data. Multiple imputation methods were employed where necessary to account for missingness.

CHAPTER 4. Exploring self-reported adherence measures to screen for elevated viral load in adolescents: A South African cohort study.

Zhou, S., Toska, E., Langwenya, N., Edun, O., Cluver L., Knight L. Exploring Self-reported Adherence Measures to Screen for Elevated HIV Viral Load in Adolescents: A South African Cohort Study. *AIDS Behav* **27**, 3537–3547 (2023). https://doi.org/10.1007/s10461-023-04068-2

Relevance of this paper to the thesis:

There is an urgent need for robust ART adherence measures to identify adolescents at risk of poor adherence to enable timely access to appropriate support. Self-reported adherence measures are one of the possible measures but there is limited evidence evaluating their validity and consistency among ALHIV in resource-limited settings using longitudinal data. This paper uses longitudinal statistical methods to compare the performance of seven self-reported measures of adherence, and their association with elevated viral load over time. A strength of this chapter is that these data were collected over three data points which enables longitudinal assessment. The self-reported adherence measures identified in this paper were used in the subsequent chapter, to explore distinct longitudinal adherence trajectories among ALHIV.

Contribution of the student and co-authors:

SZ conceptualised and led the analyses with guidance from LK and ET. SZ wrote the initial manuscript draft, and LK, ET, NL, OE, and LC reviewed and provided edits and feedback on the manuscript and analysis. ET and LC designed and implemented the overall study data collection. All authors approved the final draft.

4.1. Abstract

Background: The timely identification of ART non-adherence among adolescents living with HIV presents a significant challenge, particularly in resource-limited settings where virologic monitoring is suboptimal.

Methods: Using South African adolescent cohort data (N=933, mean age 13.6 ±2.89 years, 55.1% female, follow-up=2014-2018), we examined the association between elevated viral load (VL ≥1000 copies/mL) and seven self-reported adherence measures on missed doses, and clinic appointments –with varying recall timeframes.

Results: The best-performing measures, which were significantly associated with elevated viral load in covariate-adjusted models are: *any missed dose –past 3 days* (sensitivity =91.6% [95%CI: 90.3-92.8], positive predictive value (PPV) =78.8% [95%CI: 77.2-80.4]), *–past week* (sensitivity =87% [95%CI: 85.4-88.6], PPV =78.2% [95%CI: 76.5-79.9]), *–past month* (sensitivity =79.5% [95%CI: 77.5-81.4], PPV =78.2% [95%CI: 76.4-79.9]), *any past-month days missed* (sensitivity =86.7% [95%CI: 85.1-88.3], PPV =77.9% [95%CI:76.2-79.6]), and *any missed clinic appointment* (sensitivity =88.3% [95%CI: 86.8-89.8], PPV =78.4% [95%CI: 76.8-79.9]). Combining the three best-performing measures *missed dose –past 3 days*, *–past week*, and *any past-year missed clinic appointment* increased sensitivity to 96.4% while maintaining a PPV of about 78%.

Conclusions: The discriminatory power of simple and easy-to-administer self-reported adherence measures in detecting elevated viral load warrants consideration in resource-limited settings and may contribute to the aims of the new Global Alliance to End AIDS in children and adolescents by 2030.

4.2. Introduction

Scaling up access to antiretroviral treatment (ART) has led to global reductions in HIV-related morbidity and mortality as well as reduced risk of onward HIV transmission [1, 2]. However, for adolescents living with HIV (ALHIV) in sub-Saharan Africa (SSA), the benefits of ART use are yet to be maximised. Adolescents continue to experience life-threatening health vulnerabilities that negatively impact their well-being and survival [3]. Long-term ART adherence among ALHIV remains suboptimal, and lower compared to both younger children and adults [4-6]. For example, studies show that ALHIV are approximately 50% less likely than adults to maintain adherence [7, 8]. ALHIV are more than twice as likely to be lost-to-follow-up than adults [9], with HIV being the fourth leading cause of adolescent deaths in 2015 [10]. In South Africa, adolescents account for the largest share of new HIV infections, and over 421100 adolescents were estimated to be living with HIV in 2021 [11, 12]. Therefore, more concerted efforts aimed at monitoring and improving long-term ART adherence among ALHIV are urgently needed [13].

While the World Health Organization (WHO) recommends VL monitoring as the gold standard for monitoring HIV treatment success, several challenges exist in making this possible for the majority of countries in SSA [14]. These challenges include human resources (i.e., staffing shortages) and delays in the development of a skilled workforce; weaknesses in sample transport and laboratory workflow; poor laboratory equipment maintenance; and budget limitations [15]. Consequently, VL testing is often infrequent and poorly accessible [16]. Each of these may further delay early identification of non-adherence among ALHIV and subsequently delay interventions to support adherence and regimen switching. Therefore, alternative measures of ART adherence, such as self-reports are essential, in addition to VL monitoring. Evaluating alternative measures of adherence may facilitate understanding of adolescent medication-taking behaviour, a goal for researchers and clinicians [17].

Self-reported ART adherence measures are widely adopted in both clinical practice and research. They are often the only practical and readily available method in resource-limited settings due to their low cost, minimal patient burden, and ease of administration [18, 19]. However, there is limited evidence assessing the validity and consistency of these measures among ALHIV using longitudinal data [20]. Most tools routinely used to measure self-reported adherence have been designed for primarily use in adult populations, and very few studies have assessed the performance of these measures with adolescents [1, 21]. A study in

Zimbabwe (N=173) assessed self-reported adherence measures among older children and adolescents at 48 weeks post-ART initiation. This study found that when patients reported non-adherence measured with items reflecting missed doses in the past three days and weekends, and not taking ART medicine for two days or more in the past three months, it is a strong indicator of a high HIV viral load [22]. Similarly, another study in Cameroon (N=455) using a single self-reported item on missed doses in the past month found that self-reported adherence was associated with VL [23]. Despite these results, there is a need for more considerations to validate and adapt self-reported measures of adherence to adolescents in order to obtain more accurate measures of ART adherence. Using longitudinal data, our study compared the performance of seven self-reported ART adherence measures with varying recall timeframes and differing missed dose reporting structures in predicting elevated VL. We also assessed the association between each of the seven self-reported ART adherence measures and elevated VL over time while controlling for potential socio-demographic covariates.

4.3. Methods

Study setting and recruitment

This analysis uses data from the Mzantsi Wakho study, a longitudinal cohort of ALHIV. ART-initiated adolescents aged 10-19 years at baseline were recruited from a municipality in the Eastern Cape Province in South Africa, a province with an estimated HIV prevalence of 14% [24]. Participants were recruited by identifying all adolescents initiated on ART in the area through medical records reviews in 52 ART-providing public health facilities. Participants were then traced to their communities, homes, or schools, including those who had disengaged from care or been lost to follow-up (LTFU). HIV-negative peers from neighbouring homes and some co-resident adolescents were also recruited and interviewed to minimize stigma. Baseline interviews were conducted in 2014-2015, with follow-up interviews in 2016-2017 and 2017-2018.

Data collection

Data was collected from two sources, a self-report questionnaire, and the extraction and linking of paper and electronic medical records. *Adolescent self-report questionnaire:* Adolescents completed a tablet-based standardised questionnaire in clinics or communities with the support of research assistants trained in working with vulnerable adolescents. The

questionnaires were developed with input from a Teen Advisory Group, translated into the local language (isiXhosa), and were designed to be non-stigmatizing and engaging by including graphics, interactive games, and vignettes to introduce questions around sensitive topics. Adolescents responded to questions on their experiences at home, in their communities, and in healthcare settings, as well as self-reported adherence assessed using multiple measures. Before the interview, trained community-based research assistants sat with adolescents to demonstrate how to use the tablet properly and guide them when necessary. Participants then completed the questionnaire on their own, in either English or isiXhosa depending on their preference and lasted between 60-90 minutes. For the current analyses, self-reported survey data were only used to determine participants' sociodemographic characteristics and adherence measurements. Further study information, including study protocol, is available at www.mzantsiwakho.org.za.

Medical records review: At each of the 52 healthcare facilities, routine medical records (paper-based and electronic) were searched for every study participant aged 10-19 who had ever initiated ART treatment. This approach enabled the extraction of participants' records from all included facilities where they may have received care, including undocumented transfers to a new facility. HIV-related data were extracted in two rounds using a standardised form, covering records from 2014 to 2017. This data was later supplemented by routine laboratory test data (2014-2019) from the National Health Laboratory Services (NHLS) data warehouse. The NHLS archives all routine laboratory data from public-sector health facilities in South Africa and allowed the inclusion of laboratory tests from facilities outside the study catchment area. Demographic information (name, surname, sex, and date of birth) for adolescents in the cohort was used to link to laboratory test records from the NHLS data warehouse to study participants.

Measures

Self-reported adherence was measured using seven measures, as summarised in Table 4.1. The exact questions related to each measure are shown in Supplementary Table 4-1, of which five items were adapted from the Patient Medication Adherence Questionnaire [21]. The weekend [25] and the clinic appointment measures [26] were added based on recommendations from other studies and our qualitative research team [27]. *HIV-1 RNA VL measures* were obtained from data abstracted from participants' clinic folders and routine biomarker data from South Africa's NHLS following the linkage of participants'

sociodemographic data to the NHLS data warehouse. Given that VL measures were taken in line with the participant's clinic VL monitoring schedule and did not always align with their study interview dates, we assigned the closest VL result, within 12 months from the interview date. The median time of VL records date from the interview date was 2 months (interquartile range: 1, 5). Elevated VL was defined as VL≥1000 copies/mL.

Table 4.1: Adherence measures and coding

Measure	Questions as per the questionnaire	Study definition
Missed dose measured using positive framing of pill intake		
Any past 3-days missed dose	1. How many times did you take your ARVs or HIV medicine yesterday? 2. How many times did you take your ARVs or HIV medicine the day before yesterday? 3. How many times did you take your ARVs or HIV medicine three days ago? 4. How many times a day do you have to take your ARVs or HIV medicine?	Calculated the total number of times the adolescent took all their ARVs in the past three days. If the reported pill intake did not equal the expected prescribed number of pills for the three days, then we assigned them to the non-adherent group.
Any past-week missed timing of dose	How many days did you take all of your ARVs or HIV medicine at the right time last week?	The responses ranged from 0 to 7 days. Missed dose timing any was defined as a binary indicator for missing dose timing (did not take their ARVs at the right time) at least one day in the past week.
Any past-month days missed	How many days in the last month did you want to take your ARVs but you couldn't?	The responses ranged from 0 to 31 days. Missed dose days any was defined as a binary indicator for failing to take ARVs for at least one day in the last month.
Missed dose measure using negative framing of pill intake		
Any weekend missed dose	How many times did you not take your medication last weekend (Friday night, Saturday, and Sunday)?	Defined as 1 if the participant did not take their medication at least once in the last weekend and 0 otherwise.
Any past-week missed dose	Did you miss taking any of your ARV pills or HIV medicine in the last week?	Defined as a binary indicator of missing ARV pills at least once in the last week.
Any past-month missed dose	Did you miss taking any of your ARV pills or HIV medicine in the last month?	Defined as a binary indicator of participants missing ARV pills at least once in the last month.
Missed dose measure as delayed refill		

Any past-year missed clinic appointment	How many times in the last year were you not able to get to your clinic appointment?	Dichotomised to 1 if the participant reported missing clinic appointments at least once in the last year and 0 otherwise.

*All adherence items are dichotomised and negatively coded to represent non-adherence.

Socio-demographic characteristics included age, sex, urban/rural location, living in formal or informal housing- (based on whether the adolescent reported living in an informal house-shack), and an indicator of household poverty [3, 28]. Poverty was defined as lacking access to any of the following eight basic necessities: food, clothing, doctor, fees, shoes, toiletries, uniforms, and school equipment. These items were selected as necessities by over 80% of respondents in a nationally representative South African survey [29]. The socio-demographic factors in this study were selected based on evidence from previous systematic reviews and qualitative studies on factors associated with ART adherence in this population group [3, 28, 30]. HIV care factors included time of ART treatment (years) and mode of HIV acquisition. Mode of HIV acquisition was determined following existing SSA paediatric cohorts: age of ART initiation cut-off (≤10 years) [31-33].

4.3.1. Statistical Analysis

This analysis was restricted to participants who completed the questionnaire at all three time points. First, we assessed if there were sociodemographic and clinical differences between adolescents who completed the questionnaire at all three study rounds and those who missed at least one, and between adolescents with VL records and those without, using the t- and chi-square tests. Second, we summarised the characteristics of all participants included in the analysis at all three time points, including self-reported adherence measures (levels of non-adherence by measure) and HIV care factors. Then, using Cronbach's alpha and item correlation, we assessed how closely related the seven self-report ART adherence items are, as a group, in measuring the same concept [34, 35]. Third, we fitted unadjusted and adjusted random effects models to assess the association between each self-reported measure and elevated VL (≥1000 copies/mL). The random-effects logistic regression model was used, to utilise the repeated measures structure of the data (data from the same subjects at three-time points) as well as to be able to include time-invariant factors like sex and mode of HIV acquisition. Lastly, we assessed the accuracy of each of the self-reported measures in confirming elevated VL, by computing different measures of test accuracy –sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under

the receiver operating characteristic (ROC) curve, AUROC. We then explored the benefit of using one or more adherence measures to assess non-adherence. To achieve this, we combined the three best-performing measures significantly associated with elevated VL, to assess if they improved the ability to predict elevated VL relative to single measures, using the measures of test accuracy. SAS v.9.4 was used to estimate measures of test accuracy using repeated measures data [36, 37]. For the rest of the analysis, we used Stata v.16.0 (Stata Corporation, College Station, Texas, USA).

We conducted a sensitivity analysis to assess the impact of missingness in the VL load measure on the relationship between each adherence measure and elevated VL using missing data imputation models. Multiple imputations by chained equations were used to impute missing VL values and the multivariable random-effects logistic regression models were applied to 20 imputed data sets, and results were combined using Rubin's rules for each model [38].

Ethical approval for the Mzantsi Wakho study was granted by the University of Cape Town (UCT/CSSR/2013/4 and UCT/CSSR/2019/01), Oxford University (CUREC2/12-21), provincial Departments of Health and Education, NHLS Academic Affairs and Research Management System (2019/08/07) and ethical review boards of participating healthcare facilities. At all study waves, adolescent participants and their caregivers provided voluntary, informed, and written consent for participation, including interviews and access to adolescents' clinical records. There were no financial incentives for study participation, but all participants received a certificate of participation, snacks, and a small gift pack, including pencils and soap. Adolescents who refused to participate were still given snacks.

4.4. Results

Participant characteristics and HIV outcomes

A total of 1046 ALHIV completed the questionnaire at baseline and the study had a 90% uptake with 94% retained at Wave 2, 97% at Wave 3, and 35 (3.4%) ascertained to have died at the end of the study. 933 (89.2%) adolescents completed the questionnaire at all three waves and were included in this analysis. Overall, there were no significant differences in baseline characteristics of participants excluded in the analysis (lost-to-study follow-up) and those retained (complete), other than that those excluded were likely to be older (Supplementary Table 4-2).

The descriptive summary of adolescents retained in the analysis is shown in Table 4.2. The majority of the sample were females (55.1%) with a mean age of 13.6 years (SD=2.9) at baseline. Overall, the proportions residing in rural areas and informal housing structures were similar across the study waves, and those who lacked any of the 8 basic necessities (categorised as living in poverty) ranged between 67-78% during the study period. About 786 (84.2%) adolescents had at least one VL result at any time point, and slightly over 50% had a VL result at each time point. Adolescents without VL across the study period were also more likely to be older, live in formal housing, and have a shorter time on ART (Supplementary Table 4-3). Among those with any VL, about 300 (35.5%) had at least one elevated VL at any of the three waves of data and VL non-suppression rates increased from 20% at baseline to about 28.7% at Wave 3. In terms of self-reported ART adherence measures, the proportions reporting non-adherence ranged between 15-23% over the three waves for most measures except *–any past-week missed timing of dose* and *–any past-month missed dose* with as high as 44.3% and 32.3% respectively.

Table 4.2: Socio-demographic characteristics, self-reported ART non-adherence, and HIV care measures of the analytic sample (N=933)

	Baseline	**Wave 2**	**Wave 3**
Measures	**n (%)**	**n (%)**	**n (%)**
Socio-demographic characteristics			
Age (Mean/SD)	13.56 (2.88)	15.07 (2.88)	16.26 (2.90)
Rural	249 (26.7)	230 (24.7)	223 (23.9)
Informal housing	172 (18.5)	134 (14.4)	131 (14.1)
Poverty	633 (67.8)	726 (77.8)	630 (67.5)
HIV care			
Recently acquired HIV*	197 (21.3)	197 (21.3)	197 (21.3)
Time on treatment (in years)- (Mean/SD)	4.46 (3.21)	6.00 (3.46)	7.19 (3.51)
Any viral load result (VL)	574 (61.5)	477 (50.1)	498 (53.4)
Elevated VL (≥1000 copies/mL) (n1=574, n2=477 n3=498)[€]	114 (19.9)	104 (21.8)	143 (28.7)
Self-reported ART adherence measures			
Any past 3-days missed dose	135 (14.5)	163 (17.5)	130 (13.9)
Any past-week missed timing of dose	201 (21.5)	412 (44.3)	264 (28.4)
Any past-month days missed	202 (21.7)	159 (17.1)	142 (15.3)
Any weekend missed dose	214 (23.0)	173 (18.6)	142 (15.3)
Any past-week missed dose	204 (21.9)	193 (20.7)	148 (15.9)
Any past-month missed dose[ˣ]	301 (32.3)	246 (26.4)	182 (19.5)
Any past-year missed clinic appointment	164 (17.6)	167 (18.7)	135 (14.7)

[ˣ]11 participants missing for this variable at Wave 2 and 3; [€]n1, n2, and n3 represent the total number of participants with VL at each wave, respectively; *Based on the mode of HIV acquisition variable.

Adherence measures characteristics

As a group, the seven measures showed high internal consistency and inter-item correlation (Table 4.3). The average inter-item correlation for the test scale was 0.423, which is within the recommended range of 0.15-0.60 [39], showing that the measures are well correlated. Similarly, Cronbach's alpha (α) coefficient for the set of measures as a group was 0.837 at baseline, which is above the recommended 0.70 level, suggesting that the measures align well together and measure the same construct. Similar levels of internal consistency and item correlation were observed in Wave 2 and 3 (Supplementary Table 4-4).

Table 4.3: Summary of adherence measures characteristics using baseline data (Cronbach's alpha)

	Baseline			
Item	**Item-test correlation**	**Item-rest correlation**	**Average inter-item correlation**	**Alpha (α)**
Any past 3-days missed dose	0.602	0.449	0.459	0.836
Any past-week missed timing of dose	0.792	0.695	0.396	0.797
Any past-month days missed	0.697	0.569	0.392	0.795
Any weekend missed dose	0.663	0.525	0.454	0.833
Any past-week missed dose	0.801	0.708	0.392	0.794
Any past-month missed dose	0.804	0.711	0.427	0.817
Any past-year missed clinic appointment	0.616	0.466	0.438	0.824
Test scale			**0.423**	**0.837**

*α- Cronbach's alpha

Relationship between self-reported ART adherence measures and elevated VL

Five out of the seven self-reported ART adherence measures were significantly associated with elevated VL in both unadjusted models and covariate-adjusted models (Table 4.4). In the covariate-adjusted models, elevated VL was significantly associated with non-adherence measured as *any missed dose –past 3-days* (aOR 3.63, 95% CI 2.06-6.39), *–past week* (aOR 1.97, 95% CI 1.18-3.29), *–past month* (aOR 1.95, 95% CI 1.22-3.12), *any past-month days missed* (aOR 1.87, 95% CI 1.11-3.13), and *any missed clinic appointment* (aOR 2.45, 95% CI 1.39-4.32). The AUROC for all the covariate-adjusted models ranged between 64.0-66.2%. A sensitivity analysis assessing the impact of missingness in the VL load measure on the relationship between each adherence measure and elevated VL showed similar results (Supplementary Table 4-5, Model 1). Extending this to impute adherence measures by

assuming non-adherence for those excluded in the primary analysis also showed similar results (Supplementary Table 4-5, Model 2).

Table 4.4: Random-effects models showing the association between self-reported ART adherence measures and elevated VL (≥1000 copies/mL)

	Unadjusted models		Adjusted models		AUROC (%)
Adherence measures	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**	
Any past 3-days missed dose	3.79 (2.13-6.74)	**<0.001**	3.63 (2.06-6.39)	**<0.001**	66.2 (63.1-69.3)
Any past-week missed timing of dose	1.52 (1.00-2.30)	**0.048**	1.40 (0.93-2.11)	0.107	64.0 (60.9-67.2)
Any past-month days missed	2.13 (1.25-3.62)	**0.005**	1.87 (1.11-3.13)	**0.019**	64.5 (61.3-67.7)
Any weekend missed dose	1.77 (1.06-2.96)	**0.029**	1.65 (0.98-2.72)	0.051	64.4 (61.2-67.5)
Any past-week missed dose	2.12 (1.27-3.56)	**0.004**	1.97 (1.18-3.29)	**0.009**	64.4 (61.2-67.6)
Any past-month missed dose	2.11 (1.31-3.39)	**0.002**	1.95 (1.22-3.12)	**0.005**	64.5 (61.4-67.7)
Any past-year missed clinic appointment	2.63 (1.49-4.64)	**0.001**	2.45 (1.39-4.32)	**0.002**	64.9 (61.8-68.1)

[¥]The adjusted model controls for the following factors: adolescent age, sex, rural residence, informal housing, poverty, study wave, time on treatment, and mode of HIV acquisition. 95% CI–confidence interval; Age and time on treatment were significantly associated with elevated viral load across all the seven adjusted models. aOR: adjusted odds ratio. AUROC-area under the receiver operating characteristic curve for the covariate-adjusted models.

Predictive validity of self-reported ART adherence measures

Sensitivity, specificity, PPV, and NPV of using self-reported adherence measures to predict elevated VL (≥1000 copies/mL) are summarised in Table 4.5 and Supplementary Figure 4-1. In this study, we sought to maximize sensitivity and PPV since the focus is on identifying adolescents who are non-adherent and, therefore, likely to have elevated VL. Overall, all seven adherence measures had a high sensitivity, suggesting that having an elevated VL was mostly related to non-adherence to ART. The PPV values of all the adherence measures were fairly high (over 77%), suggesting a higher chance that adolescents who are non-adherent have an elevated VL. The *past 3-days missed dose* measure performed best compared to other measures in predicting elevated VL with relatively high sensitivity: 91.6% (90.3-92.8) and positive predictive value: 78.8% (77.2-80.4), followed by *any past-year missed clinic*

appointment with a sensitivity of 88.3% (86.8-89.8) and a positive predictive value: 78.4% (76.8-79.9).

Table 4.5: Sensitivity, specificity, PPV, and NPV for predicting elevated VL (≥1000 copies/mL).

Adherence measure	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Any past 3-days missed dose	91.6 (90.3-92.8)	18.8 (15.2-22.4)	78.8 (77.2-80.4)	40.5 (34.6-46.3)
Any past-week missed timing of dose	74.2 (71.9-76.5)	30.8 (26.6-34.9)	77.9 (76.0-79.8)	26.6 (23.3-29.9)
Any past-month days missed	86.2 (84.4-87.7)	20.0 (16.4-23.6)	78.0 (76.3-79.7)	30.3 (25.5-34.9)
Any weekend missed dose	87.0 (85.4-88.6)	20.2 (16.6-23.8)	78.2 (76.5-79.9)	32.2 (27.3-36.9)
Any past-week missed dose	86.7 (85.1-88.3)	19.1 (15.7-22.5)	77.9 (76.2-79.6)	30.4 (25.7-35.1)
Any past-month missed dose	79.5 (77.5-81.4)	27.2 (23.2-31.1)	78.2 (76.4-79.9)	28.7 (24.9-32.4)
Any past-year missed clinic appointment	88.3 (86.8-89.8)	19.9 (16.6-23.3)	78.4 (76.8-79.9)	34.1 (29.2-39.1)

Sensitivity is the proportion of adolescents with elevated VL who are identified by non-adherence; specificity is the proportion of adolescents with suppressed viral load who are identified by adherence; PPV (positive predictive value) is the probability of adolescents who are non-adherent having an elevated VL; NPV (negative predictive value) is the probability of adherent adolescents having suppressed VL. 95%CI –confidence interval in parentheses.

Accuracy of combined self-reported ART adherence measures

Table 4.6 illustrates the change in accuracy parameters for single compared to combined self-reported ART adherence measures in predicting elevated VL based on the items significantly associated with elevated VL in Table 4.5. For example, based on results in Table 4.4 and Table 4.5, combining the *past 3-days missed dose* measure with the next two best measures (*any past-year missed clinic appointment and past-week missed dose)* incrementally, improved sensitivity by approximately 5%, from 91.6% with a single best measure to 96.4% with all top three measures combined while PPV remained stable at around 78%.

Table 4.6: Sensitivity, specificity, PPV, and NPV parameters for combined versus single adherence measures in predicting elevated VL (≥1000 copies/mL) among ALHIV.

Adherence measures (combination)	Any past 3-days missed dose	Any past 3-days missed dose AND Any past-year missed clinic appointment	Any (past 3-days AND past week) missed dose AND Any past-year missed clinic appointment
Parameter			
Sensitivity (%)	91.6 (90.3-92.8)	95.8 (94.9-96.6)	96.4 (95.6-97.1)
Specificity (%)	18.8 (15.2-22.4)	9.7 (7.1-12.3)	8.0 (5.8-10.3)
PPV (%)	78.8 (77.2-80.4)	77.7 (76.2-79.3)	77.5 (76.0-79.1)
NPV (%)	40.5 (34.6-46.3)	41.2 (33.2-49.2)	40.3 (31.9-48.6)

¥95% CI–confidence interval in parentheses.

4.5. Discussion

To the best of our knowledge, this study is one of the first efforts to empirically investigate the longitudinal association of multiple self-reported ART adherence measures with elevated VL using ALHIV data from South Africa. This analysis had four main findings. First, all seven measures assessed among ALHIV demonstrated good psychometric characteristics. Second, five of the seven self-reported adherence measures: *any missed dose –past 3-days, –past week, –past month, past-month days missed,* and *missed clinic appointment,* were significantly associated with elevated VL in both univariable and multivariable models and had the best ability to predict viral non-suppression. In contrast, *missed timing of doses in the past week* and *past weekend missed doses* were not significantly predictive of elevated VL. Third, the *past 3-days missed dose* measure performed best in predicting elevated VL compared to other measures. Fourth, a combination of self-reported adherence measures maximised sensitivity in predicting elevated VL compared to single measures alone.

Self-reported measures range from single items on missed doses in a specified time to more complex items requiring a detailed recall. Five of the seven self-reported measures assessed in this study (i.e., *any missed dose* in the *past 3-days, –past week, –past month,* as well as *past-month days missed,* and *missed clinic appointment)* were significantly associated with elevated VL even after adjusting for potential confounders. Although few studies report using the same self-reported adherence measure which makes it difficult to compare results across studies [1, 18], these findings are consistent with previous studies from LMICs that also show that self-reported adherence measures were able to predict detectable VL [5, 22, 23, 25]. An early study in the US validating self-reported measures based on doses taken in the past month, past Saturday, and past non-weekend day among ALHIV found significantly lower

VL among those who were adherent based on all measures [40]. Similarly, another study in Zimbabwe assessing self-reported adherence measures among older children and adolescents found that missed doses in the past three days, weekends, and three months, were strong indicators of elevated VL [22]. More recent studies among adolescents in Cameroon [23] and in Uganda [41] using a single item on missed doses in the past month, also found an that past month was predictive of VL. These studies used measures with varying recall periods ranging from one day to three months, similar to those used in our analysis.

An important finding is that corresponding high sensitivity (over 75%), high PPV (above 77%), low specificity, and sub-optimal adjusted AUROC (slightly above 64%) were detected in this study for all the measures. The high sensitivity observed in this study suggested that non-adherence leads to elevated VL, while the low specificity suggested that good adherence was not the only factor that can be accountable for viral suppression. This is mirrored by the low AUROC obtained in this analysis (below 0.70, the minimal value for screening purposes) even after adjusting for potential confounders. Previous research has shown that, other than poor adherence to ART, factors such as viral susceptibility, drug resistance, drug interactions, the potency of the regimen, and host immunological status may also influence one's virological response [42, 43]. Although global recommendations are moving towards making VL monitoring the standard of care for ART programmes, in reality, there are still gaps in access in resource-limited settings due to logistical and financial constraints. Given the infrequent VL testing and potential delays in the feedback of results in many resource-limited settings, the adherence measures identified in this study may facilitate interim adherence assessments to allow for rapid assessment of adherence risk, and immediate feedback and counselling, particularly in this vulnerable group [22]. Our findings suggest that these simple and low-cost self-report measures may be valuable for both research and alternative models of care and support for adolescents who may benefit from adherence counselling and intervention [44].

The *past 3 days missed dose* measure performed best in predicting elevated VL compared to other measures. Previous studies, mostly among adults living with HIV, have had mixed findings on this measure, for example, a cross-sectional study evaluating self-reported adherence measures among (N=2146) participants in China found that the past one-month doses taken measure might have similar accuracy compared with the 3-day measure as both were statistically significantly associated with detectable VL [25]. In contrast, another study

in an ART-naïve cohort (N=230) of adults and adolescents (≥12 years) in South Africa found that although a 3-day self-report yielded the highest adherence, it was not a significant predictor of viral suppression [45]. This is similar to the findings in a study among 156 participants in the U.S., which found that the 3-day recall period did not perform better than longer time periods [46]. Previous research demonstrates that short-term self-reported measures may overestimate adherence due to recall and social desirability bias [18, 45, 46]. However, the measures used in our study, including the 3-day self-report, were assessed by lay community staff, trained to be sympathetic and kind to adolescents, thereby reducing the risk of social desirability bias. Therefore, our findings may suggest that following careful and adolescent-sensitive interviewing, shorter recall assessments may be better suited to predict elevated VL among ALHIV. For increased generalisability, further studies could look into the applicability of these measures to routine clinical settings in high-volume ART clinics.

Furthermore, our study showed that combining different self-reported measures of adherence results in higher sensitivity and PPV for predicting elevated VL, which may be useful in clinical and research settings. These results suggest that researchers and clinicians may use multiple self-reported measures of adherence to obtain a more comprehensive assessment of adherence, resulting in a better prediction of virologic failure [45]. This may also mitigate the ceiling effect of reportedly perfect adherence, associated with self-reported measures [18]. Further research on these combinations may help develop standardised adherence measurement tools with combined measures to be used in clinics and research.

Self-report measures are relatively easy to administer and can be an opening prompt for further discussion between a patient and their provider or peer supporter to address non-adherence. The measures used in this study are a combination of shorter recall timeframes (past 3 days) which may be less susceptible to recall bias and longer timeframes (past month) which may also capture the variation in adherence behaviours, which makes them more relevant for first-stage adherence screening. The clinic appointment measure may also be useful to peer supporters as a good indicator of non-adherence risk for adolescents transitioning or moving into adherence community support groups. In general, our findings suggest that researchers, clinicians, and other forms of care may continue to use one or multiple self-reported adherence measures with some confidence in their validity at least in terms of their associations with elevated VL, as assessment tools to facilitate subsequent VL testing and support for adolescents.

This study found no significant association between *missed timing of doses in the past week*, or *past weekend missed dose* and elevated VL. The finding of *missed timing of doses in the past week* not being predictive of elevated VL may be because newer ART regimens are more potent and forgiving of dose timing compared to the older regimen [47], although sticking to the timing of dosage is still recommended, as it helps fit medication-taking into routines. The lack of association between elevated VL and *any missed dose (weekend)* measure could be partly related to Wilson et al.'s argument that asking individuals who are unintentionally non-adherent about missed doses may increase the risk of reporting intention instead of action [48]. It is also possible that participants' responses to *any missed dose (weekend)* question were biased towards under-reporting their poor adherence behaviour since the two-and-half-days (Friday night, Saturday, and Sunday) were combined in one question.

Our study is not without limitations. First, we use self-reported adherence measures which are prone to social desirability bias and recall bias as well as question misinterpretation [18, 20, 22, 48, 49]. The low specificity observed in this analysis may also be reflective of the bias in the adherence measures. However, the questionnaire was administered by research interviewers outside of the routine ART care service and in the absence of the time constraints associated with routine ART clinics, and who were trained to work with adolescents reducing the risk of social desirability bias. Second, this cohort had 3.4% mortality, with a risk that those adolescents who died were more vulnerable, again potentially risking underestimation of effects. Third, our VL measure was missing for a number of participants, and 15.8% of the analytic sample had no VL measure at all three waves. This may have underestimated the extent of virological treatment failure. To address this, we assessed predictors of missing VL and fitted missing data imputation models to model the impact of missingness in the relationship between self-reported adherence measures and VL. Fourth, the VL data used in this analysis did not match the questionnaire dates exactly but was within 12 months from the questionnaire dates which may bias the relationship between adherence and elevated VL. The strength of this study is that it is a longitudinal study that included multiple self-reported adherence items with varying item content and recall timeframes among ALHIV. The self-reported data is also based on standardised questionnaires, administered through a study that actively traced adolescents over multiple waves, allowing the inclusion of adolescents who have moved between healthcare facilities

or disengaged from care. This study also provides evidence from a sample of adolescents initiated on ART through government services in over 53 clinics in South Africa's Eastern Cape Province, a province affected by poor health infrastructure and high rates of HIV [24]. Therefore, these findings may be generalisable to other countries or similar contexts in sub-Saharan Africa.

Conclusions

In summary, our study shows that self-reported adherence measures may be used to screen for non-adherence and potentially flag current or pending elevated VL in ALHIV. Predictive validity could potentially be improved by combining multiple self-reported measures. Adherence monitoring during adolescence requires more attention in the era of universal ART for all, therefore, we recommend that clinicians and researchers continue using self-report questions (single or in combination) in their day-to-day clinical care or research practice to detect non-adherence. These findings facilitate the development of low-cost and relatively easy-to-administer self-reported adherence tools for use among adolescents in low-resource settings.

4.6. Supplementary Tables and Figures

Supplementary Table 4-1: Questionnaire original adherence items or measures

1. Any missed dose (past 3 days)

"Sometimes people get busy and forget to take their ARVs or HIV medicine. We would like to understand if you have similar experiences when you take your ARVs or HIV medicine so we can help other teens. We need to know what is really happening, not what you think we want to hear. Nobody will get angry at you and your answers. Please be honest."

Please answer each question with a number:

a) How many times did you take your ARVs or HIV medicine yesterday?
b) How many times did you take your ARVs or HIV medicine the day before yesterday?
c) How many times did you take your ARVs or HIV medicine three days ago?
d) How many times a day do you have to take your ARVs or HIV medicine?

2. Missed dose timing any (Past week)

"Sometimes unexpected things get in the way and prevent people from taking their ARVs or HIV medicine at the same time. Some days, people do not take their ARVs or HIV medicine at all or don't take them at the right time. This is not their fault. We would like to ask you about the times you were not able to take your ARVs or HIV medicine. We simply want to better understand why teens have a hard time taking their ARVS or HIV medicine."

a) How many days did you take all of your ARVs or HIV medicine at the right time last week?

"Remember, your answers to our questions will help us understand what makes it easier and harder to take pills or medicine. Please answer as truthfully as you can. Your answers are completely confidential, and you will not be judged."

3. Last missed dose any (past week)

a) Did you miss taking any of your ARV pills or HIV medicine in the last week?

"Remember, your answers to our questions will help us understand what makes it easier and harder to take pills or medicine. Please answer as truthfully as you can. Your answers are completely confidential, and you will not be judged."

4. Last missed dose any (past month*)*

a) Did you miss taking any of your ARV pills or HIV medicine in the last month?

5. Past month days missed

a) How many days in the last month did you want to take ARVs or HIV medicine, but you couldn't?

6. Any missed dose (weekend)

"On weekends, Andiwe spends time with friends and family. Sometimes he travels to visit family members or stays out late with his friends. Some weekends he stays at home, goes to church, and helps his parents and grandparents. It is not always easy for him to take his medication during Saturdays and Sundays, but he does his best. Think about last weekend – Saturday and Sunday."

a) How many times did you not take your medication last weekend (Friday night, Saturday, and Sunday)?

7. Any missed clinic appointment

a) In the last year, were you always able to get your clinic appointment? If 'No'
b) How many times in the last year were you not able to get to your clinic appointment?

Supplementary Table 4-2: Comparison of baseline characteristics for complete cases and LFTU[¥] (N=1046)

	Total (N=1046)	Complete cases (N=933)	Lost-to-study follow-up (N=113)		
Baseline characteristics	**N (%)**	**N (%)**	**N (%)**	**Test statistic**	**p-value**
Age (Mean/SD)	13.67 (2.89)	13.56 (2.88)	14.57 (2.88)	-3.5	**<0.001**
Female	576 (55.1)	514 (55.1)	62 (54.9)	0	0.964
Rural residence	272 (26.0)	249 (26.7)	23 (20.4)	2.1	0.147
Informal housing	196 (18.7)	172 (18.5)	24 (21.2)	0.5	0.474
Poverty	708 (67.7)	633 (67.8)	75 (66.4)	0.1	0.752
Sexually acquired HIV	222 (21.2)	197 (21.3)	25 (22.9)	0.2	0.695
Time on treatment					
(Mean/SD)	4.44 (3.24)	4.46 (3.21)	4.26 (3.50)	0.6	0.565
(Median/IQR)	4 (2,7)	4 (2,7)	4 (1,7)		

[¥]LFTU represents adolescents' lost-to-study-follow-up at least one-time point. At each successive wave, participants were actively followed up. Below is the breakdown of the (N=113) loss-to-follow-up between Wave 1 and 3: (N=12) passed on between Wave 1 and 2, and (N=22) passed on between Wave 2 and 3, (N=55) were lost-to-follow-up for the following reasons between Wave 1 and Wave 2:- refusals, untraceable or avoidant. (N=24) were lost-to-follow-up between Wave 2 and Wave 3 either as refusals, untraceable or avoidant. The chi-square test was used for binary baseline characteristics while the two-sample t-test was used for continuous baseline characteristics.

Supplementary Table 4-3: Comparison of baseline characteristics for having any VL and missing VL measurements at all three-time points (N=933).

	Total (N=933)	Any viral load record[¥] (N=786)	Missing viral loads for all three years (N=147)		
Baseline characteristics	**N (%)**	**N (%)**	**N (%)**	**Test statistic**	**p-value**
Age (Mean/SD)	13.56 (2.88)	13.47 (2.85)	14.07 (2.98)	-2.4	**0.018**
Female	514 (55.1)	431 (54.8)	83 (56.5)	0.1	0.716
Rural residence	249 (26.7)	206 (26.2)	43 (29.3)	0.6	0.444
Informal housing	172 (18.5)	162 (19.2)	14 (9.6)	9.0	**0.003**
Poverty	633 (67.8)	526 (66.9)	107 (72.8)	2.0	0.162
Recently acquired HIV	197 (21.3)	162 (20.7)	35 (24.6)	1.1	0.295
Time on treatment (in years)					
(Mean/SD)	4.56 (3.21)	4.61 (3.23)	3.24 (2.84)		
(Median/IQR)	4 (2,7)	4 (2,7)	3 (1,6)	3.8	**<0.001**

[¥]Outcome based on the most recent viral load within 12 months of the interview date at each time point. Any participants without any record at all time points were defined as missing VL. Chi-square test was used for binary baseline characteristics while a two-sample t-test was used for continuous baseline characteristics.

Supplementary Table 4-4: Summary of adherence items characteristics (Cronbach's alpha)

	Wave 2		Wave 3	
Item	**Average inter-item correlation**	**Alpha (α)**	**Average inter-item correlation**	**Alpha(α)**
Any past 3-days missed dose	0.380	0.786	0.565	0.886
Any past-week missed timing of dose	0.426	0.817	0.578	0.891
Any past-month days missed	0.416	0.810	0.568	0.887
Any weekend missed dose	0.429	0.818	0.575	0.890
Any past-week missed dose	0.363	0.773	0.529	0.871
Any past-month missed dose	0.371	0.779	0.551	0.880
Any past-year missed clinic appointment	0.395	0.796	0.576	0.890
Test scale	**0.397**	**0.822**	**0.563**	**0.900**

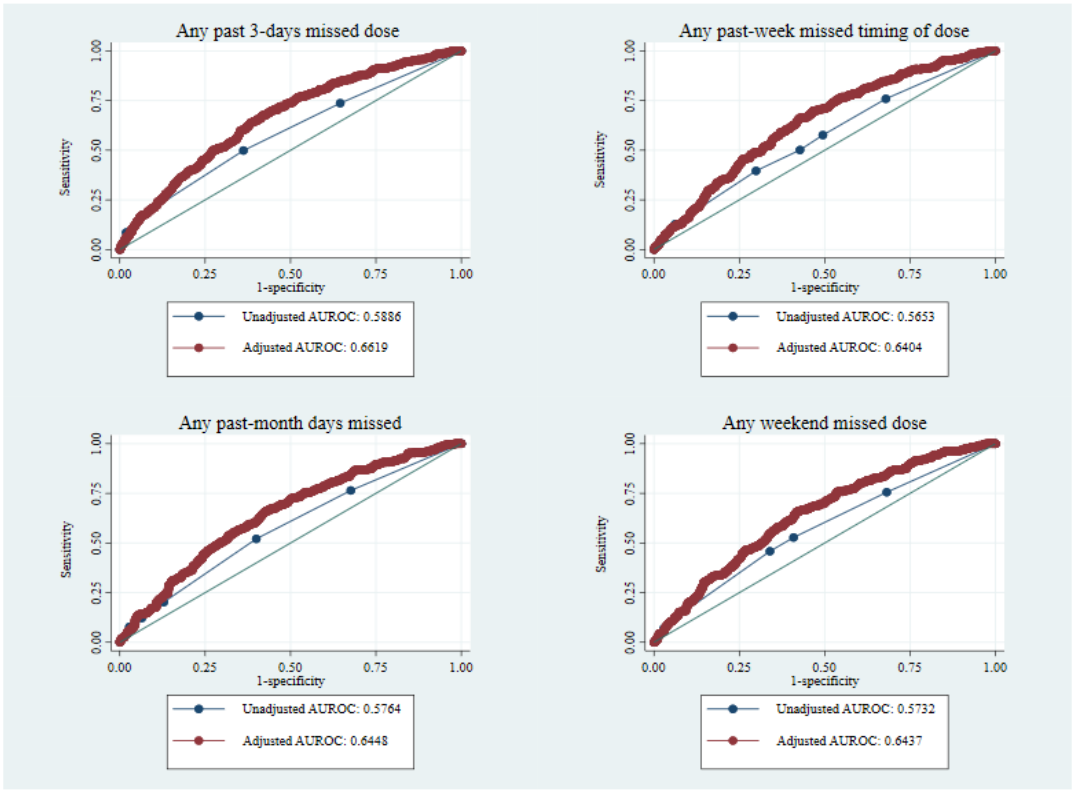
*****α- Cronbach's alpha

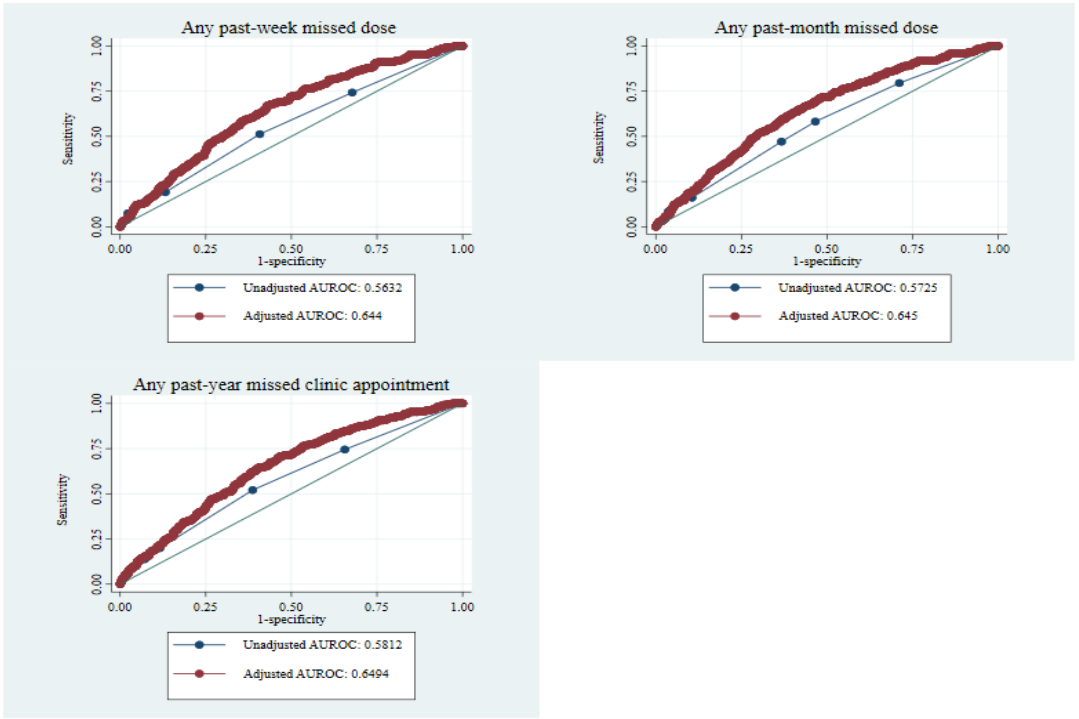
Supplementary Table 4-5: Multilevel model odds ratios for predicting elevated VL (>=1000 copies/mL) by different adherence measures after missing data imputation.

	Imputation models: Elevated VL (>=1000 copies/mL)			
	Model 1¥		**Model 2***	
Adherence measures	**aOR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Any past 3-days missed dose	3.21 (1.80-5.73)	**<0.001**	3.55 (2.07-6.10)	**<0.001**
Any past-week missed timing of dose	1.36 (0.91-2.02)	0.129	1.41 (0.96-2.10)	0.080
Any past-month days missed	1.73 (1.04-2.86)	**0.034**	1.89 (1.15-3.10)	**0.012**
Any weekend missed dose	1.58 (0.89-2.79)	0.112	1.76 (0.95-2.87)	0.092
Any past-week missed dose	2.13 (1.14-3.99)	**0.020**	2.12 (1.30-3.46)	**0.003**
Any past-month missed dose	2.14 (1.22-3.76)	**0.009**	2.21 (1.41-3.48)	**0.001**
Any past-year missed clinic appointment	2.27 (1.26-4.08)	**0.007**	2.75 (1.61-4.74)	**<0.001**

¥Multiple imputations by chained equations were used to impute missing dichotomous elevated VL values. The imputation model included adolescent age, participant sex, mode of infection, time on ART treatment and adherence measure for each imputation model. The multivariable mixed-effects regression models were applied to 20 imputed data sets, and results were combined using Rubin's rules for each model. aOR: adjusted odds ratio; 95% CI – confidence interval. *This model assumes non-adherence for those excluded in the primary analysis.

Supplementary Figure 4-1: Prediction of elevated viral load by each self-reported ART adherence measure.





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CHAPTER 5. Longitudinal trajectories of antiretroviral treatment adherence and associations with durable viral suppression among adolescents living with HIV in South Africa.

Zhou S, Cluver L, Knight L, Edun O, Sherman G, Toska E. Longitudinal Trajectories of Antiretroviral Treatment Adherence and Associations With Durable Viral Suppression Among Adolescents Living With HIV in South Africa. *J Acquir Immune Defic Syndr*. 2024 Jun 1;96(2):171-179. https://www.doi:10.1097/QAI.0000000000003408.

Relevance of this paper to the thesis:

This paper uses five self-reported adherence measures—which showed good test accuracy against viral load in Chapter 4—and a novel statistical approach (group-based trajectory modelling) to identify and describe ART adherence trajectories among ALHIV. There is a lack of evidence on adolescents' adherence patterns over time to inform the customisation of intervention strategies. This paper uncovers both heterogeneity and inconsistencies in long-term ART adherence and provides data on how inconsistencies in adherence over time impact viral load outcomes among ALHIV.

Contribution of the student and co-authors:

SZ conceptualised and led the statistical analyses including the write-up of this manuscript. LC, LK, OE, GS, and ET reviewed and provided edits and feedback on the manuscript content. All authors approved the final draft. ET and LC designed and implemented the overall study.

5.1. Abstract

Background: Compared to other age groups, adolescents living with HIV (ALHIV) are estimated to have lower levels of adherence to antiretroviral treatment (ART). Despite this, we lack evidence on adolescents' adherence patterns over time to inform the customisation of intervention strategies.

Setting: Eastern Cape province, South Africa.

Methods: We analysed data from a cohort of ALHIV (N=1046, aged 10-19 years at baseline) recruited from 53 public health facilities. The cohort comprised three waves of data collected between 2014 and 2018, and routine viral load (VL) data from the National Institute for Communicable Disease (NICD) data warehouse (2014-2019). Durable viral suppression was defined as having suppressed viral load (<1000 copies/ml) at ≥2 consecutive study waves. Group-based multi-trajectory modelling was used to identify adherence trajectories using five indicators of self-reported adherence. Logistic regression modelling evaluated the associations between adherence trajectories and durable viral suppression.

Results: Overall, 933 (89.2%) ALHIV completed all three study waves (55.1% female, mean age: 13.6 years at baseline). Four adherence trajectories were identified, namely "consistent adherence" (49.8%), "low start and increasing" (20.8%); "gradually decreasing" (23.5%), and "low and decreasing" (5.9%). Adolescents experiencing inconsistent adherence trajectories were more likely to be older, live in rural areas, and have sexually acquired HIV. Compared to the consistent adherence trajectory, the odds of durable viral suppression were lower among adolescents in the low start and increasing (aOR: 0.62, 95%CI 0.41-0.95), gradually decreasing (aOR: 0.40, 95%CI 0.27-0.59), and the low and decreasing adherence trajectories (aOR: 0.25, 95%CI 0.10-0.62).

Conclusions: Adherence to ART remains a challenge among ALHIV in South Africa. Identifying adolescents at risk of non-adherence, based on their adherence trajectories may inform the tailoring of adolescent-friendly support strategies.

5.2. Introduction

Advances in access to antiretroviral therapy (ART) have led to global reductions in AIDS-related mortality and improved quality of life for people living with HIV [1]. Consistent adherence to ART is essential to achieve and sustain viral suppression and maintain the health and well-being of an individual [2, 3]. Despite the successful rollout of ART in sub-Saharan Africa (SSA), [4, 5] adolescents living with HIV (ALHIV) continue to demonstrate poor adherence [6, 7] and fall behind global targets on viral suppression (UNAIDS 95-95-95 targets) [8-10]. For example, about 78% of adolescents on ART are estimated to be virally suppressed (defined as <1000 copies/ml) [11]. Moreover, sub-optimal adherence to ART is high among ALHIV compared to adults, with adolescents estimated to be 50% less likely to maintain optimal adherence [12, 13].

Several studies have examined ART adherence among adolescents in SSA [14-18] and demonstrated the utility of self-reported measures in adherence monitoring. However, less attention has been given to understanding variations in patterns of adherence over time in this group. Most studies on adherence among adolescents are largely cross-sectional, which does not appropriately reflect changes in patterns of adherence over time [19]. Existing longitudinal evidence on adolescents has mostly used aggregate methods, dichotomized adolescents as adherent versus non-adherent and examined within-person patterns of adherence, which is insufficient to capture the dynamic nature of long-term adherence [7, 20-22]. Therefore, there is a need for additional longitudinal analyses to distil variability in adherence patterns both between and within adolescents, as these variations can influence the likelihood of sustaining viral suppression [20, 23].

One analytic approach to address this gap is group-based trajectory modelling (GBTM), a novel data-driven approach used for modelling developmental trajectories (i.e., changes in an outcome over time) [24]. Unlike traditional analytic methods, GBTM can be used to categorize trajectories (distinct patterns over time) of ART adherence and can utilise multiple indicators of an outcome of interest simultaneously [25]. This element of GBTM is essential in ART adherence literature, particularly for adolescents, as it captures the variability in their long-term adherence behaviour. To date, few studies in SSA (mostly among adult populations) have utilised GBTM to describe ART adherence trajectories [26-28]. Applying GBTM to identify these trajectories among adolescents may be useful in the tailoring and targeting of adherence support interventions and focusing on adolescents at risk of poor

adherence and subsequent treatment failure rather than all ALHIV [29]. Given that adolescence is a period characterised by physical, sexual, emotional, and psychological development, which may influence adherence and changes over time, [30] we hypothesize that GBTM will delineate distinct trajectories of adherence over time among ALHIV. We further examine the relationship between ART adherence trajectories and durable viral suppression.

5.3. Methods

Study design

This analysis is based on a three-wave cohort study of ALHIV conducted in the Eastern Cape province of South Africa between 2014 and 2018. In the Buffalo City District in the Eastern Cape province, we identified 53 health facilities (community healthcare centres, hospitals, and primary health clinics) that provided HIV care to adolescents. In each facility, all patient files were reviewed to identify adolescents who had initiated ART and were aged 10-19 years. Eligible ALHIV (n=1176) were approached for study participation and recruited in health facilities or traced back into their home communities [31], to ensure the inclusion of those no longer engaged in care. Of all study-eligible adolescents 1046 were recruited and participated at the baseline of the study in 2014-2015, 979 (94.0%) of these were followed up at the second wave (2016-2017) of the study, 953 (91.1%) at the third wave (2017-2018), and 35 (3.4%) died during the study period. A more detailed description of the study design and data collection procedures is available elsewhere [32, 33] and further study information, including study protocol, is available at www.mzantsiwakho.org.za.

Ethical approvals were granted by the University of Cape Town (UCT/CSSR/2013/4) and (UCT/CSSR/2019/01), Oxford University (Oxford/CUREC2/12-21), provincial Departments of Health and Education, NHLS Academic Affairs and Research Management System (2019/08/07) and the ethical review boards of participating healthcare facilities. At all study waves, adolescent participants and their caregivers (when adolescents were <18 years old) provided voluntary written informed consent for participation in their language of choice (Xhosa or English), including interviews and access to adolescents' medical records.

Study data and procedures

The sample for the current analysis included adolescents who participated at all three study visits. At each study visit, data was collected using tablet-based standardized questionnaires

(translated into the local language: isiXhosa) that assessed adolescents' experiences at home, in their communities, and healthcare settings, including self-reported ART adherence. The questionnaires were designed to be non-stigmatising through extensive consultation with South African ALHIV, included graphics and vignettes to introduce questions about sensitive topics. Tools were pre-piloted on n=25 adolescents at baseline [34]. Adolescents then completed the questionnaire at each study visit—in their communities or at clinics—in their preferred language (English or Xhosa), with the help of trained research assistants.

Data were collected on sociodemographic characteristics, including age (divided into 10-14 and ≥15 year age groups), sex, urban/rural residence, and access to eight socially perceived necessities for children and adolescents validated in a nationally representative South African Social Survey (e.g. enough food) [35]. HIV treatment factors included knowledge of HIV status, [36] estimated or self-reported time on ART (years), and mode of HIV acquisition. Mode of HIV acquisition (perinatally versus sexually acquired HIV) was defined following existing sub-Saharan African paediatric cohorts: age of ART initiation cut-off [≤10 years] [37] validated and updated with a detailed algorithm that considered other strong evidence (i.e. self-reported sexual history and parental death) in the absence of definitive clinic notes ascribing mode of HIV acquisition [38].

Self-reported data on ART adherence was also collected at each visit using various measures on missed doses—with varying recall timeframes—and missed clinic appointments. The measures used in this analysis included four on missed doses *in the past 3 days*, *past week,* and *past month and any past-month days missed* adapted from the Patient Medication Adherence Questionnaire, [39] and one on *missed clinic appointments* which was added to the questionnaire based on recommendations from other studies [34, 40]. All adherence measures were dichotomised and positively coded to represent adherence. These five measures showed good test accuracy against viral load (VL) ≥ 1000 copies/mL and have been described in full elsewhere [41].

Following the completion of the study waves, adolescents' VL test data (2014-2019) were obtained through the National Health Laboratory Services (NHLS) routine laboratory data at the National Institute for Communicable Disease (NICD) data warehouse of South Africa. The NICD archives all routine laboratory data from public-sector health facilities including from facilities outside the study catchment area. Demographic information (name, surname, sex, and date of birth) for adolescents in the cohort was used to link laboratory test records in

the NICD data warehouse. Given that the dates of VL test results were in line with the participant's clinic VL monitoring schedule and did not always match the study visit dates, VL results were assigned to each visit if they were within 12 months from the adolescents' interview date. For participants with more than one result within this window, we selected the VL result closest to the study visit date. The median interval between the date of the selected VL result and the study visit was two months (interquartile range: 1 to 5 months), across all three study visits. The mean interval between VL records assigned at Wave 1 and Wave 2 was 19 months; for those at Wave 2 and Wave 3, the interval was 15 months. Each of these aligns with the mean interval between study visits: 18 and 14 months, respectively. We defined viral suppression as VL <1000 copies/ml.

Data Analysis

Primary exposure: ART adherence trajectories as categorized by GBTM based on five self-reported adherence measures.

Outcome measure: The outcome measure was durable viral suppression, defined as having a suppressed VL (<1000 copies/mL) at 2 or more consecutive study waves.

5.3.1. Statistical Analysis

We used GBTM, a specialised finite mixture model first introduced by Nagin and colleagues [25] to identify groups of adolescents that follow similar longitudinal progressions of adherence over time [24]. This model assumes that the overall population is made up of distinct, unobserved subpopulations that follow different behavioural patterns [25]. To identify adolescents' groups that follow joint adherence trajectories using multiple (five binary measures) indicators over three time points, we performed a multi-trajectory analysis which is an extension of the GBTM that simultaneously estimates joint trajectories for multiple indicators [24].

The following steps were taken to identify the number and shape of adherence trajectory groups. Since the number of groups and the order of the trajectory polynomials (i.e., linear, quadratic, cubic) are not known a priori, we first tested a series of model specifications with varying the number of groups systematically to determine the appropriate number of trajectory groups. The second step entailed visual inspections for the interpretability of the trajectories and determining trajectory shapes across a series of model specifications. To determine model fit, consistency, and the optimal number of trajectory groups, we considered the following criteria: (1) Bayesian information criteria (BIC) with smaller values indicating

better fit, (2) within each group, the average posterior probability of group membership was compared 0.7 threshold (values greater than 0.7 indicate adequate internal reliability or acceptable classification), (3) assessed the tightness of the confidence intervals around the estimated group membership probabilities, (4) compared the odds of correct classification (OCC) with a minimum threshold of 5, (5) compared the probability that a model with j groups is the correct model from a set of J different models (the best-fitted model has a probability close to one) [24]. Additionally, we aimed for the smallest group to have at least 5% of the sample [42]. Since our five adherence measures were all dichotomous, adherence was modelled assuming a binomial distribution and a logit link function. The GBTM model was estimated using *Traj* plugin in Stata version 17.1 (StataCorp, College Station, Tx, USA).

Descriptive Statistics

First, we assessed differences between trajectory groups by sociodemographic and HIV-related characteristics using the chi-squared, Kruskal-Wallis, or Fisher's exact tests. Second, we used multinomial logistic regression to assess the association between baseline factors and trajectory group membership. Our model included an interaction between age group and sex. We estimated predictive margins to report the results as the expected distribution of trajectory across baseline characteristics.

Adherence Trajectories and Durable Viral Suppression

We used a multivariate logistic regression model to assess the association between adherence trajectory groups and durable viral suppression, controlling for known confounders measured at baseline. Potential confounders were selected based on literature and expert knowledge. This analysis was limited to participants with VL data at 2 or more study visits during the study period. A sensitivity analysis of the associations between adherence trajectories and durable viral suppression using alternative viral load cut-offs (50 and 400 copies/mL respectively) to define durable viral suppression was conducted. We also used the chi-squared (χ^2) test to compare the baseline characteristics of those participants included in the outcome versus those who did not meet the criteria for durable viral suppression. All analyses were conducted with Stata version 17.1 (Stata Corp LLC, College Station, TX).

5.4. Results

Participant characteristics

Of the 1046 ALHIV recruited in this study, N=933 (89.1%) completed all three study waves, which formed our analytic sample. The analytical sample comprised 55.1% females and the mean age of 13.6 years (SD=2.9) at baseline. About one-third resided in rural areas and two-thirds reported lacking at least one of the eight basic necessities. The majority (78.7%) had acquired HIV sexually and median time on ART was 4.7 years (IQR: 2.7, 7.3). Two-thirds of the participants knew their HIV status (Table 5.1). Among female participants, 105 (20.4%) had been ever pregnant across the three waves, with 63.8% of these reported at baseline.

Table 5.1: Baseline participant characteristics (N=933)

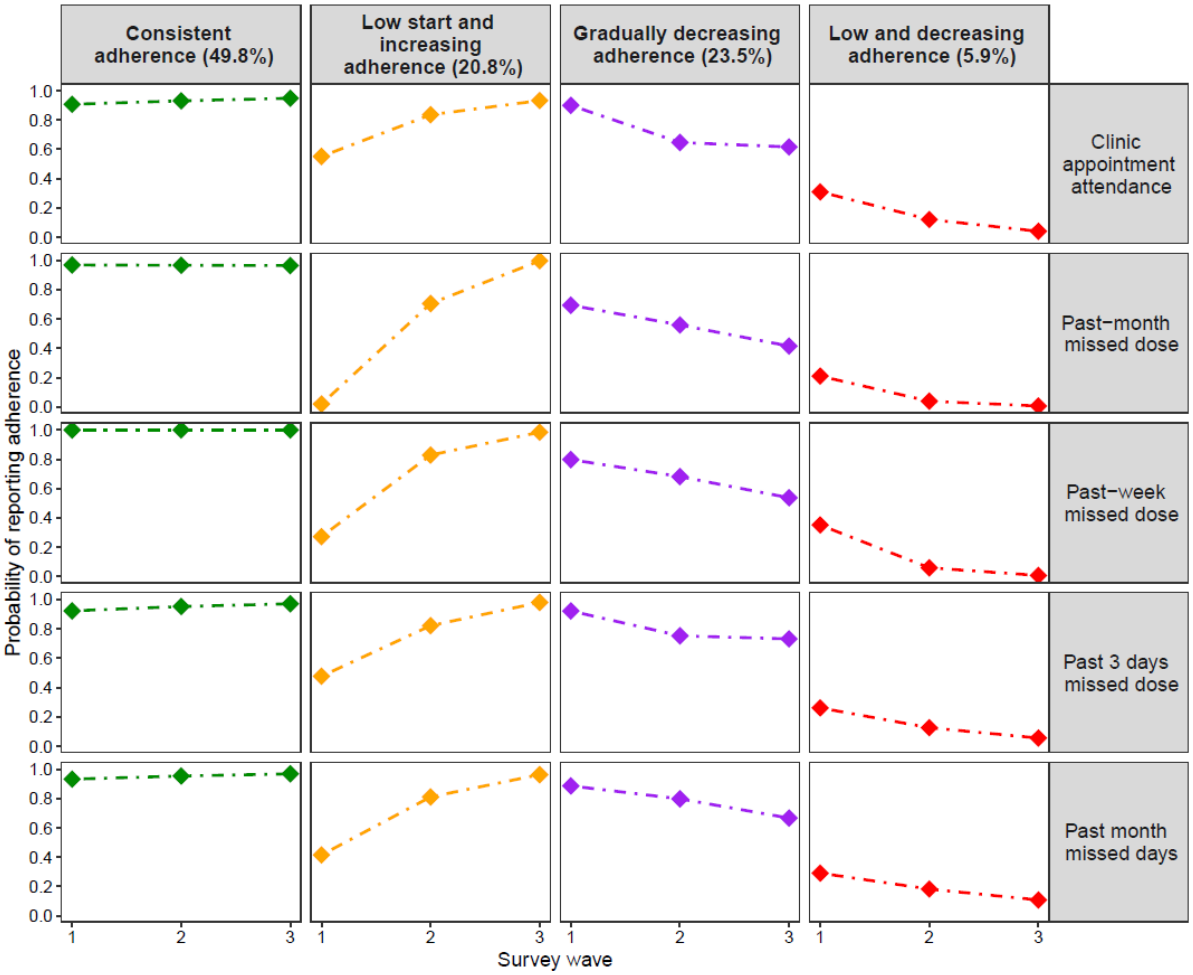
Characteristic	N (%)
Age (mean/SD)	13.6 (2.9)
Age group	
<15 years	609 (65.3%)
≥15 years	324 (34.7%)
Sex	
Male	419 (44.9%)
Female	514 (55.1%)
Place of residence	
Urban	684 (73.3%)
Rural	249 (26.7%)
Socio-economic factors	
Access to eight basic necessities	300 (32.2%)
HIV treatment factors	
Knowledge of HIV status	627 (67.2%)
Mode of HIV acquisition	
Perinatally	734 (78.7%)
Sexually	199 (21.3%)
Time on ART (median/IQR: years)	4.7 (2.2, 7.3)

Description of adherence trajectory groups

Based on the five self-reported adherence measures, GBTM revealed four distinct trajectories of adherence to ART (Figure 5.1). The first trajectory group "consistent adherence" was made up of adolescents who were more likely to report adherence across all measures at all three waves, accounting for 49.8% of the sample. The second trajectory group "low start and increasing adherence," 20.8% of the sample, was made up of adolescents who were less likely to report adherence early in the period, who then improved after baseline. The third group "gradually decreasing adherence," 23.5% of the sample, were adolescents who reported adherence early in the period (on all measures) but then decreased gradually after

baseline. The fourth group "low and decreasing adherence," 5.9% of the sample, comprised adolescents who were less likely to report being adherent across all measures throughout the study period. The model with four trajectory groups was identified as optimal based on the information criterion (BIC), good separation of groups, and interpretability (Supplementary Table 5-2). The average posterior probabilities for each group were greater than 0.7 and ranged from 0.94 to 0.97. Odds of correct classification, measuring improvement in membership probability of individuals belonging to trajectory group 1 compared to all other trajectory groups, which were all greater than 5, suggesting a reasonable fit for the model (Supplementary Table 5-3).

Figure 5.1: Longitudinal adherence trajectories by adherence measure (4-group model)



*Estimated longitudinal trajectories for adolescents that were categorised into four groups based on group-based multi-trajectory analysis. Since the adherence measures were dichotomous, the y-axis represents the percentage who reported adherence based on each item in each trajectory group. All adherence measures were coded positively, 1 (adherence) and 0 (non-adherence). Columns represent trajectory groups, while rows represent adherence indicators.

Baseline factors associated with trajectory group membership.

The distribution of adolescents' characteristics in each trajectory group is shown in Table 5.2, Table 5.3 and Supplementary Table 5-1. Overall, age, sex, place of residence, access to eight basic necessities, mode of HIV acquisition, and time on ART were statistically significantly different between the trajectory groups. In multinomial logistic regression, participants in the "consistent adherence" group were most likely to be younger adolescents (<15 years) with perinatally acquired HIV (Table 5.3). Participants in the "low start and increasing adherence" group were more likely to be older females, to reside in a rural residence at baseline, and to have sexually acquired HIV. Participants in the "gradually decreasing adherence" group were most likely to be older males (≥15 years) at baseline. Participants in the "low and decreasing adherence" group were more likely to be older females with sexually acquired HIV and shorter time on ART. Despite these patterns, however, overall differences in the distribution of distinct trajectory groups across baseline characteristics were small.

Table 5.2: Distribution of baseline participant and HIV-related characteristics by trajectory group (N=933)

	Consistent adherence (N=465, 49.8%)	**Low start and increasing adherence (N=194, 20.8%)**	**Gradually decreasing adherence (N=219, 23.5%)**	**Low and decreasing adherence (N=55, 5.9%)**	
Baseline characteristics	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**p-value**
Age (mean/SD)	13.1 (2.69)	14.1 (3.02)	13.6 (2.89)	15.3 (2.95)	**<0.001**
Age group					**<0.001**
<15 years	143 (65.3%)	112 (57.7%)	333 (71.6%)	21 (38.2%)	
≥15 years	76 (34.7%)	82 (42.3%)	132 (28.4%)	34 (61.8%)	
Sex					**<0.001**
Male	114 (52.1%)	73 (37.6%)	218 (46.9%)	14 (25.5%)	
Female	105 (47.9%)	121 (62.4%)	247 (53.1%)	41 (74.5%)	
Place of residence					**0.007**
Urban	175 (79.9%)	126 (64.9%)	344 (74.0%)	39 (70.9%)	
Rural	44 (20.1%)	68 (35.1%)	121 (26.0%)	16 (29.1%)	
Socio-economic factors					
Access to eight basic necessities	160 (34.4%)	47 (24.2%)	78 (35.6%)	15 (27.3%)	**0.037**
HIV-related factors					
Knowledge of HIV status	155 (70.8%)	128 (66.0%)	311 (66.9%)	33 (60.0%)	0.440
Mode of HIV acquisition					**<0.001**
Perinatally	169 (77.2%)	140 (72.2%)	400 (86.0%)	25 (45.5%)	
Sexually	50 (22.8%)	54 (27.8%)	65 (14.0%)	30 (54.5%)	
Time on ART (median/IQR: years)	5.1 (2.8, 7.8)	4.2 (1.8, 6.9)	4.4 (1.8, 7.3)	2.6 (1.4, 5.2)	**0.001**

Table 5.3: Predicted probabilities of trajectory group distribution across baseline adolescent's characteristics from multinomial logistic regression (N=933).

Baseline characteristics	Consistent adherence (N=465, 49.8%)	Low start and increasing adherence (N=194, 20.8%)	Gradually decreasing adherence (N=219, 23.5%)	Low and decreasing adherence (N=55, 5.9%)
Age group				
<15 years Male	53.6% (48.1%-59.1%)	16.5% (12.5%-20.5%)	27.8% (22.8%-32.7%)	2.2% (0.8%-3.5%)
<15 years Female	53.9% (48.5%-59.3%)	21% (16.6%-25.5%)	21.2% (16.9%-25.6%)	3.9% (1.8%-5.9%)
≥15 years Male	45.8% (38.4%-53.2%)	21.4% (15.2%-27.5%)	27.4% (20.7%-34.2%)	5.4% (1.8%-9.1%)
≥15 years Female	44.3% (37.6%-51.1%)	26.2% (20.1%-32.3%)	20.2% (15%-25.3%)	9.3% (4.9%-13.8%)
Place of residence				
Urban	49.7% (46.1%-53.4%)	18.7% (15.7%-21.6%)	25.4% (22.2%-28.7%)	6.1% (4.3%-7.9%)
Rural	50.2% (44.1%-56.4%)	26.4% (21%-31.9%)	18% (13.2%-22.8%)	5.4% (2.9%-7.9%)
Socio-economic factors				
Access to eight basic necessities	53.4% (47.6%-59.1%)	16.7% (12.3%-21.1%)	26.2% (21.1%-31.3%)	3.7% (1.4%-6.1%)
HIV-related factors				
Knowledge of HIV status				
Yes	45.7% (40.1%-51.3%)	22.2% (17.2%-27.2%)	20.8% (16.1%-25.6%)	11.3% (6.8%-15.7%)
No	51.5% (47.6%-55.4%)	19.7% (16.6%-22.8%)	24.4% (21.1%-27.8%)	4.4% (2.9%-5.8%)
Mode of HIV acquisition				
Perinatally	53.7% (50%-57.4%)	19.9% (16.9%-22.9%)	22.7% (19.6%-25.7%)	3.7% (2.2%-5.1%)
Sexually	35.8% (28.4%-43.2%)	24.2% (17.9%-30.6%)	27.6% (20.6%-34.5%)	12.4% (7.4%-17.4%)

Durable viral suppression by trajectory group membership

Of the 933 ALHIV, 655 (70.2%) participants had VL data at 2 or more visits across the study period and thus had sufficient VL tests to be included in this analysis. A comparison between those included versus those excluded showed no differences (Supplementary Table 5-4), except that those excluded were likely to be older and not aware of their HIV-positive status. The rates of viral suppression decreased over time across all trajectory groups, and the decrease was higher among adolescents in the inconsistent adherence trajectories (Supplementary Figure 5-1). The *"low and decreasing adherence"* group had the lowest rates of viral suppression at all study waves. Of those with sufficient VL data (N=655), 359 (54.8%) had durable viral suppression. Table 5.4 summarises the unadjusted and adjusted estimates of the association between adherence trajectory membership and durable viral suppression from the logistic regression model. Compared to the *"consistent adherence"*

group, the *"low start and increasing adherence"* group (aOR: 0.62, 95%CI 0.41-0.95, p=0.029), the *"gradually decreasing adherence"* group (aOR: 0.40, 95%CI 0.27-0.59, p<0.001), and the *"low and decreasing adherence"* group (aOR: 0.25, 95%CI 0.10-0.62, p=0.003) had significantly lower odds of durable viral suppression.

Table 5.4: Logistic regression models of the association between trajectory membership and durable viral suppression (VLS) (N=655)

Outcome	**Durable viral suppression¥**			
Characteristic	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Trajectory group				
Consistent adherence (Reference)	1		1	
Low start and increasing adherence	**0.54 (0.36-0.81)**	**0.003**	**0.62 (0.41-0.95)**	**0.029**
Gradually decreasing adherence	**0.40 (0.27-0.59)**	**<0.001**	**0.40 (0.27-0.59)**	**<0.001**
Low and decreasing adherence	**0.18 (0.07-0.43)**	**<0.001**	**0.25 (0.10-0.62)**	**0.003**
Baseline characteristics				
Age (15+ years)	-	-	**0.66 (0.44-0.98)**	**0.042**
Female	-	-	1.18 (0.85-1.65)	0.322
Rural residence	-	-	**0.66 (0.46-0.96)**	**0.030**
Access to eight basic necessities	-	-	1.29 (0.92-1.83)	0.144
Knowledge of HIV status	-	-	0.79 (0.54-1.17)	0.247
Sexually acquired HIV	-	-	0.71 (0.43-1.16)	0.174
Time on ART (years)	-	-	1.03 (0.98-1.08)	0.325

¥Sub-sample analysis of those with at least 2 viral load measurements. Durable viral suppression was defined as having at least two viral loads <1000 copies/ml across the three study waves. OR odds ratio; aOR-Adjusted odds ratio. A comparison of the participants included (N=655) and (N=278) not included (Supplementary Table 4-3), showed no differences on most baseline characteristics, except that participants excluded were more likely to be older and less likely to know their HIV status.

Further assessment of the associations between adherence trajectories and durable viral suppression using lower VL thresholds—50 and 400 copies/ml respectively—to define durable viral suppression showed similar and consistent results, reflecting that even small reductions in adherence can lead to measurable increases in viral replication (Table 5.5).

Table 5.5: Association between adherence trajectory membership and durable viral suppression defined using lower VL cut-offs 50 and 400 copies/ml (N=655).

Outcome	Durable viral suppression[¥]			
	Model 1 (50 copies/ml)		Model 2 (400 copies/ml)	
Characteristic	**aOR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Trajectory group				
Consistent adherence (Reference)	1		1	
Low start and increasing adherence	**0.64 (0.42-0.99)**	**0.045**	**0.65 (0.43-0.99)**	**0.047**
Gradually decreasing adherence	**0.52 (0.35-0.77)**	**0.001**	**0.43 (0.29-0.64)**	**<0.001**
Low and decreasing adherence	**0.27 (0.10-0.76)**	**0.012**	**0.29 (0.12-0.73)**	**0.008**
Baseline characteristics				
Age (15+ years)	0.68 (0.45-1.01)	0.056	**0.79 (0.53-1.18)**	**0.256**
Female	1.30 (0.93-1.82)	0.121	1.16 (0.83-1.61)	0.376
Rural residence	**0.62 (0.42-0.91)**	**0.014**	**0.61 (0.43-0.89)**	**0.009**
Access to eight basic necessities	1.05 (0.74-1.48)	0.792	1.21 (0.86-1.71)	0.271
Knowledge of HIV status	**0.67 (0.46-0.98)**	**0.040**	0.76 (0.52-1.11)	0.148
Sexually acquired HIV	0.87 (0.52-1.45)	0.596	0.67 (0.41-1.10)	0.115
Time on ART	1.04 (0.98-1.09)	0.190	1.03 (0.98-1.08)	0.318

[¥]Sub-sample analysis of those with at least 2 viral load measurements within the study period. For Model 1, durable viral suppression is defined based on a viral suppression cut-off of 50 copies/ml while in Model 2, the outcome is defined based on a cut-off of 400 copies/ml. aOR- adjusted odds ratio.

5.5. Discussion

GBTM revealed four latent trajectories of adherence to ART amongst South African ALHIV, with approximately 5.9% in the low and decreasing adherence group and about half (49.8%) classified in the consistent adherence group. The rest of the adolescents were grouped into the low start and increasing adherence (20.8%) and the gradually decreasing adherence trajectories (23.5%). While it is encouraging that about half of the ALHIV in this study were classified in the consistent adherence group, the remaining trajectories reflected inconsistent adherence over time. These inconsistent adherence trajectories had lower odds of durable viral suppression compared with adolescents who followed the consistent adherence trajectory. The consistency of the association between durable viral suppression and adherence trajectories across viral load thresholds (1000, 400 and 50 copies/ml) underscores the importance of promoting consistent adherence to ensure durable viral suppression. Given the lack of evidence on adherence trajectories among adolescents, these findings provide

initial evidence on the evolution of adherence (self-reported) over time and its effects on viral load outcomes among ALHIV in South Africa.

Our study further identified a few baseline characteristics associated with adherence trajectory group membership. Participants in the "consistent adherence" group were more likely to be younger adolescents (<15 years) with perinatally acquired HIV, while those in the "low and decreasing adherence" group were more likely to be older females (≥ 15 years) with the least median time on ART, who acquired HIV sexually. These findings corroborate existing evidence, which shows that younger adolescents rely more on their primary caregivers for clinic visits and ART uptake, [43] while recent HIV diagnoses coupled with increasing responsibility for self-health care among older adolescents [44] can result in failure to adapt to medication routines [31] contributing to poor adherence. Participants in the "gradually decreasing adherence" group were more likely to be older males (≥ 15 years). This may be explained in part by societal norms of manhood and healthcare engagement, [45] and increased mobility associated with older adolescents as they transition out of school towards a search for livelihoods leading to disengagement from HIV care [46]. Participants in the "low start and increasing adherence" group were more likely to be older females (≥ 15 years) who sexually acquired HIV and live in rural residences. This group may have poor access to care which may lead to delays in establishing workable ART medication routines hence poor adherence at the start [47]. There was no significant association between knowledge of HIV status and the categorization into four adherence trajectories. This may be partly explained by the fact that the majority of adolescents already knew their HIV status at baseline, [36] potential confounding effects of age at ART initiation and the duration of ART, [48] or that the disclosure process or pattern may influence adherence more than knowledge of status [49].

The heterogeneity observed in the adherence trajectories among ALHIV in this study is very relevant to improving their HIV-related health outcomes, given that it is highly associated with VL outcomes. This study showed that, compared to the group who were more likely to report adherence consistently over time ("consistent adherence"), the remaining groups were associated with significantly lower odds of durable viral suppression. Therefore, the extent to which the variations in long-term adherence influence adolescents' health treatment outcomes is noteworthy. These findings highlight the importance of understanding the dynamics of adherence to anticipate changes in adolescents' capacity to sustain adherence. Moreover, it is

important that we support adolescents to adhere to their ART treatment at the start and retain adherence over time, which is associated with improved HIV treatment outcomes. Overall, current strategies targeting high-risk adolescents should utilize this understanding of longitudinal adherence trajectories to guide the development of tailored support and intervention strategies—which are critical to improving adolescents' treatment outcomes [12, 50].

Characterizing longitudinal trajectories of adherence provides a more nuanced understanding of adolescents' ART adherence than more traditional metrics. However, little is known about the dynamics of adherence among adolescents over time. Previous research using self-reported measures of ART adherence [44, 51] mostly employed traditional metrics such as proportions, which may mask heterogeneity and inconsistencies in adherence over time [52]. Even in longitudinal studies, heterogeneity between adolescents is obscured by population-level averages [53]. Moreover, most of these studies use single or composite measures of adherence. A few studies among adult populations living with HIV have assessed adherence trajectories over time [26-28]. For example, a study among adults in the Swiss HIV Cohort Study using data on self-reported missed doses identified four behavioural groups associated with specific adherence patterns namely: good, worsening, improving, and poor adherence [54]. The adherence trajectory groups identified in these previous studies are generally comparable with those in the current study, although most of these studies use singular indicators to define trajectories among adult populations. The current study extends this work in three ways: first, by applying multi-trajectory GBTM to examine adherence trajectories among ALHIV–a group with relatively poor HIV-related outcomes and high mortality [12, 41]; second, by using multiple (five) indicators of self-reported adherence, which may reduce measurement bias; and third, by conducting these analyses using cohort data from resource-limited settings in South Africa.

This study is not without limitations. First, we use self-reported adherence measures which are prone to social desirability bias and recall bias [55-59]. However, the questionnaire was administered by research assistants trained to work with adolescents, and outside of routine HIV care reducing the risk of social desirability bias. Second, the assignment of adolescents into distinct trajectory groups only represents systematic attempts to characterize and classify adolescents based on the available data, which may lead to classifications that do not seem intuitive. However, model fit diagnostics indicated a good fit for the data with clear distinct

trajectory groups. Third, VL data used in this analysis did not match the questionnaire dates exactly, and 29.8% did not have sufficient VL data to be included in the analysis of durable suppression, which may bias the relationship between adherence trajectories and viral suppression. Fourth, this study excluded adolescents who died (N=35, 3.4%) or were lost-to-study follow-up (N=78, 7.5%) in estimating trajectories, which may underestimate the extent of inconsistent adherence over time. However, there were no significant differences between participants excluded in the analysis and those retained, other than that those excluded were likely to be older and not aware of their HIV-positive status [41]. Fifth, the age of the data may impact the relevance of these findings to current practice. The strength of this study is that it is longitudinal and includes multiple self-reported indicators of adherence from a sample of ALHIV. Therefore, findings from this study may be generalizable to other countries in sub-Saharan Africa as well as other resource-constrained settings. Overall, these findings demonstrate the utility of self-reported measures for adherence monitoring among ALHIV over time. Future research should seek to understand why adolescents fall into these adherence trajectory groups and identify malleable factors contributing to the distinct groups of ALHIV over time. Additional research is also needed to establish at what point in the care of an adolescent trajectories can be assigned. Further exploration of trajectories could potentially assess other thresholds or multiple categories of adherence measures, instead of dichotomising each item (any vs none).

In conclusion, our study demonstrates that adherence to ART remains a major challenge among ALHIV in the Eastern Cape province in South Africa because about half (50.2%) of the adolescents reflected inconsistent adherence trajectories over time. Our analysis further shows that the adolescent population is composed of distinct groups with different adherence behaviour trajectories and varying degrees of risk of viral non-suppression over time. This nuanced understanding of the heterogeneity in adolescent ART adherence behaviours over time ultimately paves the way to a shift from one-size-fits-all approaches and may be useful in developing tailored behavioural interventions or support programs for ALHIV.

5.6. Supplementary Tables and Figures:

Supplementary Table 5-2: Model fit statistics

Model	Log-likelihood	BIC (N=933)	AIC	>5% per group	p_j^*
1 group	-6821.69	-6872.97	-6836.69	Yes	<0.001
2 groups	-5907.14	-5989.20	-5931.14	Yes	<0.001
3 groups	-5641.54	-5730.44	-5667.54	Yes	<0.001
4 groups	**-5349.57**	**-5503.43**	**-5394.57**	**Yes**	**0.972**
5 groups	-5346.30	-5507.01	-5393.30	No	0.027

*The probability that a model with j groups is the correct model from a set of J different models- if close to one then would be considered the best-fitted model

¥ $p_j = \frac{e^{BIC_j - BIC_{max}}}{\sum_{j=1}^{J} e^{BIC_j - BIC_{max}}}$ where BIC_{max} is the maximum score of different J models.

Supplementary Table 5-3: Summary of trajectory allocation (4-group model)

Trajectories	N	Average posterior probability for each group	Odds of correct classification (un-weighted)	Odds of correct classification (weighted)	Observed probability of groups	Total proportion
Trajectory 1	465	0.953	20.60	21.55	0.498	0.487
Trajectory 2	194	0.941	60.30	61.73	0.208	0.204
Trajectory 3	219	0.940	54.33	49.97	0.235	0.250
Trajectory 4	55	0.971	538.4	540.9	0.060	0.057

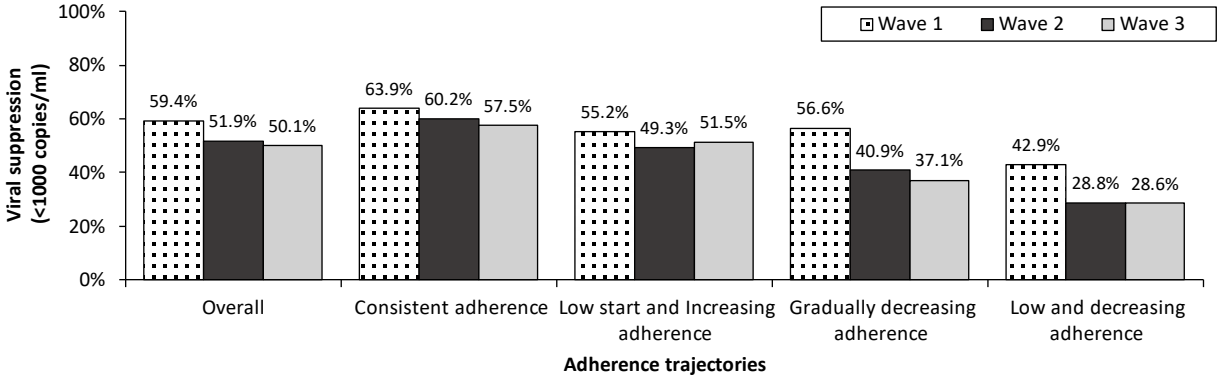
Supplementary Table 5-4: Comparison of baseline characteristics for included versus those excluded (N=933)

	Total (N=933)	Included (N=655)	Excluded (N=278)	p-value
Baseline characteristics	**N (%)**	**N (%)**	**N (%)**	
Age (15+ years)	324 (34.7%)	206 (31.5%)	118 (42.5%)	**0.001**
Female	514 (55.1%)	359 (54.8%)	155 (55.8%)	0.790
Rural residence	249 (26.7%)	174 (26.6%)	75 (26.9%)	0.896
Poverty	633 (67.9%)	438 (66.9%)	195 (70.1%)	0.328
Knowledge of HIV status	627 (67.2%)	456 (69.6%)	171 (61.5%)	**0.016**
Sexually acquired HIV	199 (21.3%)	136 (20.8%)	63 (22.7%)	0.517

Supplementary Table 5-5: Multinomial logistic regression of the association between baseline adolescent's characteristics and four adherence trajectories (N=933).

	Consistent adherence (N=465, 49.8%)	Low start and increasing adherence (N=194, 20.8%)		Gradually decreasing adherence (N=219, 23.5%)		Low and decreasing adherence (N=55, 5.9%)	
Baseline characteristics	**Reference group**	**aOR (95%CI)**	**p-value**	**aOR (95%CI)**	**p-value**	**aOR (95%CI)**	**p-value**
Age group (15+ years)	1	1.50 (0.99-2.28)	0.057	1.14 (0.77-1.69)	0.516	2.94 (1.39-6.21)	**0.005**
Female	1	1.24 (0.87-1.77)	0.240	0.73 (0.52-1.02)	0.067	1.85 (0.94-3.62)	0.075
Rural residence	1	1.45 (0.99-2.10)	0.052	0.72 (0.48-1.08)	0.108	0.86 (0.44-1.66)	0.645
Access to eight basic necessities	1	0.67 (0.45-0.98)	**0.039**	1.09 (0.78-1.54)	0.604	0.90 (0.47-1.75)	0.763
Knowledge of HIV status	1	0.76 (0.51-1.13)	0.169	1.04 (0.71-1.51)	0.852	0.31 (0.16-0.62)	**0.001**
Mode of HIV acquisition	1	1.67 (1.02-2.75)	**0.043**	1.55 (0.96-2.52)	0.075	5.65 (2.65-12.1)	**<0.001**
Time of ART (<2 years)	1	1.27 (0.84-1.92)	0.261	1.43 (0.97-2.11)	0.069	0.86 (0.43-1.73)	0.679

Supplementary Figure 5-1: Differences in viral suppression rates across four adherence trajectories among ALHIV with viral load measurements at 2 or more study visits (N=655)



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CHAPTER 6. Age-specific all-cause mortality rates among adolescents and youth living with HIV in South Africa.

Zhou, S., Toska, E., Gwampi, B., Johnson, LF., Tolmay, J., Saal, W., Knight, L., Cluver, L. Age-specific all-cause mortality rates among adolescents and youth living with HIV in South Africa. *Manuscript submitted to the Journal of International AIDS Society.*

Relevance of this paper to the thesis:

Existing evidence shows that mortality remains high among ALHIV compared to all other age groups. However, there have been few mortality evaluations for ALHIV and no disaggregated data on mortality for this group. This paper explores rates of all-cause mortality among adolescents disaggregated by HIV status and sex and compares age-adjusted, sex-stratified mortality rates by mode of HIV acquisition. The paper further examines differences in all-cause mortality across longitudinal trajectories of ART adherence among adolescents.

Contribution of the student and co-authors:

SZ conceptualised and led the statistical analyses including writing the full draft of the manuscript. ET, BG, JK, LFJ, JT, WS, LK and LC reviewed and provided feedback on the manuscript content. All authors approved the final draft which is being prepared for submission to Plos One. ET and LC designed and implemented the overall study.

6.1. Abstract

Background: Mortality among adolescents living with HIV (ALHIV) remains a global health problem. We lack granular (age- and sex-disaggregated) data on mortality among ALHIV, hence this study aims to assess all-cause mortality among ALHIV in a low-resource setting.

Methods: All adolescents ever initiated on antiretroviral therapy (ART), N=1107 (70.8%) and their HIV-negative peers (N=456) aged 10-19 years, recruited as part of the Mzantsi Wakho study cohort, were followed up between 2014 and 2022 (yielding 12427.7 person-years of follow-up). First, we assessed the proportion of deaths stratified by HIV status, sex, and mode of HIV acquisition (vertical vs sexual). We then estimated crude mortality incidence rates per 100 person-years of follow-up and their 95% CIs, stratified by age, sex and mode of HIV acquisition. Last, we estimated adjusted incidence rate ratios (IRR) using Poisson regression adjusted for time-varying age, sex, and time on ART.

Results: A total of 1563 adolescents and young people were included in this analysis, comprising 1107 (70.8%) ALHIV and 57% female. More deaths occurred in ALHIV compared to their HIV-negative peers (8.3% versus 0.4%, p<0.001). Among ALHIV, we observed a significantly higher proportion of deaths among males compared to females (10.7% vs 7.1%, p=0.036). Mortality rates increased as age increased for both males and females across both mode of HIV acquisition groups. Comparing mortality rates by mode of HIV acquisition, overall mortality rate ratios were similar for both males (IRR: 1.02/100 person-years; 95% CI: 0.46–2.25) and females (IRR: 1.03/100 person-years; 95% CI: 0.52–2.07). Among youth aged 20+ years, mortality risk was higher among females who acquired HIV vertically (IRR =3.61, 95% CI: 1.48–8.82) compared to females who acquired HIV sexually. In a sub-sample analysis sustained ART adherence was associated with a lower risk of death (aHR=0.43, 95%CI 0.22-0.83).

Conclusion: Adolescents and youth living with HIV experience higher all-cause mortality than their HIV-negative peers, despite having initiated ART. Among ALHIV, mortality risk was higher among males and older females who acquired HIV vertically. Strategies to improve survival among ALHIV, including adolescent-tailored care and support for adherence to ART, are urgently needed.

6.2. Introduction

Adolescents and youth represent a growing proportion of people living with HIV worldwide [1]. About 90% of the world's population of adolescents living with HIV (ALHIV) live in sub-Saharan Africa [2-4] and South Africa alone has the highest number of HIV infections worldwide [5]. As of 2021, over 421,100 adolescents were estimated to be living with HIV in South Africa [6, 7]. Despite being initiated on ART, adolescents continue to experience life-threatening health vulnerabilities which significantly impact their survival [1, 8, 9].

Studies of mortality in adults who initiate ART—in early disease—generally show that they have life expectancies close to HIV-negative adults of the same age [10, 11]. However, there have been a few similar investigations for ALHIV. Existing evidence shows that mortality among adolescents and youth living with HIV remains high compared to all other age groups [12, 13]. Suboptimal adherence to ART has been cited as one of the factors which makes adolescents vulnerable to morbidity and mortality [3, 14]. To address this, adolescent-centred interventions are needed to improve health outcomes and reduce mortality in this population group. However, there is a dearth of disaggregated data on mortality for this group to guide these interventions, or to inform the most widely used global estimates of HIV indicators such as UNAIDS estimates [12]. Current data are characterized by inconsistencies due to small sample sizes, limited follow-up periods, and gaps. Other data—from clinics or hospitals—are not representative of overburdened government health services, do not include comparison with HIV-negative peers, and there is a lack of capacity to know if they dropped out, moved, or died.

The objectives of this paper are two-fold. First, we explore incidence rates of all-cause mortality among adolescents disaggregated by HIV status and sex and compare age-adjusted, sex-stratified mortality rates by mode of HIV acquisition (vertical vs sexual). Second, we explored differences in all-cause mortality rates by ART adherence using cohort data from ALHIV.

6.3. Methods

Study design and setting

This prospective cohort study of ALHIV was conducted in the Eastern Cape province of South Africa, a province characterized by challenges in meeting social and human development goals, poor infrastructure, and the highest percentage of people living below the

poverty line in the country [15], with an estimated overall HIV prevalence of 15.8%, and an adult prevalence of 25.2% (ages 15-49) [16, 17].

Study population and data collection

Mzantsi Wakho is a prospective cohort study of adolescents (aged 10-19 years), ever initiated on ART recruited from 52 government health facilities (identified through medical records review) in the Eastern Cape province of South Africa. To ensure a representative sample of ALHIV, participants were traced to their communities, homes, or schools, including those who had disengaged from care or been lost to follow-up (LTFU). This study also recruited and interviewed HIV-negative peers (N=456) from neighbouring homes and co-resident adolescents to minimize stigma. The adolescents (N=1563) were followed up three times from 2014 to 2018 and completed a self-reported questionnaire on their health experiences at home, in their communities, and in healthcare settings with the support of research assistants trained in working with vulnerable adolescents. An additional follow-up check-in was conducted on all participants between 2021 and 2022 using a short version of the questionnaire as part of long-term cohort maintenance, including participant mobility and mortality.

Ethics approval

Ethical approvals were obtained from the University of Cape Town (UCT/CSSR/2013/4, UCT CSSR/2022/01) and (UCT/CSSR/2019/01), Oxford University (Oxford/CUREC2/12-21). Data-sharing agreements were obtained from provincial Departments of Health and Education, and the review boards of participating healthcare facilities. Participants and their caregivers (when adolescents were <18 years old) provided voluntary written informed consent for participation at all study waves including follow-up check-ins. There were no financial incentives for study participation, but all participants received a certificate of participation, snacks, and a small gift pack. Adolescents who refused to participate were still given snacks and a small gift pack.

Outcome: All-cause mortality

We ascertained all-cause mortality through community-based reporting i.e., caregiver reports or reports from relatives for the adolescents followed up between 2014 (baseline) and 2022. Baseline was defined as the date of study entry (Wave 1 interview date). Follow-up time included the time from the Wave 1 interview date until death (for those who died) or

November 8, 2022 (for living participants). Person-time was defined as an estimate of the actual time-at-risk – in years– that all participants contributed to the study (calculated for the follow-up period: 2014-2022). For this analysis, data were censored when the following appeared first (1) death, (2) lost-to-study follow-up (censored at the last interview or contact date), and (3) alive (censored at the end of follow-up). Since we did not have the exact date of death for the majority of participants, we used the median dates between the previous date of contact and the latest date of follow-up as an estimate of the date of death.

Key variables

Mode of HIV acquisition (vertical vs sexual) was determined by following standard methods in sub-Saharan African paediatric cohorts: age of ART initiation ≤10 years [18, 19], validated and updated with a detailed algorithm that considered other factors (i.e. self-reported sexual history and parental death) in the absence of definitive clinic notes or data ascribing mode of HIV acquisition [20]. The age of ART initiation cut-off before age 10 years was selected as a conservative proxy for participants who acquired HIV through mother-to-child transmission.

Antiretroviral (ART) Adherence: Five self-reported measures of adherence were evaluated for sensitivity in detecting elevated viral load [21]. These five measures included missed doses in the past three days, last missed dose –past week and –past month, and any missed clinic appointment adapted from the Patient Medication Adherence Questionnaire [22] and the clinic appointment measure was added based on recommendations from other studies [23]. All five measures had high test accuracy in detecting elevated viral load (sensitivity over 75%) and were significantly associated with viral load [21]. The five measures were then used to categorise adherence over the three time points, into four distinct longitudinal trajectories using Group-based trajectory modelling (GBTM) [24]. The four distinct adherence trajectories were consistent adherence, low start and increasing adherence, gradually decreasing adherence, and low start and decreasing adherence described in more detail elsewhere [24]. The derived categorical ART adherence trajectories were used as an outcome in the sub-sample analysis assessing differences in mortality rates by adherence patterns. We defined sustained adherence as 1 if the participant categorised in the consistent adherence trajectory and 0 otherwise.

6.3.1. Statistical Analysis

Analyses were conducted in Stata (version 17.0, College Station, StataCorp LP, TX). First**,** we calculated the all-cause mortality rates stratified by HIV status and sex. We then described mortality outcomes among ALHIV by mode of HIV acquisition. Second, we estimated crude mortality rates per 100 person-years of follow-up, stratified by age (10–14, 15–19, and 20+ years) and sex across adolescent HIV acquisition groups (vertical and sexual). Since age is time-varying, to estimate mortality by age-at-risk, we conducted Lexis expansion on the data to stratify follow-up into age-specific intervals [25]. This converts the one observation per person to one observation for each age (time) interval per person so that each participant contributes to each age stratum until death or censoring [25]. Mortality rates were calculated as the number of deaths divided by the total number of person-years of follow-up for each age group and sex stratum using the *stptime* function in Stata. Third, we used Poisson regression with robust variances [25] to estimate adjusted incidence rate ratios (IRR) of mortality and their 95% CIs for ALHIV with vertically acquired HIV compared to those with sexually acquired HIV. All IRRs were adjusted for time-varying age (10–14, 15–19, and 20+ years), sex, and time on ART treatment. Fourth, we used the Kaplan–Meier approach to describe differences in cumulative incidence of mortality by sustained adherence. The log-rank test was used to determine the statistical significance of the mortality differences. Last, we use the Cox proportional hazards regression model to estimate the risk of all-cause mortality (death) by ART adherence adjusting for age, sex, mode of HIV acquisition and time on ART treatment. This is a sub-sample analysis of those who completed the questionnaire at all three-time points (survivors of the immortal period) to remove immortal bias [26, 27].

6.4. Results

Overall, 1563 adolescents aged 10-19 years at baseline had a follow-up (post-ART initiation) between 2014 and 2022, yielding 12427.7 person-years of follow-up. Table 6.1 shows the characteristics at baseline and mortality outcomes by HIV status. The majority of the participants were living with HIV and contributed 8722.7 person-years of follow-up while HIV-negative contributed 3705 person-years of follow-up. Across these two groups, the proportion of female participants was similar (57% for ALHIV versus 60.3% for HIV-negative peers). Mortality was high among ALHIV, and they were 18 times more likely to die during adolescence than their HIV-negative peers: (8.7% vs 0.4%, $p<0.001$) over the four

years. Furthermore, among ALHIV, we observed a significantly higher proportion of deaths among males compared to females (10.7% vs 7.1%, p=0.036).

Table 6.1: Baseline characteristics and mortality among adolescents and youth in a South African cohort (N=1563) by HIV status

	ALHIV	**HIV-negative**
	Adolescents n (%)	**Adolescents n (%)**
Overall	1107 (70.8%)	456 (29.2%)
Person-years	8722.7	3705
Baseline characteristics		
Age (years): median (IQR)	13 (11-16)	15 (12-17)
Female (%)	631 (57%)	275 (60.3%)
Reported deaths		
Overall	96 (8.7%)	2 (0.4%)
Sex		
Male	51 (10.7%)	1 (0.6%)
Female	45 (7.1%)	1 (0.4%)

Mortality outcomes among adolescents and youth living with HIV

Table 6.2 shows the characteristics of mortality for ALHIV. Among ALHIV, 833 (75.2%) acquired HIV vertically and contributed 6625.2 person-years with a median age at ART initiation of 7 years, and a median of eight years on ART treatment. The remaining 274 acquired HIV sexually and contributed 2097.5 person-years with a median age at ART initiation of 16 years and median time on treatment of four years. Overall, more females had sexually acquired HIV than vertically acquired HIV (75.9% vs 50.8%, p<0.001). Overall, the rates of mortality for both adolescent HIV acquisition groups were comparable (8.9% versus 8.0% respectively). Comparing rates by sex, we observed a higher proportion of deaths among males than females for both those who acquired HIV vertically (10.5% versus 7.3%) and sexually (12.1% versus 6.7%).

Table 6.2: Baseline characteristics and mortality among adolescents and youth in a South African cohort (N=1107) by mode of HIV acquisition.

	ALHIV with vertically acquired HIV	**ALHIV with sexually acquired HIV**
	n (%)	**n (%)**
Overall	833 (75.2%)	274 (24.8%)
Person-years	6625.2	2097.5
Baseline characteristics		
Female (%)	423 (50.8%)	208 (75.9%)
Age at ART initiation (years): median (IQR)	7 (3-10)	16 (12-18)
Time on ART treatment: median (IQR)	8 (5, 12)	4 (2, 6)
Reported deaths		
Overall	74 (8.9%)	22 (8.0%)
Sex		
Male	43 (10.5%)	8 (12.1%)
Female	31 (7.3%)	14 (6.7%)

Among ALHIV who acquired HIV vertically, the overall mortality incidence rate was 1.12/100 person-years (95%CI: 0.88-1.40) (Figure 6.1 and Supplementary Table 6-1). Mortality rates increased as age increased and was over four-fold higher among 20+ years olds (4.46/100 person-years; 95%CI: 3.09-6.21) compared to 15-19 years (0.98/100 person-years; 95%CI: 0.68-1.37) and 10-14 years (0.32/100 person-years; 95%CI 0.14-0.63). Among ALHIV who acquired HIV sexually, the overall mortality incidence rate was 1.05/100 person-years (95% CI: 0.66-1.58), which is similar to the mortality incidence rate estimated among those who acquired HIV vertically (1.12/100 person-years, 95%CI: 0.88-1.40). There were no significant differences in mortality rates across age groups or by sex.

Figure 6.1: Mortality incidence rates per 100 person-years and 95% confidence intervals, by time-updated age and sex among ALHIV.

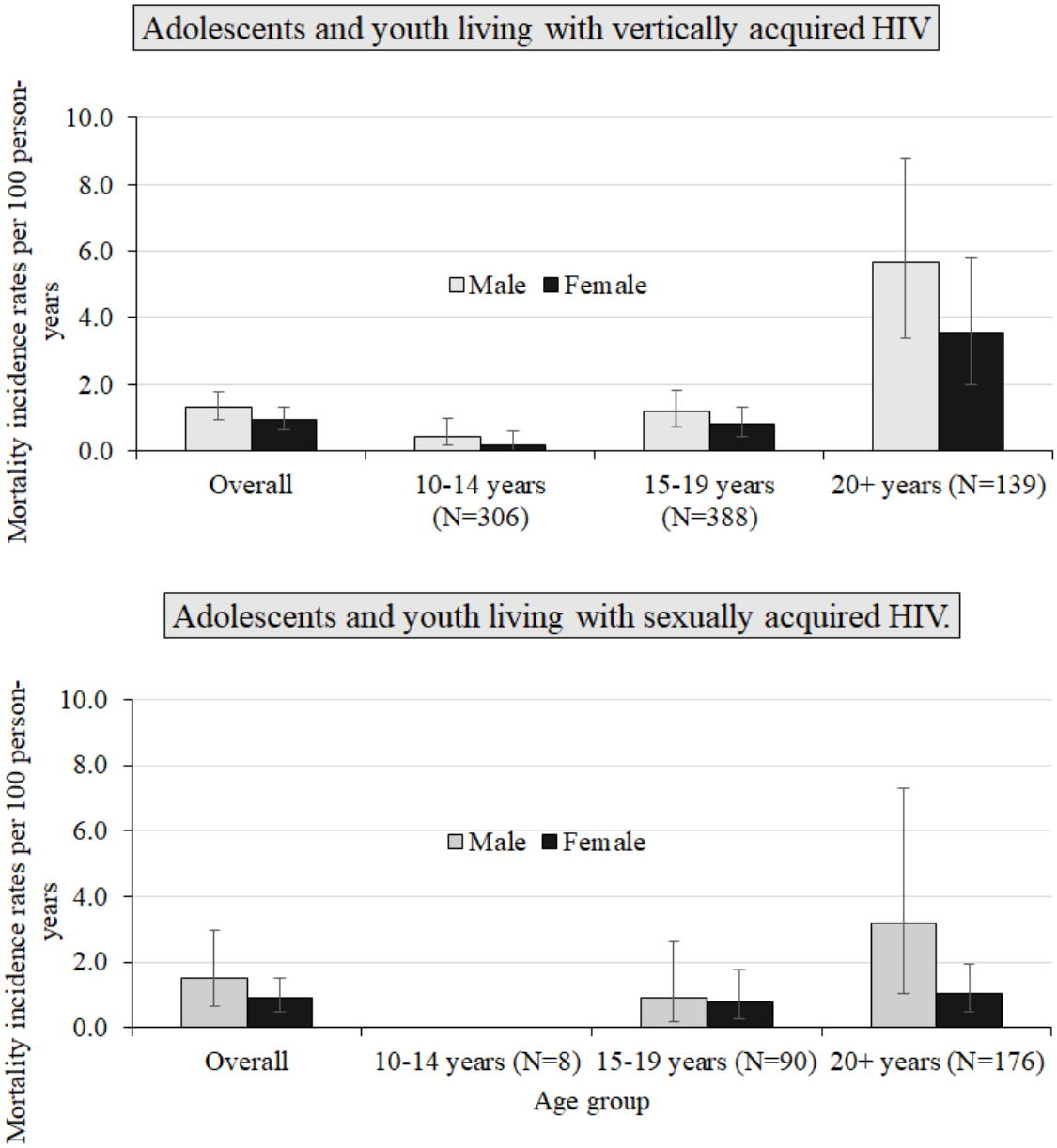
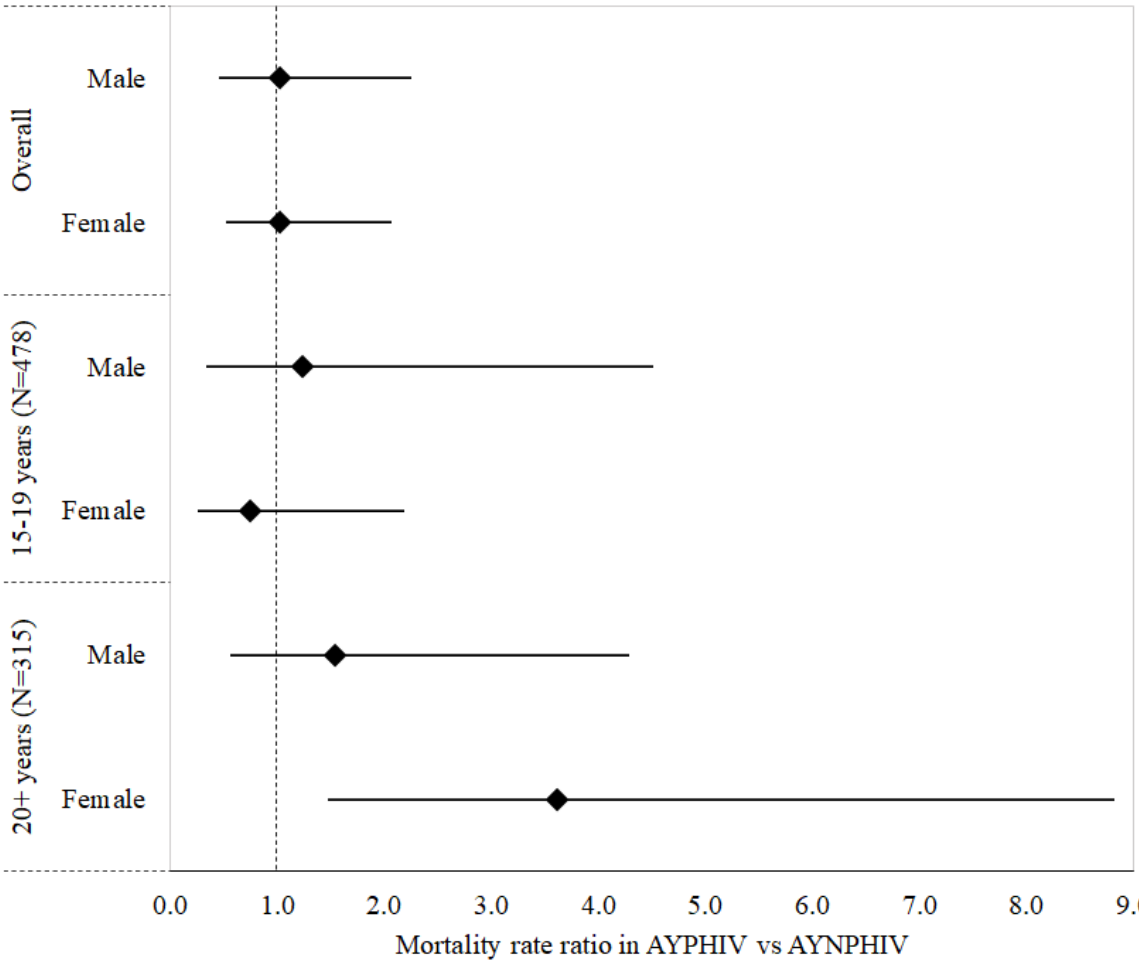


Figure 6.2 and Supplementary Table 6-2 show the mortality incidence rate ratios (IRR) comparing vertical vs sexual acquisition groups, stratified by sex and time-updated age adjusted for time on treatment. Overall, we found no significant differences in mortality incidence rates between these adolescent HIV acquisition groups, in both males and females. These results were similar for the 15–19-year-olds. However, for 20+ year-olds, we found a higher risk of mortality for vertical compared to the sexual HIV acquisition group among females (IRR =3.61, 95% CI: 1.48–8.82).

Figure 6.2: Mortality incidence rate ratios (IRR) comparing mode of HIV acquisition groups, stratified by sex and time-varying age.



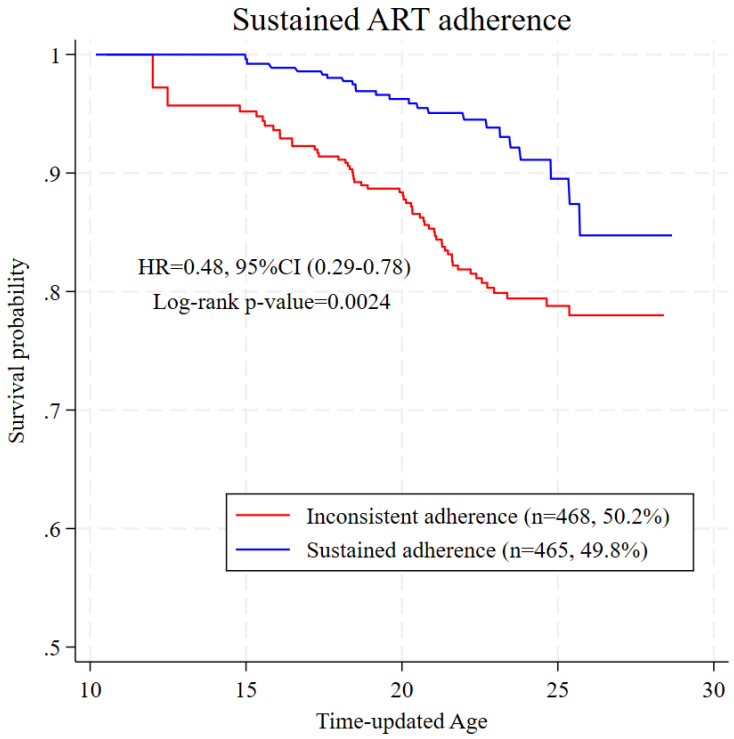
*The 10-14 age group was dropped from Figure 2 as there were no deaths in the sexually acquired HIV group, such that the ratio is undefined.

All-cause mortality rates by ART adherence

A total of 933 adolescents and youth living with HIV were interviewed across all three time points and were categorised into four longitudinal ART adherence trajectories [28]. The proportion of deaths by adherence trajectory group was: 8.2% gradually decreasing, 5.3% low start and increasing, 5.1% consistent adherence and 9.1% low start and decreasing group. In total, 6.1% (N=57) of adolescents and youth died after the third wave of data collection. There were noticeably different risks of mortality based on trajectory group membership (Supplementary Figure 6-1). The results suggest a dose-dependent relationship—although not statistically significant—between mortality and various adherence trajectories, with mortality decreasing consistently as ART adherence improves. Overall, compared to all other trajectory groups combined, adolescents with sustained ART adherence (consistent adherence

trajectory) had significantly higher survival rates than those with inconsistent adherence (log-rank p=0.0024) (Figure 6.3). The risk of death was 57% lower in adolescents with sustained adherence than in those with inconsistent adherence over time (aHR, 0.43; 95% CI 0.22–0.83; p=0.013) after adjusting for covariates (Supplementary Table 6-3).

Figure 6.3: Kaplan–Meier estimates of all-cause mortality by ART adherence (N=933).



¥HR- hazard ratio for adolescents. CI-confidence interval.

6.5. Discussion

This study provides disaggregated data on all-cause mortality by HIV status, age, sex, and mode of HIV acquisition using a large prospective cohort of adolescents from a low-resource setting in South Africa. In this study, we make several observations. First, we observed higher proportions of deaths among ALHIV compared to HIV-negative peers. We further observed significantly higher proportions of deaths among ALHIV males compared to ALHIV females. Second, among adolescents with vertically acquired HIV, we observed higher overall mortality rates in those aged 20+ years compared with those aged 10–14 years and 15–19 years. No significant differences in mortality rates by age were observed among adolescents with vertically acquired HIV. Third, overall mortality rates were comparable by mode of HIV acquisition, however, for 20+year-old females, we found a higher risk of

mortality for those with vertical compared to those with sexually acquired HIV. Fourth, compared to adolescents with inconsistent adherence to ART over the follow-up period, those with sustained adherence had significantly lower rates of all-cause mortality time (aHR=0.29; 95% CI 0.16–0.54).

Despite a notable decline in mortality among people living with HIV since the introduction of antiretroviral therapy (ART) [29], we observed significantly higher all-cause mortality among ALHIV compared to their HIV-negative peers. This finding is similar to those reported in other studies [30-32]. It suggests that although survival has improved considerably among ALHIV due to advancements in ART and care, a significant gap remains in this population compared with the general population. We further found marked sex differences in the proportions of deaths, with higher mortality among males than in females. These sex differences have been noted in several studies [31, 33, 34], for example, a Global Burden of Disease Study assessing the global burden of adolescent mortality showed that sex differences in adolescent mortality continue to widen in most regions of the world [34]. These differences are likely to be driven by poor progress in reducing deaths in males and older adolescents [33] and may reflect the increasing burden of deaths due to violence and substance misuse, which predominantly affect young men [35]. As adolescents age into adulthood, more data on the cause of death will be needed to allow for more accurate assessments.

Among adolescents with vertically acquired HIV, 8.9% died and the overall estimated mortality rate was 1.12/100 person-years compared to 8.0% (overall mortality incidence rate: 1.05/100 person-years) among ALHIV with sexually acquired HIV. These rates were comparable among both males and females in both groups of ALHIV and are similar to those reported in other cohorts of ALHIV in Southern Africa [33, 36]. For older, female adolescents and youth aged 20 years and above, we observed significantly higher mortality rates (3.61 times) among those with vertically acquired HIV compared to those with sexually acquired HIV. This may be partly explained by the fact that female adolescents who have acquired HIV more recently may be benefiting from early diagnosis, improved care, and the availability of modern ART. In turn, this group may have a lower risk of mortality compared to female adolescents with vertically acquired HIV [4], a group with long-term exposure to limited paediatric formulations of ART regimens which may have led to drug resistance and subsequent poor virological response [37]. Moreover, as female adolescents

living with vertically acquired HIV grow they face a transition from dependence on adult caregivers for ART adherence support to becoming responsible for their health, which may impact their treatment outcomes [38]. Lastly, older female adolescents and youth aged 20 years and above are of reproductive age, hence may experience challenges related to pregnancy, with those living with vertically acquired HIV at greater risk of pregnancy related complications [39, 40].

This analysis also found that ALHIV with sustained ART adherence had a 57% lower risk of death compared to those who had inconsistent adherence over the study follow-up period. The observed dose-dependent relationship between mortality and various adherence trajectories underscores the importance of sustaining high adherence to reduce mortality risk. These findings are consistent with research documented in other low- and middle-income countries [41-43] that demonstrate that adherence to ART can prolong survival among ALHIV. Empirical research suggests that poor adherence to ART leads to viral non-suppression, reductions in CD4 T cell count, increased risk of HIV transmission, and subsequent clinical failure, which increases the risk of death [44]. Therefore, sustained adherence to ART is critical to the survival of ALHIV.

This study has limitations which need to be considered when interpreting the findings. First, it describes all-cause mortality as we were not able to ascertain the cause of death for the participants. Further studies could investigate the cause of death among adolescents, which was not possible with this dataset. Although we asked family members about what happened, we were unable to verify the cause of mortality and the cause of mortality is poorly documented due to limited diagnostic testing in these study settings, particularly among people living with HIV [45]. Second, the use of median dates for the date of death may bias the estimated rates of mortality. Third, the focus on adolescents 10 to 19 years of age results in a survivor bias, as individuals with vertically acquired HIV would have had to survive childhood to be eligible for inclusion. Fourth, neighbouring and co-resident young people may still have significant differences in mortality—clustering effects which we were not powered enough to assess. The key strength of this study is that we used appropriate HIV-negative peers as a comparison group. Future analyses should further describe the socio-economic and clinical characteristics such as the history of ART interruption.

This study provides mortality data disaggregated by HIV status, age, and sex, as well as comparing mortality by mode of HIV acquisition. Most importantly, we found that ALHIV

have high mortality rates compared to their HIV-negative peers, indicating that a significant gap in mortality persists between these two groups, despite substantial improvements in life expectancy achieved through advances in HIV care and treatment. Moreover, the high mortality rates among ALHIV suggest an urgent need to prioritize their vulnerabilities including enhancing ART adherence support for adolescents and addressing inequities to improve life expectancy. There is also an urgent need to improve the availability and quality of mortality data, including the causes of death in ALHIV to inform UNAIDS estimates for low-resource settings [14].

6.6. Supporting Tables and Figures

Supplementary Table 6-1: Mortality incidence rates (per 100 person-years) and 95% confidence interval among adolescents and youth living with HIV and on ART during follow-up, by sex and time-updated age.

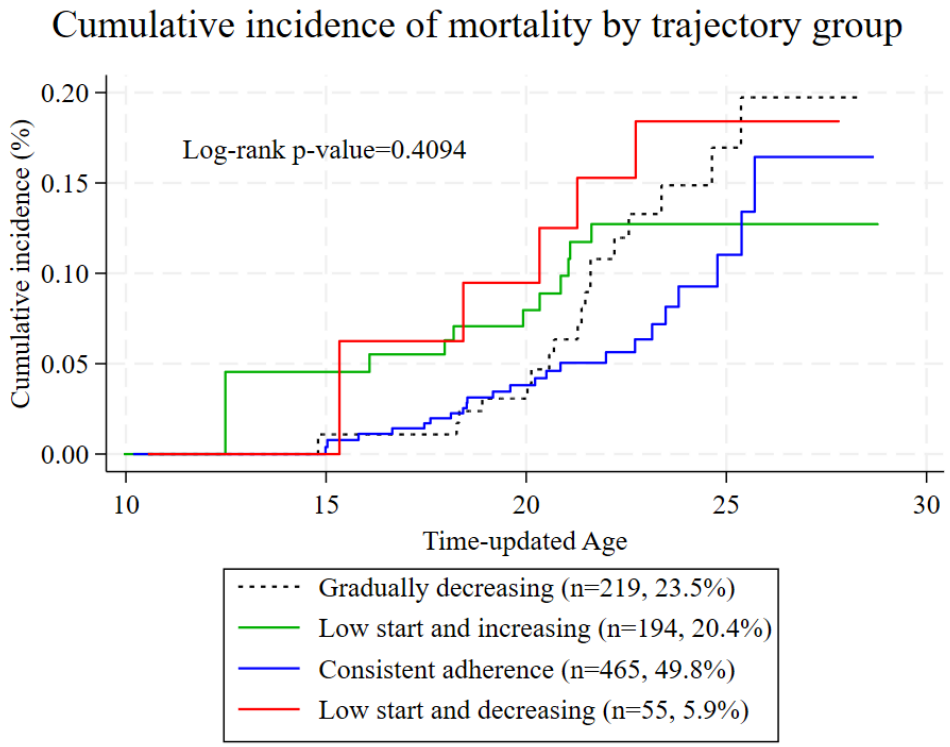
	AYPHIV			AYNPHIV		
Time-varying age	**Male**	**Female**	**Overall**	**Male**	**Female**	**Overall**
10-14 years	0.45 (0.17-0.98)	0.17 (0.02-0.61)	**0.32 (0.14-0.63)**	-	-	-
15-19 years	1.18 (0.71-1.84)	0.79 (0.43-1.33)	**0.98 (0.68-1.37)**	0.91 (0.19-2.64)	0.76 (0.25-1.77)	**0.81 (0.35-1.60)**
20+ years	5.66 (3.39-8.80)	3.56 (2.01-5.81)	**4.46 (3.09-6.21)**	3.18 (1.04- 7.28)	1.02 (0.47- 1.93)	**1.35 (0.74-2.25)**
Overall	**1.32 (0.96-1.78)**	**0.92 (0.62-1.30)**	**1.12 (0.88-1.40)**	**1.52 (0.66-2.97)**	**0.89 (0.49-1.49)**	**1.05 (0.66-1.58)**

Supplementary Table 6-2: Mortality incidence rate ratios among adolescents and youth living with vertically acquired HIV compared with those living with sexually acquired HIV, stratified by sex and time-updated age.

	Male		Female	
	IRR[a]	**95% CI[b]**	**IRR[a]**	**95% CI[b]**
Overall	**1.02**	**(0.46-2.25)**	**1.03**	**(0.52-2.07)**
Age-group				
10-14 years	-	-	-	-
15-19 years (N=478)	1.24	(0.34-4.52)	0.75	(0.26-2.19)
20+ years (N=315)	1.54	(0.56-4.29)	3.61	(1.48-8.82)

[a] Incidence rate ratio.
[b] 95% confidence interval.

Supplementary Figure 6-1: Kaplan–Meier estimates of the cumulative incidence of all-cause mortality by trajectory group (N= 933).



Supplementary Table 6-3: Adjusted Cox proportional hazards model results: Predicting all-cause mortality by sustained ART adherence (N=933)

Variables	aHR (95%CI)	P-value
Sustained adherence	0.43 (0.22 - 0.83)	**0.013**
Baseline age (15+ years)	2.32 (0.86 - 6.26)	0.096
Female	0.56 (0.32 - 0.96)	**0.035**
Rural residence	0.75 (0.39 - 1.43)	0.381
Time of treatment (years)	0.96 (0.89 - 1.04)	0.354
Sexually acquired HIV	0.69 (0.32 - 1.50)	0.350

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CHAPTER 7. Exploring socio-ecological barriers contributing to distinct longitudinal trajectories of antiretroviral adherence among adolescents in South Africa.

Zhou, S., Toska, E., Knight, L., Cluver, L. Exploring socio-ecological barriers contributing to distinct longitudinal trajectories of antiretroviral adherence among adolescents in South Africa. *Manuscript being prepared for submission to the Lancet Child & Adolescent Health.*

Relevance of this paper to the thesis:

This paper seeks to understand factors that shape distinct ART adherence trajectories among ALHIV. In particular, it focuses on baseline barriers of adherence and explores pathways linking them to distinct longitudinal trajectories. This paper is anchored by the socio-ecological model, which informed the hypothesised relationships between barriers to adherence. This paper confirmed some of the direct relationships between several barriers and adherence and further identified indirect pathways linking co-occurring multi-level barriers to longitudinal adherence that were unique for each trajectory.

Contribution of the student and co-authors:

SZ conceptualised the analysis with guidance from ET and LK. SZ conducted all the statistical analyses and wrote the full manuscript draft. All authors reviewed the manuscript and provided feedback on the content. All authors approved the final draft which is being prepared for submission to the Lancet Child & Adolescent Health. ET and LC designed and implemented the overall study.

7.1. Abstract

Background: Adherence to antiretroviral therapy (ART) among adolescents remains low and is influenced by many barriers. No studies have explored the integrative pathways linking these barriers to longitudinal ART adherence trajectories among adolescents living with HIV (ALHIV). Anchored by socio-ecological theory, this study explored the mechanisms linking socio-ecological barriers to longitudinal ART adherence using adolescent cohort data.

Methods: We used data from a prospective cohort of 1046 adolescents living with HIV (55% female aged on average 13.8 years), conducted in the Eastern Cape Province of South Africa. Adolescents aged 10-19 were recruited at baseline (2014) and followed up twice between 2016 and 2018. The ART adherence outcome was categorised into four distinct longitudinal trajectories modelled over three study waves, namely: (1) consistent adherence, (2) low start and increasing adherence, (3) gradually decreasing adherence, and (4) low start and decreasing adherence. Bivariate logistic regression was used to select baseline barriers for inclusion ($p<0.20$) in subsequent path models —for each trajectory depicting inconsistent adherence over time— compared with the consistent adherence trajectory. Path analysis examined the direct (DE) and indirect (IE) associations of baseline individual, household, community, and healthcare barriers and longitudinal adherence trajectories.

Results: Experiencing any mental health symptoms (aOR^{DE}=1.33, 95%CI 1.07-1.67), and medication side effects (aOR^{DE}=1.33, 95%CI 1.04-1.72) at baseline were directly associated with the low start and increasing adherence trajectory, while experiencing food insecurity (aOR^{DE}=1.42, 95%CI 1.02-2.0) and clinic travel time (>1 hour) (aOR^{DE}=1.60, 95%CI 1.12-2.28), was directly associated with the gradually decreasing adherence trajectory. Any mental health symptoms (aOR^{DE}=1.49, 95%CI 1.02-2.21), medication side effects (aOR^{DE}=1.86, 95%CI 1.25-2.77), internalised HIV stigma (aOR^{DE}=2.30, 95%CI 1.55-3.44), clinic travel time (>1 hour) (aOR^{DE}=2.72, 95%CI 1.15-6.43), and witnessing domestic violence or conflict (aOR^{DE}=1.67, 95%CI 1.01-2.78) was directly associated with the low start and decreasing adherence trajectory. The association between medication side effects and low start and increasing adherence trajectory was partially mediated by experiencing any mental health symptoms (aOR^{IE}=1.14, 95%CI 1.02-1.31), while the association between emotional bullying and low start and increasing adherence trajectory was fully mediated by mental health symptoms (aOR^{IE}=1.12, 95%CI 1.01-1.25). The pathways linking co-occurring barriers, and mental health symptoms to longitudinal adherence were unique for each trajectory.

Conclusions: Our findings show that unique pathways linking socio-ecological barriers contribute to the dynamic nature of ART adherence. Indirect pathways point to existing multi-level mechanisms leading to distinct adherence trajectories among ALHIV. Present findings suggest the need to be sensitive to adolescents' experiences to interrupt pathways of risk to poor ART adherence. These findings may inform the development of support interventions by clarifying when and how to target adherence support for ALHIV.

7.2. Introduction

The health and social benefits of the use of lifelong antiretroviral therapy (ART) are dependent on sustained adherence to ART to achieve long-term viral suppression [1, 2]. Despite the scale-up of access to ART and implementation of differentiated HIV care services [3], adolescents living with HIV (ALHIV) in sub-Saharan Africa (SSA) continue to experience sub-optimal ART adherence compared to adults and younger children, leading to poorer HIV treatment outcomes [4-7]. Therefore, a nuanced understanding of barriers to attaining sustained ART adherence for this population —and strategies to alleviate these—is thus paramount.

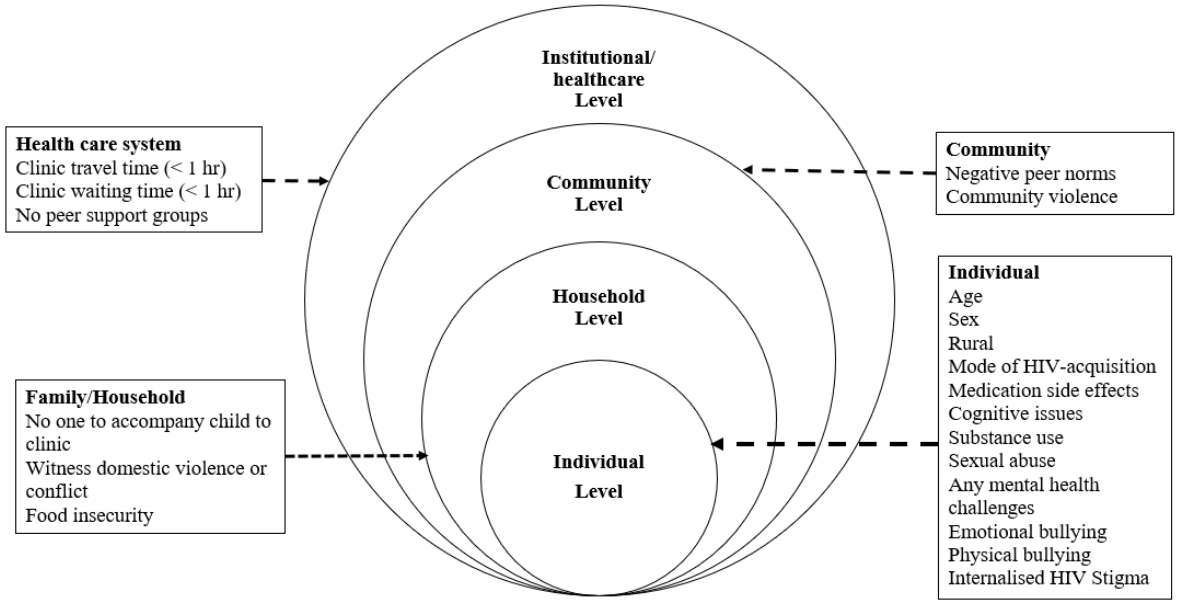
The socio-ecological model is widely accepted as a framework to describe the interrelatedness between people and their environment, and how factors along multiple levels interact and influence health behaviour [6, 8]. Practically, adherence is a complex and dynamic process involving a complex interplay of individual (e.g., mental health issues [9]), household (e.g., food insecurity [10]), community (e.g., HIV-related stigma [10, 11]), healthcare (e.g., clinic proximity [12]), and structural-level barriers (e.g., poverty [13, 14]) (Figure 7.1) [8, 15, 16]. These barriers may interact within and across these multiple levels and compound their influence on ART adherence. However, no studies have empirically tested the socio-ecological models using longitudinal data on ART adherence—categorised as longitudinal trajectories—to explore potential pathways of risk linking multi-level barriers to adherence patterns among ALHIV. Most quantitative studies measure direct relationships [17], and the few studies that have investigated pathways linking factors associated with ART adherence, have mostly used data from adults living with HIV [18-20] or have relatively smaller sample sizes [18, 21, 22]. Moreover, most of these studies focus on singular specific pathways, for example, the mediation pathways between economic empowerment and ART adherence [22, 23].

Most studies assessing barriers to ART adherence use models (e.g., multiple regression analyses) that do not capture the relationships between these barriers. For example, low socio-economic status is associated with poor adherence but this effect may be mediated through food insecurity [20]. In addition, most evidence is largely cross-sectional and dichotomises adolescents into adherence and non-adherence groups, which do not appropriately reflect how these barriers influence changes in adherence among ALHIV over time [24]. Longitudinal data offers a unique opportunity to use structural equation models to

disentangle potential sequential and integrative pathways through which multi-level barriers contribute to changes in long-term ART adherence [8, 20]. The use of the trajectory ART adherence outcome compared to traditional definitions of adherence will enable us to isolate pathways of risk for unique groups of adolescents based on their longitudinal trajectories which is essentially for targeting adherence support.

This study aims to identify pathways of associations between individual, household, community and healthcare barriers and ART adherence trajectories among ALHIV in South Africa. It examines factors identified by previous quantitative and qualitative research on barriers to ART adherence among ALHIV and is guided by the socio-ecological model to hypothesize and test pathways of risk.

Figure 7.1: Hypothesized pathways linking individual, household, community, and health care barriers to ART adherence outcomes among ALHIV –Adaptation of the socio-ecological model.



*Individual-level factors comprise biological and behavioural characteristics, including some HIV and ART-related factors. Household-level factors comprise family, social, and interpersonal factors. The distal level factors comprise of the community (group-level relationships with organisations such as schools and peers, social community- neighbours and others within social networks) and institutional (healthcare-related) factors. The structural level was excluded from the analysis due to data limitations, and we assumed that the sample is a homogeneous group from the same population affected by similar structural factors.

7.3. Methods

Study design and data

This analysis is based on a longitudinal cohort study of ALHIV conducted in South Africa's Eastern Cape. Adolescents who had ever-initiated HIV care were recruited from 52 health facilities (primary health clinics, community healthcare centres, and hospitals) providing HIV care to adolescents identified in the Buffalo City District [25]. At each healthcare facility, patient registers were reviewed to identify all adolescents aged 10–19 years who had ever initiated ART. To ensure the inclusion of those who were no longer engaged in care, adolescents were then traced into their communities, homes, or schools, approached for study participation, and completed a standardised questionnaire at their preferred location. Baseline questionnaires were administered in 2014-2015, with a follow-up in 2016-2017 and a second follow-up in 2017-2018.

Adolescent self-reported questionnaires- Adolescents completed tablet-based standardized questionnaires in their preferred language (isiXhosa or English), with the support of research assistants trained in working with South African adolescents. Questionnaires assessed adolescents' experiences at home, in their communities, and in healthcare settings including self-reported adherence at each of the three time points over four years. The questionnaires were designed to be non-stigmatising by including graphics, interactive activities, and vignettes to introduce questions around sensitive topics, designed through extensive stakeholder consultation, including with South African ALHIV, and pre-piloted (n=25 adolescents) at baseline. The questionnaires were adapted at each successive survey wave based on prior data collection, with feedback from participants and the study team to ensure age-appropriate language. Individual questionnaire completion was conducted in communities with the help of researchers trained in working with vulnerable adolescents. At baseline, 1046 adolescents living with HIV were interviewed. The cohort had 94% retention at one and half year follow-up (2016-2017), and 97% retention at three-year follow-up (2017-2018).

Ethics approval

Ethical approvals were given by the University of Cape Town (UCT/CSSR/2013/4 and UCT/CSSR/2019/01), Oxford University (Oxford/CUREC2/12-21), provincial Departments of Health and Education, and ethical review boards of participating healthcare facilities. Ethics approval for this analysis was obtained from the University of Cape Town Human Research Ethics Committee (HREC-REF 121/2022). At all study waves, adolescent participants, and their caregivers (when adolescents were <18 years old) provided voluntary,

informed, and written consent for participation, including interviews and access to adolescents' medical records.

Measures

Longitudinal adherence outcome: Five self-reported measures of adherence were evaluated for sensitivity in detecting elevated viral load [26]. These five measures included missed doses *in the past 3 days*, last missed dose *–past week* and *–past month*, and *any missed clinic appointment* adapted from the Patient Medication Adherence Questionnaire [27] and added based on recommendations from other studies [28]. All five measures were significantly associated with viral load and had high test accuracy (sensitivity over 75%) [26]. These five measures were then used to categorize adherence into four distinct longitudinal trajectories based on Group-based trajectory modelling (GBTM) [29]. The main advantage of this derived multi-trajectory outcome is that it uses multiple (five) adherence indicators which may reduce measurement bias, characterize changes in adherence over time, and potentially summarise variability in adherence patterns within and between ALHIV. This analysis used the derived categorical ART adherence trajectories as an outcome [23]. Our main outcome (Figure 5.1 in Chapter 5) comprised four distinct adherence trajectories over three data points, namely: (i) consistent adherence:- a group of adolescents who start at high levels of adherence and report taking their ART consistently over time, (ii) low start and increasing adherence: those who start low but improve with time, (iii) gradually decreasing adherence: those that start high but gradually decreases with time, and (iv) low start and decreasing adherence: those that are consistently non-adherent at all three-time points [29].

Potential barriers: The potential baseline barriers to ART adherence at multiple levels of a socio-ecological model measured in this study data are described in detail in Table 7.1 below. All factors were hypothesized to influence ART adherence through direct and indirect pathways. *Covariates* included sociodemographic characteristics: age, sex, and urban/rural residence as well as the mode of HIV acquisition. Mode of HIV acquisition (sexually versus perinatally acquired HIV) was estimated following existing sub-Saharan African paediatric cohorts: age of ART initiation cut-off [≤10 years] [30] validated and updated with a detailed algorithm that considered other strong evidence (i.e. self-reported sexual history and parental death) in the absence of definitive clinic notes ascribing mode of HIV acquisition.

Table 7.1: Baseline individual, household, community, and institutional/health care variables in the socio-ecological framework identified from the study data.

Variable name	Socio-ecological model level	Variable description
Medication side-effects	Individual	Participants were asked how often they experienced any of the following physical symptoms (e.g., rash, headache, getting fat in unusual places, nausea, vomiting, diarrhoea) after taking ARVs or HIV medicine in the past year. If the participant responded (sometimes or often) we coded as 1 (experienced side effects) and 0 if they reported never.
Substance use	Individual	Substance use was defined based on whether the adolescent used any drugs that interfered with their physical functions (adapted from the WHO AUDIT scale), and whether they drank alcohol without caregivers knowing or approving, an item validated with similar populations in South Africa [31].
Ay mental health symptoms	Individual	Defined based on adolescent's experiences of depression symptoms, suicidality, and anxiety. Depression symptoms (in the past two weeks) were measured using the Child Depression Inventory (CDI-S) short form, a widely used 10-item version [32] validated in other South African studies. Suicidality was defined based on suicidal thoughts and behaviour (in the past month) whether the adolescent had thought of a way or tried to kill him or herself. This was measured using the Mini International Psychiatric Interview for Children and Adolescents suicidality and Self-harm subscale. Anxiety symptoms (past month) were measured using the widely used Children's Manifest Anxiety Scale-Revised (RCMAS), a 14-item abbreviated version.
School progression	Individual	School progression was defined as a binary indicator of whether the adolescent did not repeat the last grade.
Sexual abuse	Individual	Sexual abuse was measured as reporting either sexual assault and/or rape in the last year using items from the Sexual Victimization module of the Juvenile Victimization Questionnaire [33].
Adolescents accompanied to the clinic	Individual	This was defined based on whether the adolescent reported being accompanied to the clinic (either by someone from home or by clinic support staff).
Bullying victimization (physical and emotional)	Individual	Bullying victimization was measured using the 9-item based on Social and Health Assessment Peer Victimization Scale [34]. The items include being called names, hit, or threatened, and having possessions broken or stolen. The

		resulting scale was dichotomized to 1 (if they reported experiencing any form of bullying) and 0 (no experience of bullying i.e., when the adolescent answered 'not at all' to all items).
Food insecurity	Household	Food insecurity was measured as the number of days that the adolescent spent without enough food in the past seven days (week).
Domestic violence	Household	Past-week witnessing of domestic altercations or violence between adults in the home was measured using UNICEF Measures for National-level Monitoring of Orphans and Vulnerable Children [35].
HIV-related stigma	Community	Defined based on adolescents' experiences of any of the stigma items from the ALHIV Stigma Scale (ALHIV-SS) developed in collaboration with ALHIV in South Africa [36].
Negative peer norms	Community	Measured as a scale through a series of items assessing peer support for unsafe sex and adolescent pregnancy [37].
Peer support groups	Health care	Measured as a binary indicator of whether an adolescent was attending a structured HIV support group or not.
Clinic waiting time (<1 hour)	Health care	Measured based on self-reported approximate time (in minutes) spent waiting to see a healthcare provider.
Clinic travel time (<1 hour)	Health care	Measured based on self-reported approximate time (in minutes) spent travelling to a health facility.

7.3.1. Statistical Analysis

First, we examined the frequencies of baseline barriers including socio-demographic characteristics by adherence trajectory. Second, we fitted separate bivariate logistic regression models for all potential barriers listed in Table 7.1 to assess the association with each adherence trajectory using the consistent adherence trajectory as the comparison group. Purposeful selection with a cut-off significance level of $p < 0.20$, was used to select variables for inclusion into each path model [38]. We further checked for multicollinearity among selected variables (variance inflation factor>5 indicates multicollinearity) [39]. Third, we fitted generalized structural equation models (GSEM) [40] to evaluate pathways and the underlying mechanisms linking barriers selected in the second step above—which fall across multiple levels of the socio-ecological model—to ART adherence trajectory outcomes among ALHIV. Using the maximum likelihood method, GSEM estimates multiple pathways simultaneously, which allows us to estimate direct (DE), indirect (DE), and total (TE) effects. Since our variables are categorical (binary), we used the binomial family with a logit link to fit GSEM. Hypothesized pathways were established based on the socio-ecological model described in Figure 7.1. The final path models were adjusted for baseline age, sex, rural residence, and mode of HIV acquisition. All other modifiable variables were included as either intermediate variables or outcomes.

Model fit was assessed based on the likelihood ratio test, Bayesian information criteria (BIC), and statistical significance of path coefficient and clinical interpretability [41]. The indirect effects were calculated using the product method while the total effects were calculated as the sum of direct and indirect effects [42]. We used the "*nlcom*" command in Stata to calculate indirect and total effects. To obtain bias-corrected and normal-based confidence intervals for all estimated effects we conducted bootstrapping with 600 samples using the "*program*" command in Stata. If the bootstrapped confidence interval for the direct, indirect, and total effects did not include zero then they were considered significant and the interpretation of the pathways was informed by MacKinnon et al. [43]. To analyse barriers to long-term ART adherence, we categorised the consistent adherence trajectory as the reference group for all regression models. The path analysis results were adjusted for multiple hypothesis testing using the Benjamini–Hochberg method which controls the false discovery rate (FDR) using sequential modified Bonferroni correction [44]. All statistical analyses were conducted in Stata 17 (StataCorpLLC) with statistical significance set to less than 5%.

7.4. Results

Of the 1046 ALHIV recruited in this study, 89.2% (N=933) completed the study questionnaires at all three time points. Table 7.2 shows detailed adolescent characteristics overall and by ART adherence trajectory. There were notable differences across the trajectories by age, sex, and mode of HIV acquisition (all with $p<0.001$). There were also notable differences across the trajectories, with a greater proportion of adolescents in the low start adherence trajectories reporting medication side effects ($p<0.001$), substance use ($p=0.001$), sexual abuse ($p=0.020$), food insecurity ($p=0.002$) and internalized HIV stigma ($p<0.001$) at baseline visits compared with other groups. The proportion reporting any mental health symptoms at baseline was high across all four groups –ranging from 46% to 72.7% – with the highest percentage in the low start and decreasing adherence trajectory ($p<0.001$). Witnessing domestic violence/conflict ($p<0.001$) and negative peer norms ($p<0.001$) were higher for all other groups compared to the consistent adherence trajectory. Experiences of bullying (both physical and emotional), cognitive issues, and community violence at baseline were similar across groups. Reporting of clinic travel time above one hour, clinic waiting time above one hour, and not attending a support group at baseline was similar across all groups, except that the majority of adolescents in the low start and decreasing adherence were more likely to report clinic waiting time above one hour ($p=0.011$). The bivariate association results are shown in Supplementary Table 7-1. All variables which met the cut-off significance level of $p < 0.20$ during the purposeful selection step (Supplementary Table 7-1), were included in the final path analysis.

Table 7.2: Baseline sociodemographic characteristics, individual, household, community, and healthcare factors by adherence trajectory among ALHIV (N=933).

Trajectories	Overall (N=933)	Consistent adherence (N=465)	Low start and increasing adherence (N=194)	Gradually decreasing adherence (N=219)	Low start and decreasing adherence (N=55)	Corresponding Socio-Ecological Level(s)
Measures at baseline	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	
Age (Mean/SD)*	13.6 (2.88)	13 (2.69)	14.1 (3.01)	13.7 (2.89)	15.3 (2.95)	Individual: Socio-demographic characteristics
Female*	514 (55.1)	247 (53.1)	121 (62.4)	105 (47.9)	41 (74.5)	
Rural*	249 (26.7)	121 (26.0)	68 (35.1)	44 (20.1)	16 (29.1)	
Sexually acquired HIV*	199 (21.3)	65 (14.0)	54 (27.8)	50 (22.8)	30 (54.5)	
Medication side effects*	235 (25.2)	88 (18.9)	67 (34.5)	48 (21.9)	32 (58.2)	Individual
Substance use*	77 (8.3)	24 (5.2)	21 (10.8)	22 (10.0)	10 (18.2)	Individual
Sexual abuse*	60 (6.4)	21 (4.5)	21 (10.8)	13 (5.9)	5 (9.1)	Individual
Any mental health symptoms*	499 (53.5)	214 (46.0)	124 (63.9)	121 (55.3)	40 (72.7)	Individual
Emotional bullying	381 (40.8)	182 (39.1)	90 (46.4)	84 (38.4)	25 (45.5)	Individual
Physical bullying	448 (48.0)	211 (45.4)	100 (51.5)	107 (48.9)	30 (54.5)	Individual
Cognitive issues	368 (39.4)	183 (39.4)	75 (38.7)	87 (39.7)	23 (41.8)	Individual
Internalised HIV Stigma*	233 (25.0)	109 (23.4)	42 (21.6)	55 (25.1)	27 (49.1)	Individual
Food insecurity*	212 (22.7)	83 (17.8)	59 (30.4)	53 (24.2)	17 (30.9)	Household
No one to accompany the child to the clinic*	269 (28.8)	113 (24.3)	67 (34.5)	68 (31.1)	21 (38.2)	Household
Witness domestic violence or conflict*	113 (12.1)	37 (8.0)	30 (15.5)	33 (15.1)	13 (23.6)	Household
Negative peer norms (Mean/SD)*	0.84 (1.59)	0.57 (1.27)	1.08 (1.86)	0.99 (1.75)	1.72 (1.88)	Community
Community violence	556 (59.6)	259 (55.7)	116 (59.8)	142 (64.8)	38 (69.1)	Community
Clinic travel time (> 1 hr)*	829 (88.9)	402 (86.5)	170 (87.6)	203 (92.7)	54 (98.2)	Health care
Clinic waiting time (> 1 hr)	446 (47.8)	208 (44.7)	91 (46.9)	114 (52.1)	33 (60.0)	Health care
Not in a support group	770 (82.5)	374 (80.4)	167 (86.1)	179 (81.7)	50 (90.9)	Health care

*****Factors significantly different by trajectory grouping at 5% significance level.

Path model(s) results

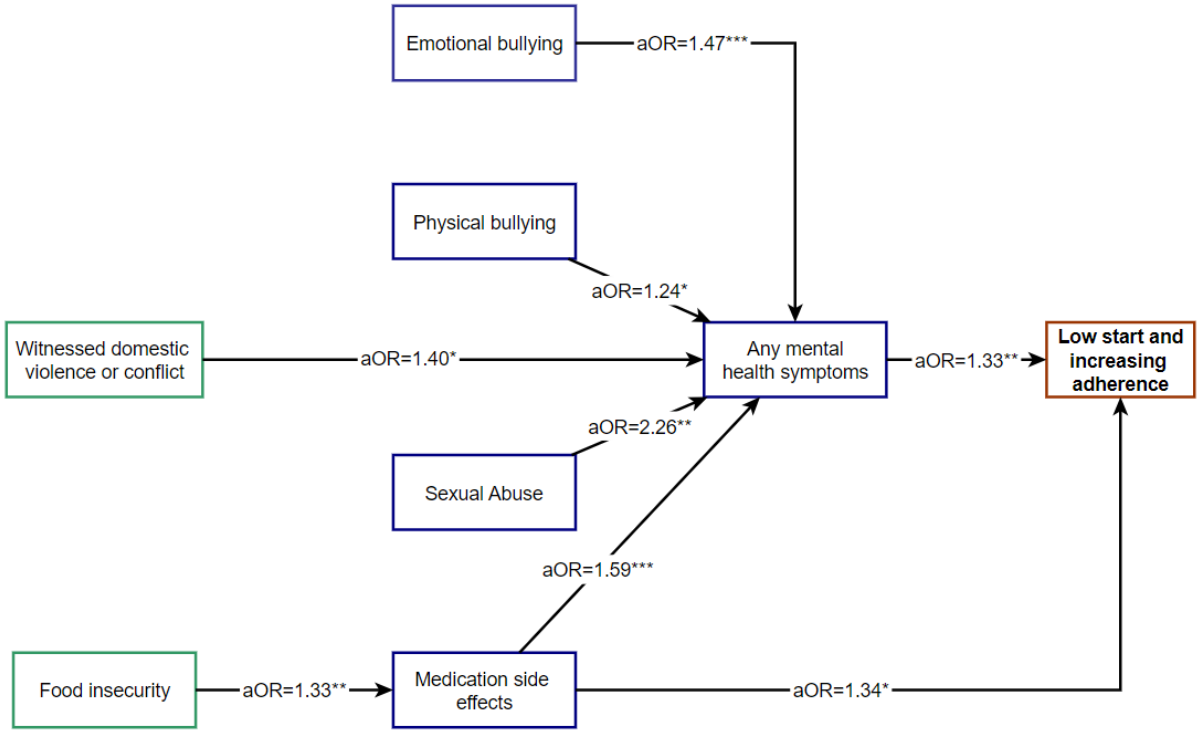
Table 7.3 and Figure 7.2-Figure 7.4 below show the total (TE), direct (DE), and indirect effects (IE) and the pathways linking individual, household, community, and healthcare barriers at baseline and ART adherence trajectories. For each trajectory, these effects are described in detail below across multiple levels of the socio-ecological model, and a summary of all effects is given in Table 7.4.

Low start and increasing adherence vs consistent adherence trajectory

Pathways of direct, indirect, and total effects for low start and increasing adherence trajectory were complex.

Individual level effects: Adolescents who reported experiencing mental health symptoms (aOR^{DE}=1.33, 95%CI 1.07-1.67), and medication side effects (aOR^{DE}=1.33, 95%CI 1.04-1.72) at baseline were directly associated with higher odds of being in the low start and increasing adherence trajectory (Figure 7.2). The association between medication side effects at baseline and being in the low start and increasing adherence trajectory was partially mediated by mental health symptoms—the only observed significant indirect effect at the individual level—(aOR^{IE}=1.14, 95%CI 1.02-1.31) (Table 7.3). Overall, experiencing medication side effects was associated with higher odds of being in the low start and increasing adherence trajectory (aOR^{TE}=1.52, 95%CI 1.14-2.03). Although reporting physical bullying, emotional bullying, and sexual abuse at baseline is directly associated with reporting any mental health symptoms, the respective direct, indirect, and total effects of the associations were not significant, except for emotional bullying (aOR^{IE}=1.12, 95%CI 1.01-1.25), suggesting that the association between emotional bullying and the low start and increasing adherence trajectory is fully mediated by poor mental health functioning.
Household/Family level effects: The direct and indirect associations between witnessing domestic violence/conflict and low start and increasing adherence trajectory were not statistically significant. However, the total effect showed that witnessing domestic violence/conflict at baseline was associated with higher odds of being in the low start and increasing adherence trajectory (aOR^{TE}=1.52, 95%CI 1.04-2.24). Although reporting food insecurity at baseline was found to be directly associated with reporting medication side effects, the respective indirect association with being in the low start and increasing adherence trajectory was not statistically significant. However, the total effect for food insecurity (aOR^{TE}=1.42, 95%CI 1.07-1.90) was significant. At the *community and healthcare level,* there were no significant direct, indirect, or total effects on the low start and increasing adherence trajectory.

Figure 7.2: Path diagram showing direct effects of individual, household, community, and health care barriers to ART adherence among ALHIV (Consistent adherence trajectory as the reference group)



*Statistically non-significant pathways not shown. Parameter estimates are displayed only for statistically significant paths. Adjusted odds ratio (aOR) are presented for categorical factors. *p<.05, **p<.01, ***p<.001. Adjusted for age, sex, rural residence, and mode of HIV acquisition. Effect sizes are direct effects. blue (individual), green (household), purple (community), orange (healthcare) and brown (outcome).

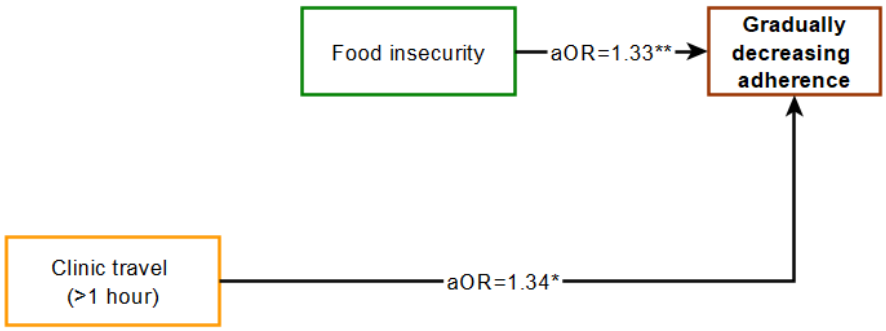
Gradually decreasing adherence vs consistent adherence trajectory

Pathways of direct, indirect, and total effects for gradually decreasing adherence trajectory were simpler.

Individual level effects: There were no significant direct, indirect, or total effects on the gradually decreasing adherence trajectory (Table 7.3 and Figure 7.3). *Household/Family level effects:* Food insecurity at baseline was directly associated with higher odds of being in the gradually decreasing adherence trajectory (aOR^{DE}=1.29, 95%CI 1.02-1.65). Although the direct and indirect associations between reporting witnessing domestic violence/conflict and being in the gradually decreasing adherence trajectory were not statistically significant, the total effect of the pathway linking witnessing domestic violence/conflict, experiencing mental health symptoms and the gradually decreasing adherence trajectory was significant (aOR^{TE}=1.42, 95%CI 1.02-2.0). *Community level effects:* At the community level, there were no significant direct, indirect, or total effects on the gradually decreasing adherence trajectory. *Healthcare level effects:* Clinic proximity measured based on clinic travel time (>1

hour) was directly associated with higher odds of being in the gradually decreasing adherence trajectory (aOR^{DE}=1.60, 95%CI 1.12-2.28).

Figure 7.3: Path diagram showing direct effects of individual, household, community, and health care barriers to ART adherence among ALHIV (Consistent adherence trajectory as the reference group)



*Statistically non-significant pathways not shown. Parameter estimates are displayed only for statistically significant paths. Adjusted odds ratio (aOR) are presented for categorical factors. *p<.05, **p<.01, ***p<.001. Adjusted for age, sex, rural residence, and mode of HIV acquisition. Effect sizes are direct effects. blue (individual), green (household), purple (community), orange (healthcare) and brown (outcome).

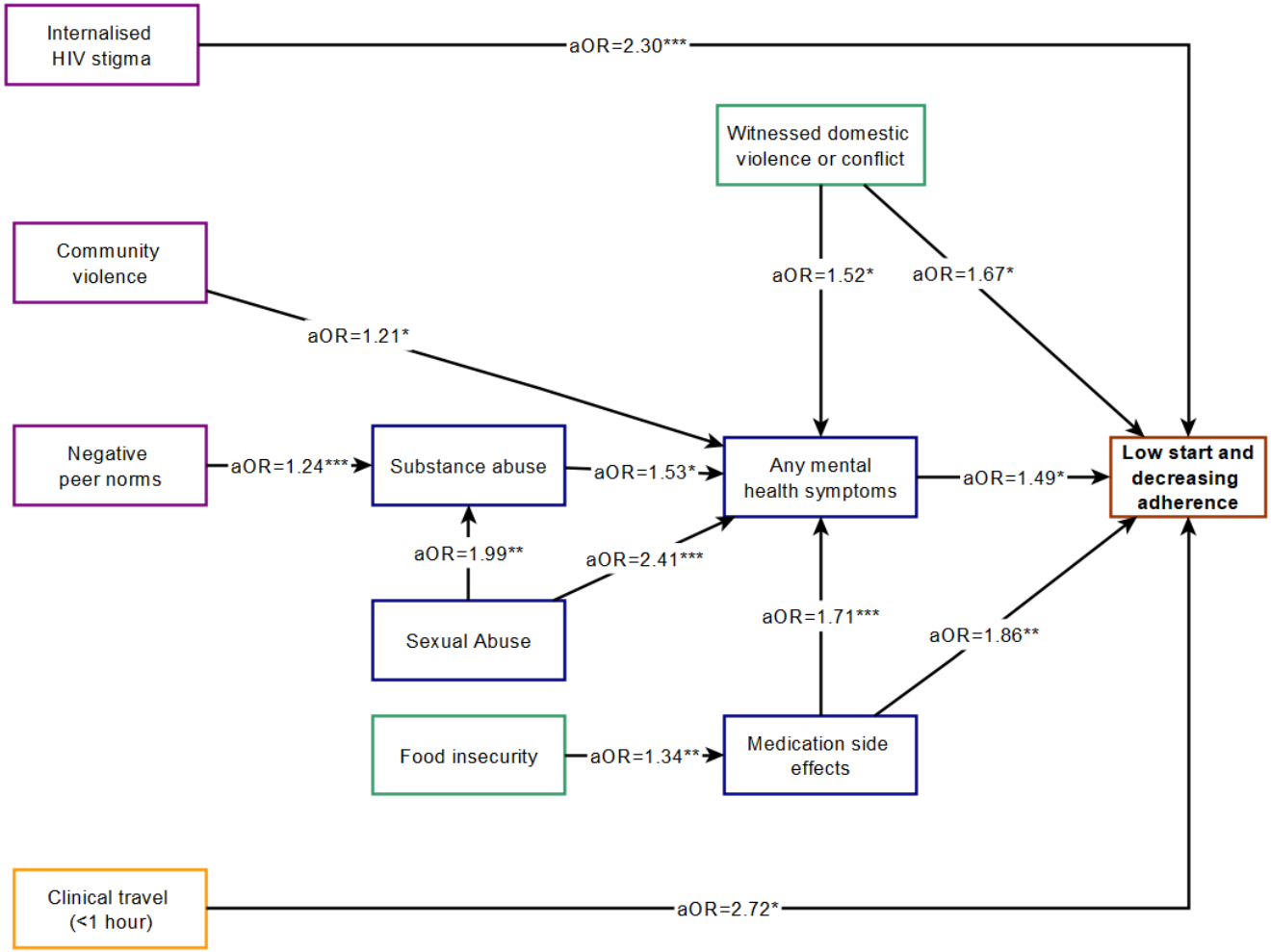
Low start and decreasing adherence vs consistent adherence trajectory

Pathways of direct, indirect, and total effects for low start and decreasing adherence trajectory were much more complex.

Individual level effects: Medication side effects (aOR^{DE}=1.86, 95%CI 1.25-2.77) and mental health symptoms (aOR^{DE}=1.49, 95%CI 1.02-2.21) were directly associated with higher odds of being in the low start and decreasing adherence trajectory (Table 7.3 and Figure 7.4). The total effect of medication side effects on the low start and decreasing adherence trajectory was (aOR^{TE}=2.31, 95%CI 1.42-3.75). Although the respective direct, indirect, and total effects of the associations with being in the low start and decreasing adherence trajectory were not significant, substance use and sexual abuse were directly associated with mental health symptoms. *Household/Family level effects:* Witnessing domestic violence/conflict (aOR^{DE}=1.67, 95%CI 1.01-2.78) was significantly associated with being in the low start and decreasing adherence trajectory, and the total effect showed that witnessing domestic violence/conflict at baseline was associated with 1.97 times higher odds of being in the low start and decreasing adherence trajectory (aOR^{TE}=1.97, 95%CI 1.10-3.53). Although the respective direct, indirect, and total effects of the associations with being in the low start and decreasing adherence trajectory were not significant, food insecurity was directly associated with reporting medication side effects. *Community level effects:* Internalized HIV stigma

(aOR^{DE}=2.30, 95%CI 1.55-3.44) was associated with 2.3 times higher odds of being in the low start and decreasing adherence trajectory. Although the direct, indirect, and total effects of their association with being in the low start and decreasing adherence trajectory were not significant, community violence and negative peer norms were directly associated with mental health symptoms. *Healthcare level effects:* Only clinic proximity measured based on clinic travel time (>1 hour) was directly associated with higher odds of being in the low start and decreasing adherence trajectory (aOR^{DE}=2.72, 95%CI 1.15-6.43).

Figure 7.4: Path diagram showing direct effects of individual, household, community, and health care barriers to ART adherence among ALHIV (Low start and decreasing adherence trajectory versus consistent adherence as the reference group)



*Statistically non-significant pathways not shown. Parameter estimates are displayed only for statistically significant paths. Adjusted odds ratio (aOR) are presented for categorical factors. *p<.05, **p<.01, ***p<.001. Adjusted for age, sex, rural residence, and mode of HIV acquisition. Effect sizes are direct effects. blue (individual), green (household), purple (community), orange (healthcare) and brown (outcome).

Table 7.3: Total, direct, and indirect effects among the pathways between individual, household, community, and health care baseline risk factors and inconsistent adherence trajectories among ALHIV (consistent adherence trajectory as the reference group)

Adherence trajectories		Low start and increasing		Gradually decreasing		Low and decreasing	
		Path model A		Path model B		Path model C	
Factors	**Effects on Adherence**	**aOR (95%CI)**	**p-value**	**aOR (95%CI)**	**p-value**	**aOR (95%CI)**	**p-value**
Individual-level							
Any mental health symptoms	Direct	**1.33 (1.07-1.67)**	**0.012**	1.18 (0.96-1.45)	0.124	**1.49 (1.02-2.21)**	**0.045**
Medication side effects	**Total**	**1.52 (1.14-2.03)**	**0.004**	-	-	**2.31 (1.42-3.75)**	**0.001**
	Direct	**1.33 (1.04-1.72)**	**0.027**	-	-	**1.86 (1.25-2.77)**	**0.002**
	Indirect						
	via Any mental health symptoms	**1.14 (1.02-1.31)**	**0.046**	-	-	1.24 (0.97-1.59)	0.089
Emotional bullying	**Total**	1.10 (0.83-1.44)	0.510	-	-	-	-
	Direct	1.01 (0.77-1.25)	0.883	-	-	-	-
	Indirect						
	via Any mental health symptoms	**1.12 (1.01-1.25)**	**0.048**	-	-	-	-
Physical bullying	**Total**	1.12 (0.87-1.44)	0.369	-	-	-	-
	Direct	1.06 (0.83-1.34)	0.649	-	-	-	-
	Indirect						
	via Any mental health symptoms	1.06 (0.99-1.15)	0.113	-	-	-	-
Sexual abuse	**Total**	1.57 (0.92-2.69)	0.098	-	-	0.89 (0.30-2.63)	0.828
	Direct	1.17 (0.76-1.79)	0.489	-	-	0.55 (0.26-1.20)	0.133
	Indirect						
	via Any mental health symptoms	1.26 (0.98-1.62)	0.066	-	-	1.42 (0.91-2.23)	0.125
	via Substance use → Poor mental health functioning	1.07 (0.95-1.20)	0.260	-	-	1.13 (0.92-1.38)	0.263
Household or family-level							
Witness domestic violence or conflict	**Total**	**1.52 (1.04-2.24)**	**0.031**	**1.42 (1.02-2.00)**	**0.043**	**1.97 (1.10-3.53)**	**0.023**
	Direct	1.38 (0.99-1.94)	0.059	1.32 (0.95-1.83)	0.096	**1.67 (1.01-2.78)**	**0.048**
	Indirect						
	via Any mental health symptoms	1.10 (0.98-1.24)	0.115	1.07 (0.96-1.19)	0.219	1.18 (0.95-1.46)	0.126
Food insecurity	**Total**	**1.42 (1.07-1.90)**	**0.017**	-	-	1.57 (0.99-2.49)	0.055
	Direct	1.26 (0.97-1.63)	0.081	**1.29 (1.02-1.65)**	**0.047**	1.23 (0.79-1.91)	0.351
	Indirect						

	via Medication side effects	1.09 (0.97-1.22)	0.151	-	-	1.20 (0.97-1.47)	0.089
	via Medication side effects → Any mental health symptoms	1.04 (0.99-1.09)	0.120	-	-	1.06 (0.97-1.17)	0.181
Community level							
Internalised HIV stigma	Direct	-	-	-	-	**2.30 (1.55-3.44)**	**<0.001**
Community violence	**Total**	-	-	1.19 (0.95-1.49)	0.125	1.35 (0.85-2.14)	0.202
	Direct	-	-	1.18 (0.94-1.46)	0.149	1.25 (0.84-1.87)	0.277
	Indirect						
	via Any mental health symptoms	-	-	1.03 (0.98-1.08)	0.278	1.08 (0.97-1.21)	0.173
Negative peer norms	**Total**	1.05 (0.94-1.16)	0.392	1.28 (0.93-1.76)	0.134	1.05 (0.88-1.25)	0.568
	Direct	1.02 (0.93-1.12)	0.606	1.27 (0.94-1.70)	0.114	1.01 (0.87-1.18)	0.848
	Indirect						
	via Substance use → Any mental health symptoms	1.02 (0.99-1.06)	0.202	1.06 (0.95-1.19)	0.294	1.04 (0.98-1.10)	0.236
Healthcare level							
Clinic travel (> 1 hour)	Direct	**-**	**-**	**1.60 (1.12-2.28)**	**0.009**	**2.72 (1.15-6.43)**	**0.022**

aOR: adjusted odds ratios; 95% Confidence Intervals in parentheses. In each path model, the consistent adherence trajectory was used as the reference group for each model. "-" Factors not tested –did not meet inclusion criteria for path model, p-value<0.20. All the models were adjusted for age, sex, rural residence, and mode of HIV acquisition. The p-values were adjusted for multiple comparisons using the Benjamini–Hochberg method which controls the false discovery rate (FDR).

Table 7.4: Summary of effects by adherence trajectory among ALHIV (N=933)

		Adherence trajectory		
Effects	**Variable or factor**	**Low start and Increasing Adherence**	**Gradually Decreasing Adherence**	**Low start and Decreasing Adherence**
Direct	**Poor mental health functioning**	Poor mental health functioning ^{DE}	-	Poor mental health functioning ^{DE}
	Medication side effects	Medication side effects ^{DE}	-	Medication side effects ^{DE}
	Internalised HIV stigma	-	-	Internalised HIV stigma ^{DE}
	Clinic travel (> 1 hour)	-	Clinic travel time ^{DE}	Clinic travel time ^{DE}
	Food insecurity	-	Food insecurity ^{DE}	-
	Witness domestic violence or conflict	-	-	Witness domestic violence or conflict ^{DE}
Indirect/ Mediatory	**Emotional bullying**	Poor mental health functioning ^{IE}	-	-
	Medication side effects	Poor mental health functioning ^{IE}	-	-
Total	**Poor mental health functioning**	Poor mental health functioning $^{DE=TE}$	-	Poor mental health functioning $^{DE=TE}$
	Medication side effects	Medication side effects $^{DE+IE=TE}$	-	Medication side effects $^{DE=TE}$
	Emotional bullying	Emotional bullying $^{IE=TE}$	-	-
	Witness domestic violence or conflict	Witness domestic violence or conflict ^{TE}	Witness domestic violence or conflict ^{TE}	Witness domestic violence or conflict $^{DE=TE}$
	Food insecurity	Food insecurity ^{TE}	Food insecurity $^{DE=TE}$	-
	Clinic travel (> 1 hour)	-	Clinic travel time $^{DE=TE}$	Clinic travel time $^{DE=TE}$
	Internalised HIV stigma	-	-	Internalised HIV stigma $^{DE=TE}$

7.5. Discussion

This study uses longitudinal data from adolescents in resource-limited settings to explore the pathways of change in ART adherence —categorized as distinct longitudinal ART adherence trajectories over time—expanding applications of the socio-ecological model. Our findings reveal that adolescents' long-term ART adherence is influenced by several barriers operating at multiple levels of the socio-ecological model. At the individual level of the socio-ecological model, mental health symptoms were directly associated with being in the low start and increasing, and the low start and decreasing adherence trajectories relative to the consistent adherence trajectory, which aligns with previous research [6, 47-50]. Further

exploration of the pathways linking mental health symptoms and the low start and increasing adherence trajectory showed that both emotional and physical bullying were directly associated with mental health symptoms. For the low start and increasing adherence trajectory, the effect of emotional bullying was fully mediated by mental health symptoms [51]. These findings show the impact of bullying on ALHIV, and the observed improvement in adherence with time may be related to the decline in bullying rates as adolescents grow older [52]. Further exploration of the pathways linking mental health symptoms and the low start and decreasing adherence trajectory showed a unique set of barriers. Negative peer norms, substance use, and community violence but not bullying, were directly associated with mental health symptoms. Other important barriers linked to mental health symptoms, common to both trajectories, were sexual abuse [53], medication side effects [54-56], and witnessing domestic violence or conflict [57]. There was no direct association between reporting any mental health symptoms and being in the gradually decreasing adherence trajectory. These findings highlight that adolescents experience unique challenges which may influence their mental health leading to distinct adherence trajectories over time. Overall, these findings highlight the independent role of mental health in adolescent HIV care, and the need to address underlying causes of poor mental health among ALHIV [22, 58, 59]. These findings underscore the need for tailored interventions that address the mental health needs of ALHIV, along with the strengthening of mental health services early in adolescents' HIV care.

This analysis also documents the direct impacts of medication side effects. Like mental health, medication side effects were associated with the low start and increasing, and the low start and decreasing adherence trajectories compared to the consistent adherence trajectory. While the effect of medication side effects was partially mediated by mental health symptoms for the low start and increasing trajectory, no indirect effect of medication side effects was confirmed for the low start and decreasing adherence trajectory. The partial mediation by mental health symptoms could be linked to doubt and feelings of discouragement around the benefits of ART medication [58]. Several studies have documented that treatment-related side effects –real or anticipated—hinder ART adherence among young populations [9, 14, 50]. Our study corroborates this, showing that experiencing medication side effects contributes to distinct inconsistent adherence trajectories over time.

At the household level, this study found a direct association between food insecurity and belonging to the gradually decreasing adherence trajectory. Food insecurity is a perceived barrier to ART adherence, and evidence suggests that the experience or fear of food insecurity may influence one's perceived self-efficacy to adhere to ART [60, 61]. ALHIV with inadequate access to food may lose confidence to maintain life-long adherence and may believe they are less likely to benefit from treatment. For the low start and increasing trajectory, and the low start and decreasing trajectory, we observed a direct effect between food insecurity and medication side effects. This may be partly explained by the fact that for most of their lives and treatment histories, before current drug combinations were developed, taking ART medication without food created intolerable side effects [60, 62].

We also found that witnessing domestic violence or conflict was directly associated with the low start and decreasing trajectory group. Although no indirect effects of witnessing domestic violence or conflict were found in this analysis, existing evidence from other health behaviours among children and adolescents shows that witnessing domestic violence is associated with negative health effects including poor mental health [57, 63].

At the community level, reporting internalized HIV-related stigma was directly associated with being in the low start and decreasing adherence trajectory, a group that has persistently poor adherence over time. This is in line with previous research which has shown that HIV-related stigma acutely influences ART adherence among ALHIV [64, 65], and is one of the major reasons why some patients discontinue ART, fail to meet clinic appointments or miss dosages [17, 21, 62]. Previous studies have also shown that HIV-related stigma is associated with poor mental health, however, this analysis did not find a direct effect of stigma on mental health [66]. In terms of other community-level factors, this study did not establish any significant direct or indirect effect of community violence and negative peer norms on the low start and decreasing adherence trajectory, although they were directly associated with any mental health symptoms.

At the healthcare level, clinic travel time (above 1 hour) was directly associated with being in the gradually decreasing adherence trajectory and the low start and decreasing adherence trajectory, groups that exhibit a decrease in ART uptake over time. Clinic travel time is directly related to clinic travel distance, which has been reported to hinder retention in HIV care and ART adherence [67]. In areas where ART clinics are sparsely distributed travel distance may be a barrier to timely access to care and subsequent sustained ART adherence.

Implications for service providers and research

This analysis identified unique pathways linking barriers to distinct adherence trajectories. Indirect pathways suggest multi-level mechanisms leading to adherence trajectories. The gradually decreasing adherence trajectory had simpler pathways, while the remaining two inconsistent trajectories with poor adherence at the start of the cohort, had more complex pathways. These findings show that adolescents in the gradually decreasing trajectory need help sustaining adherence over time, and food insecurity and proximity of health services are the major challenges. Adolescents in the other two inconsistent adherence trajectories are exposed to multiple interlinked barriers, and these may need to be identified early on for immediate access to support. These findings have the potential to influence clinical practice and HIV care and further inform future support interventions for ALHIV in low-resource settings.

Mental health—implicated in multiple unique pathways across the distinct adherence trajectories—accentuates the need to identify and address the underlying causes of common mental symptoms among ALHIV at diagnosis. Healthcare providers can utilise reporting of trauma experiences (bullying, sexual abuse, domestic and community violence), negative peer norms, and substance abuse which were directly associated with mental health symptoms to identify probable cases of poor mental health [58, 59, 68]. More recently, access to emerging long-term injectable HIV medication [70] and newer ART drug regimens that include dolutegravir (DTG) in low-resource settings may also mean reduced experiences of medication side effects among ALHIV. However, efforts to reduce medication side effects should include addressing food insecurity to reduce hunger-related side effects [69]. Furthermore, our findings highlight an urgent need for community-coordinated initiatives and efforts to deal with HIV-related stigma and its impact [71]. Other factors such as clinic proximity and food insecurity point to socio-economic challenges faced by adolescents and could be addressed through social protection programmes [72], including providing mobile clinics such as the Tutu Teen Truck, implemented by the Desmond Tutu HIV Foundation in Cape Town could also enhance sustained ART adherence among ALHIV [73].

For researchers, these findings could facilitate the development of new screening tools for adolescent wellbeing, and the refining of existing checklists such as the WHO's HEADSS/HEADSS+ [74]. Healthcare providers, counsellors or other service providers could use some of these barriers as prompts for conversation at first contact with the patient, to

anticipate major challenges that ALHIV face in their lives and the course they may take in their medication-taking journey. Most importantly, when adolescents seek healthcare, they already have a complex history, which includes the iterative interaction with the healthcare system for adolescents who acquired HIV vertically, and this history may be useful in determining their future healthcare needs. Therefore, using findings on the direct effects of self-reported barriers on adherence trajectories as initial prompts may facilitate the development of tailored multi-level adherence support strategies for ALHIV to optimise resource allocation.

Strengths and limitations

This study has several strengths and limitations. Strengths include the use of longitudinal data with participants followed up three times over four years, which is sufficient to examine the short- and mid-term effects of the selected barriers (exposures). The longitudinal design strengthens the precision of the associations between the exposures, mediators, and adherence outcome, via temporal ordering. Additionally, the GSEM analytic approach used in this analysis facilitates the exploration of interrelationships between multiple factors simultaneously, by examining total, direct, and indirect effects between exposure variables and the outcome of interest. The GSEM offers robust findings validating the plausibility of the hypothesized pathways. The visual representation of the direct pathways in the GSEM reveals insightful information on the relative contribution of each barrier to adolescents' adherence trajectories. However, this study had some limitations. Adherence was defined based on self-report measures which are prone to recall and social desirability biases. However, we used five self-reported adherence items –validated against viral load– and generated a latent construct (using a novel analytic method) representing distinct longitudinal trajectories of adherence, which is more robust and corrects for measurement bias [75]. Despite the limitations, this study provides a better understanding of the individual, household, community, and healthcare-level barriers influencing ART adherence among ALHIV in South Africa. Some other hypothesized pathways –especially linking higher multiple-level barriers— in the socio-ecological model were also not confirmed. Future research should include data with assessments over a longer period and identify pathways linking both barriers and facilitators of ART adherence among ALHIV.

Conclusion

Overall, these study findings suggest that several key barriers, located across multiple levels of the adolescents' ecological environment, contribute to their adherence trajectory over time. Their social and economic realities explain why some ALHIV follow certain adherence trajectories, and understanding these realities may be essential in determining their HIV care needs. Our findings suggest that addressing mental health, medication side effects, HIV-related stigma, and socio-economic challenges such as food insecurity and clinic proximity [31, 36, 60, 68] is key to sustaining adherence to ART among ALHIV. Present findings also suggest that tackling the underlying issues (bullying and violence exposure) leading to mental health symptoms may be essential to interrupt pathways of risk to ART adherence. There is also a need to integrate mental health support into HIV care in the short and long term. More importantly, our study contributes to the literature on empirical research of socio-ecological theory, and the findings could inform the development of targeted interventions for ALHIV in low-resource settings.

7.6. Supplementary Tables and Figures:

Supplementary Table 7-1: Bivariate logistic regression analyses of baseline risk factors by adherence trajectory group (N=933, the reference group is consistent adherence).

Measures	Low start and increasing vs. Consistent adherence		Gradually decreasing vs. Consistent adherence		Low start and decreasing adherence vs. Consistent adherence		Corresponding Socio-Ecological Level(s)
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	
Age	1.13 (1.07- 1.20)	**<0.001**	1.08 (1.02- 1.14)	**0.013**	1.29 (1.18- 1.43)	**<0.001**	Sociodemographic characteristics
Female	1.46 (1.04- 2.06)	**0.030**	0.81 (0.59- 1.12)	0.207	2.58 (1.37- 4.87)	**0.003**	
Rural	1.53 (1.07- 2.20)	**0.020**	0.72 (0.48- 1.06)	0.092	1.17 (0.63- 2.16)	0.625	
Recently acquired HIV	2.37 (1.58- 3.57)	**<0.001**	1.82 (1.21- 2.74)	**0.004**	7.38 (4.09- 13.3)	**<0.001**	
Medication side effects	2.26 (1.55- 3.29)	**<0.001**	1.20 (0.81- 1.79)	0.361	5.96 (3.32- 10.7)	**<0.001**	Individual
Substance use	2.23 (1.21- 4.11)	**0.010**	2.05 (1.12- 3.75)	**0.019**	4.08 (1.84- 9.08)	**0.001**	Individual
Sexual abuse	2.57 (1.37- 4.82)	**0.003**	1.33 (0.65- 2.72)	0.427	2.11 (0.76- 5.85)	0.150	Individual
Poor mental health functioning	2.08 (1.47- 2.93)	**<0.001**	1.45 (1.05- 1.99)	**0.025**	3.13 (1.68- 5.82)	**<0.001**	Individual
Emotional bullying	1.35 (0.96- 1.89)	0.085	0.97 (0.70- 1.35)	0.845	1.30 (0.74-2.27)	0.367	Individual
Physical bullying	1.28 (0.92- 1.79)	0.149	1.15 (0.83- 1.59)	0.394	1.45 (0.82-2.53)	0.199	Individual
Cognitive issues	0.97 (0.69- 1.37)	0.868	1.01 (0.73- 1.41)	0.926	1.11 (0.63- 1.95)	0.724	Individual
Internalised HIV Stigma	0.90 (0.60- 1.35)	0.618	1.10 (0.75- 1.59)	0.633	3.145 (1.78- 5.57)	**<0.001**	Individual
Food insecurity	2.01 (1.37- 2.96)	**<0.001**	1.47 (0.99- 2.17)	0.053	2.06 (1.11- 3.82)	**0.022**	Household
No one to accompany the child to the clinic	1.64 (1.14- 2.36)	**0.007**	1.40 (0.98- 2.01)	0.063	1.92 (1.07- 3.45)	**0.028**	Household
Witness domestic violence or conflict	2.12 (1.27- 3.54)	**0.004**	2.05 (1.25- 3.38)	**0.005**	3.58 (1.76- 7.26)	**<0.001**	Household
Negative peer norms	1.24 (1.11- 1.38)	**<0.001**	1.21 (1.09- 1.34)	**<0.001**	1.52 (1.30- 1.77)	**<0.001**	Community
Community violence	1.17 (0.84- 1.66)	0.348	1.46 (1.05- 2.04)	**0.026**	1.77 (0.97-3.23)	0.063	Community
Clinic travel time (> 1 hr)	1.11 (0.67-1.84)	0.684	1.98 (1.12- 3.53)	**0.019**	4.46 (1.15- 6.27)	**0.036**	Health care
Clinic waiting time (> 1 hr)	1.09 (0.78- 1.53)	0.609	1.34 (0.97- 1.85)	0.074	1.85 (1.05- 3.28)	**0.034**	Health care
Not in a support group	1.51 (0.94- 2.40)	0.086	1.09 (0.72- 1.64)	0.686	2.43 (0.94-6.27)	0.066	Health care

*All variables with a p-value less than 0.20 are selected for subsequent path analysis

7.7. References

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CHAPTER 8. Impact of psychosocial and economic support on HIV treatment outcomes among adolescents living with HIV in South Africa.

Zhou, S., Cluver, L., Orkin, M., Rudgard, W., Bachman, G., Knight, L., Sherman, G., Toska, E. Impact of social-economic support on HIV treatment outcomes among adolescents living with HIV in South Africa. *Manuscript being prepared for submission to the Lancet HIV.*

Relevance of this paper to the thesis:

There is an urgent need for support for ALHIV to achieve optimal HIV treatment outcomes, particularly for adolescents at risk of non-adherence to ART over time. Social protection and psychosocial support are valuable in reducing gaps in HIV care. However, we lack longitudinal evidence on their role in improving HIV treatment outcomes among ALHIV in government healthcare services. This paper examines the associations of government-provided social protection and psychosocial support with longitudinal non-ART adherence and elevated viral load, and disengagement from HIV care among adolescents living with HIV.

Contribution of the student and co-authors:

SZ conceptualised the analysis with guidance from ET, LC, and LK. SZ conducted all the statistical analyses and wrote the full manuscript draft. LC, MO, WR, GB, LK, GS, and ET reviewed and provided feedback on the manuscript content. All authors approved the final draft being prepared for submission to the Lancet HIV. ET and LC designed and implemented the overall study.

8.1. Abstract

Background: There is an urgent need for scalable services that can reduce poor HIV treatment outcomes among adolescents living with HIV. Social protection and psychosocial support may be valuable to reduce gaps in HIV care, but we lack longitudinal evidence.

Methods: A three-wave cohort of adolescents living with HIV (N=1046, 55.1% female aged 10-19 at baseline) was interviewed between 2014 to 2018 in South Africa's Eastern Cape province. Viral load data were obtained through clinic records and linkage with the National Health Laboratory Service data warehouse. Multinomial logistic regression was used to evaluate the relationship between baseline access to government social protection and family psychosocial support and longitudinal ART adherence trajectories. Mixed-effects logistic regressions were used to model associations of accessing government social protection and family psychosocial support with (1) elevated VL/non-adherence (combined elevated viral load (≥1000 copies/ml) and past-week non-adherence), and disengagement from HIV care. To aid interpretation, we estimated average adjusted probabilities of associations of each or both forms of support on the combined outcome.

Results: Over half 59.5% of adolescents had elevated VL/non-adherence at least once, over the three study rounds. Accessing social protection and psychosocial support was predictive of adherence trajectory membership. In multivariable analyses, accessing social protection was associated with lower odds of elevated VL/non-adherence (aOR: 0.51, 95%CI 0.32-0.81), and lower odds of disengagement from HIV care (aOR: 0.52, 95%CI 0.36-0.77). Access to psychosocial support was also associated with lower odds of elevated VL/non-adherence (aOR: 0.65, 95%CI 0.49-0.85) and lower odds of disengagement from HIV care (aOR: 0.46, 95%CI 0.35-0.59). A combination of social protection and psychosocial support was associated with reductions in elevated VL/non-adherence from 64% to 24%; (-26.3 percentage points) and disengagement from HIV care from 34.3% to 11.8% (-22.5 percentage points).

Conclusions: The combination of government-provided social protection and family psychosocial support could substantially reduce disengagement from HIV care, ART non-adherence and elevated viral load among ALHIV as they grow into young adults.

8.2. Introduction

Adolescents and young people are disproportionately affected by HIV. Adolescents living with HIV (ALHIV) comprise a growing proportion of new HIV cases globally, for example, the 2021 UNAIDS estimates demonstrated persistently high rates of new HIV infections among adolescents, representing roughly 11% of new HIV infections [1]. HIV treatment deaths among adolescents have increased, particularly in sub-Saharan Africa where 90% of the world's population of ALHIV live [1-3]. These increasing mortality rates reflect gaps in adolescent HIV care which is critical to adolescents' survival [1, 4, 5].

The effectiveness of the current essential biomedical ART interventions is compromised by gaps in the HIV care continuum among ALHIV [4, 6-10]. For example, systematic reviews show that adolescents have poor rates of adherence to ART [11, 12], and retention in HIV care remains substantially lower and reduces over time for this age group compared to children or adults in government healthcare services [6, 13]. Furthermore, research shows that adolescents continue to experience inadequate viral suppression, with average rates of 50% in adolescents compared to 90% for adults on similar regimens [4, 7, 14-17]. These gaps suggest the need for important non-clinical add-on support strategies to strengthen effectiveness [10, 18].

The role of poverty and inequality in impeding progress towards achieving the UNAIDS 95-95-95 treatment targets has been widely recognised [19]. Consequently, social protection has gained traction as a key programmatic area in the recently adopted Global AIDS Strategy 2012-2026. Social protection can be defined as a set of programs that protect people against poverty, vulnerability, and exclusion, with a particular focus on vulnerable population groups. The most widely implemented social protection tools in Africa are cash transfers or payments to households with objectives related to poverty reduction and health promotion [20]. South Africa has one of the largest government-run cash transfers in the form of social grants, which have the potential to reach large populations, including those living with HIV [21]. The impacts of social protection—either through spillover or indirect effects—on HIV treatment outcomes among adolescents and young people have not been widely evaluated.

Psychosocial interventions such as peer-led psychosocial support have also been identified, through systematic review and meta-analysis of randomised control trials (RCTs), as potentially effective in improving HIV treatment outcomes [5, 22]. Psychosocial support is

defined as interpersonal activities aimed at improving one's mental health and well-being [5, 9]. However, a few studies—mostly from RCTs—have demonstrated the effectiveness of social protection [23, 24] and psychosocial support [5, 25]. In particular, two recent RCTs from sub-Saharan Africa identify the effectiveness of a family-based economic empowerment intervention [26, 27] and NGO-led peer psychosocial support models [28] in improving ART adherence and viral load suppression among adolescents. Social protection mitigates structural deprivations by providing financial support to relieve some of the burdens of poverty [2, 23, 24], while psychosocial support promotes mental health [5, 9] which may influence adolescents' HIV treatment outcomes [29]. However, important questions remain: are such support strategies effective in improving HIV treatment outcomes among ALHIV, when implemented within national government health, economic and community services [5, 18, 23, 30].

No known longitudinal study in sub-Saharan Africa has examined the role of social protection [31] and psychosocial support, individually or simultaneously, in reducing poor HIV treatment outcomes among ALHIV in government healthcare services. To this end, this study sought to examine the associations of government-provided social protection, and psychosocial support with elevated VL, ART adherence, and disengagement from HIV care using a 3-wave cohort of ALHIV in South Africa.

8.3. Methods

Study design and sample

We collected data from adolescents ever-initiated on ART, recruited from South Africa's Eastern Cape province [32]. Adolescents were recruited from healthcare facilities (n=52), within the Buffalo City health district. At each healthcare facility, patient files were reviewed to identify all adolescents aged 10-19 years who had ever initiated ART, including those who were lost to follow-up (LFTU) within the healthcare system. To ensure the inclusion of those who were no longer engaged in care, adolescents identified through clinical records (90% uptake) were traced to >180 communities, approached for study participation, and, if consenting, interviewed at their preferred location. At baseline, 1046 adolescents living with HIV were interviewed. Additionally, N=473 (not included in this study) adolescent peers not living with HIV co-resident or in neighbouring households were also interviewed to avoid the risk of stigma.

Adolescents completed tablet-based questionnaires in their preferred language, with the support of research assistants trained in working with South African adolescents. Questionnaires assessed adolescents' experiences at home, in their communities, and in healthcare settings. The questionnaires were designed to be non-stigmatising and engaging through extensive stakeholder consultation, including with South African adolescents and were pre-piloted among (n=25) adolescents at baseline.

Viral load (VL) data used in this study was obtained from routine medical records searched for every study participant, across both paper-based and electronic records at each of the 52 healthcare facilities where participants received care. The medical record data was further supplemented by laboratory test data from the South African National Health Laboratory Services (NHLS) data warehouse (2014-2019). Study participants were linked to laboratory test records from the NHLS data warehouse using demographic information (name, surname, sex, and date of birth). Given that the viral load measures were conducted in line with the participant's clinic viral load monitoring schedule and did not always match the questionnaire dates, we assigned the closest viral load result, within 12 months from the interview date.

Ethics and informed consent

The main study was approved by the ethical review boards from the University of Cape Town (UCT/CSSR/2013/4) and (UCT/CSSR/2019/01), Oxford University (Oxford/CUREC2/12-21), and NHLS Academic Affairs and Research Management System (2019/08/07). Data-sharing agreements were granted by the provincial Departments of Health and Education and other participating healthcare facilities. Study participants provided written informed consent, including access to adolescents' clinical records.

Measures

Outcomes: The study's primary outcomes were (i) the categorical ART adherence trajectories derived in Chapter 5, (ii) a composite measure of elevated VL (≥1000 copies/ml) and non-adherence (elevated VL/non-adherence), and (iii) disengagement from HIV care –defined as having missed any clinic appointment in the past 12 months or no longer attending HIV services. Five best-performing self-reported measures of adherence evaluated for sensitivity in detecting elevated viral load were used to categorise longitudinal adherence, into four distinct trajectories using Group-based trajectory modelling (GBTM) [33, 34]. The four adherence trajectories were consistent adherence, low start and increasing adherence, gradually decreasing adherence, and low start and decreasing adherence described in more

detail elsewhere [33]. The composite measure of elevated VL and non-adherence was defined as having an elevated VL measure (≥1000 copies/ml) or reporting past-week non-adherence (one of the best-performing self-reported measures described in Chapter 4 [34]). Since the VL measurements did not align with the self-report interview dates we used VL closest to the interview date for each participant (within 12 months from the interview date). Self-reported ART non-adherence was measured as a binary indicator of missed doses in the past seven days (including weekdays and weekends and currently taking ART) [35]. This measure was assessed using adapted items from the Patient Medication Adherence Questionnaire [36]. Based on evidence from earlier studies including a study on this data which showed high test accuracy (agreement) between self-reported measures of adherence and VL measurements among ALHIV [34, 37-39] we combined viral load and adherence as VL was missing for some participants due to infrequent VL testing in this study setting [40]. Support strategies: Social protection was defined as the receipt of any direct government social grants in the adolescent's household. The government social grants included the following grants offered in South Africa: child support, foster, dependency, disability grants and old age pension [41]. Psychosocial support was measured using the Medical Outcomes Study Social Support Survey (MOS-SSS) scale's seven of the nineteen support items measured in this study data [42]. These included items on availability of someone to *(1) listen to you; (2) give you good advice; (3) share worries with; (4) turn to for suggestions; (5) help if confined in bed; (6) take you to the doctor; and (7) prepare meals*. Respondents were asked to rate how often each type of support is available when they need it and chose one of the three options ranging from 'never' (0) to 'always' (2). Participants who rated 'always' on all seven items were coded as accessing higher levels of psychosocial support. The reliability statistic for the MOS-SSS scale in this sample was very high ($\alpha = 0.94$).

Socio-demographic controls included: adolescent age, sex, residence (urban/rural, using the census definition), and housing type—defined as informal if an adolescent lived in a shack. Mode of HIV acquisition was defined as either perinatally or sexually acquired HIV. This was determined by following existing sub-Saharan African paediatric cohorts: age of ART initiation cut-off [≤10 years] [43, 44], validated and updated with a detailed algorithm that considered other factors (i.e. self-reported sexual history and parental death) in the absence of definitive clinic notes ascribing mode of HIV acquisition [45]. All covariates were selected based on prior literature indicating their importance.

Data analysis

Primary outcomes: the proportion of adolescents who had elevated VL (≥1000 copies/ml) or reported past-week ART non-adherence, ART adherence trajectories, and disengagement from HIV care . *Primary exposure*: (i) access to any government grant (social protection), and (ii) family psychosocial support.

8.3.1. Statistical Analysis

All analyses were performed in Stata version 17 (Stata Corporation, College Station, TX). Means and standard deviations or frequencies were used to present descriptive statistics of all measures across all study rounds. Differences between participants retained at all study rounds (analysis sample) and those lost-to-study-follow-up were assessed using the student *t*-test for continuous variables and the chi-square test for categorical variables. Similarly, differences between those with VL and those missing VL records were evaluated. Multinomial logistic regression was used to evaluate the relationship between baseline access to government social protection and family psychosocial support and longitudinal adherence trajectories. Mixed-effects logistic regression model to examine the association between social protection and psychosocial support and elevated VL/non-adherence, and their association with disengagement from HIV care, utilising the full repeated-measures data. All models were adjusted for known covariates. To aid the interpretation of the relationships between the two predictors and the outcome, we estimated the average adjusted probabilities of the impact of each or combination of two support strategies on elevated VL/non-adherence using the *margins* command in Stata version 17.

We also separately present associations of the two support strategies with each measure in the combined outcome elevated VL/non-adherence. For the VL load measure, we conducted multiple imputations by chained equations to impute missing VL values and the multivariable random-effects logistic regression model was applied to 20 imputed data sets, and results were combined using Rubin's rules for each model [46].

8.4. Results

Participant baseline characteristics

Of the 1 046 ALHIV (aged 10-19 years) who completed the questionnaire at baseline, 933 participants were retained at all three study rounds, forming the analytic sample for this study. This study had a 90.1% uptake with an average of 94.3% retention rate across the three

study rounds, and by the end of the third study visit, n=35 participants (3.4%) had passed away. There were no significant differences between participants retained at all study rounds and those lost-to-study-follow-up except that those lost-to-study follow-ups were likely to be older (Supplementary Table 8-1). At baseline, the mean age of the analytic sample (N=933) was 13.56 with a standard deviation ± 2.88. The proportion of female adolescents was slightly higher compared to males (55%), 27% lived in rural settings, and 18% in informal settlements. A fifth of this sample has likely recently (sexually) acquired HIV [43] (Table 8.1). The proportion of adolescents living in households accessing government-provided social protection was high: 94.6% (round 1) 91.3% (round 2), and 88.2% (round 3), with comparable proportions of adolescents who reported access to psychosocial support: 70% of adolescents (round 1), 79% (round 2), and 81% (round 3).

Rates of adherence, elevated VL, and disengagement from HIV care

In Table 8.1, self-reported past-week non-adherence was 34.1% at baseline, 35.2% (round 2), and 25.0% (round 3). Among those with a viral load record at each study round (n1=746; n2=656; n3=578), the proportion with elevated VL (≥1000 copies/ml) was 21.9% (round 1), 19.7% (round 2), and 26.1% (round 3). Over half 59.5% of adolescents had elevated VL/non-adherence at least once between study round 1 and round 3. A comparison of those with VL and those missing VL records completely (Supplementary Table 8-2) showed that older adolescents who recently acquired HIV at baseline were likely to be missing a VL record. About a third of those with any viral load record had at least one episode of elevated VL during the study period. 387 (41.5%) reported disengaging from care at least once between study round 1 and round 3.

Table 8.1: Summary of participant characteristics of the analytic sample over three study rounds (n=933)

Study	Round 1 (N=933)	Round 2 (N=933)	Round 3 (N=933)
Variables	**N (%)**	**N (%)**	**N (%)**
Outcome measures			
Past-week non-adherence	318 (34.1%)	328 (35.2%)	233 (25.0%)
Any VL record	746 (80.0%)	656 (70.3%)	578 (62.0%)
Viral load outcomes [¥]			
Elevated VL (≥1000 copies/ml)	164 (21.9%)	129 (19.7%)	151 (26.1%)
Suppressed (<1000 copies/ml)	582 (78.1%)	527 (80.3%)	427 (73.9%)
Outcome(s)			
Adherence trajectories[*]			
Consistent adherence	465 (49.8%)	465 (49.8%)	465 (49.8%)
Low start and increasing	194 (20.4%)	194 (20.4%)	194 (20.4%)
Gradually decreasing	219 (23.5%)	219 (23.5%)	219 (23.5%)
Low start and decreasing	55 (5.9%)	55 (5.9%)	55 (5.9%)
Elevated VL/non-adherence	330 (35.4%)	292 (31.3%)	229 (24.6%)
Disengagement from care	164 (17.6%)	216 (23.2%)	161 (17.3%)
Social-economic support			
Social protection	883 (94.6%)	852 (91.3%)	823 (88.2%)
Psychosocial support	649 (69.6%)	735 (78.8%)	755 (80.9%)
Covariates			
Age (Mean/SD)	13.56 (2.88)	15.07 (2.88)	16.26 (2.90)
Female	514 (55.1%)	514 (55.1%)	514 (55.1%)
Rural	249 (26.7%)	230 (24.7%)	223 (23.9%)
Informal housing	172 (18.4%)	134 (14.4%)	131 (14.0%)
Sexually acquired HIV	197 (21.1%)	197 (21.1%)	197 (21.1%)

[¥]Percentages calculated based on those with viral load data. [*]The trajectory groups are static hence the proportions are the same at each wave.

Associations of baseline psychosocial and economic support and trajectory membership.

The multivariate results in Table 8.2, show that access to government social protection at baseline was associated with lower odds of being in the low start and increasing adherence trajectory than in the consistent adherence trajectory (aOR 0.47, 95%CI 0.23-0.98, p=0.044). Baseline psychosocial support was associated with lower odds of being in the low start and decreasing than in the consistent adherence trajectory (aOR 0.42, 95%CI 0.23-0.76, p=0.004) adjusting for known covariates. Although significantly associated with adherence trajectory membership, viral load was not included in this model as it was viewed as an outcome rather than a predictor of adherence.

Table 8.2: Multivariable associations between psychosocial and economic support and ART adherence trajectories: A multinomial logistic regression analysis

Outcome	Low start and increasing		Gradually decreasing		Low and decreasing	
Baseline factors	**aOR (95%CI)**	**p-value**	**aOR (95%CI)**	**p-value**	**aOR (95%CI)**	**p-value**
Psychosocial and economic support						
Social protection	**0.47 (0.23-0.98)**	**0.044**	0.74 (0.36 -1.55)	0.428	0.56 (0.19-1.61)	0.283
Psychosocial support	0.73 (0.50-1.07)	0.107	0.86 (0.60 -1.23)	0.398	**0.42 (0.23-0.76)**	**0.004**
Covariates						
Age	1.58 (1.10-2.28)	0.014	1.37 (0.97-1.95)	0.077	**3.32 (1.88-5.85)**	**<0.001**
Female	1.34 (0.95-1.91)	0.100	0.79 (0.57-1.10)	0.158	**2.24 (1.18-4.25)**	**0.014**
Rural	**1.51 (1.04-2.21)**	**0.031**	0.7 (0.47-1.04)	0.075	1.01 (0.53-1.93)	0.971
Informal housing	0.74 (0.46-1.18)	0.200	0.99 (0.65-1.50)	0.946	0.71 (0.33-1.52)	0.374
Sexually acquired HIV	**1.88 (1.18-2.97)**	**0.007**	**1.84 (1.17-2.89)**	**0.008**	**5.31 (2.67-10.5)**	**<0.001**

Reference adherence group: Consistent adherence trajectory.
Legend: aOR Adjusted Odds Ratio, CI 95% 95% Confidence Interval,

Associations of psychosocial and economic support with HIV treatment outcomes.

In multivariate random-effects logistic regression models (Table 8.3), both social protection and psychosocial support were significantly associated with reductions in elevated VL/non-adherence. Adjusting for age, sex, rural residence, informal housing, and mode of HIV acquisition, accessing social protection in the household was associated with lower odds of elevated VL/non-adherence (aOR: 0.51, 95%CI 0.32-0.81, p=0.004), and disengagement from care (aOR: 0.52, 95%CI 0.36-0.77, p=0.001). Similarly, accessing psychosocial support was associated with lower odds of elevated VL/non-adherence (aOR: 0.65, 95%CI 0.49-0.85, p=0.001) and disengagement from HIV care (aOR: 0.46, 95%CI 0.35-0.59, p<0.001).

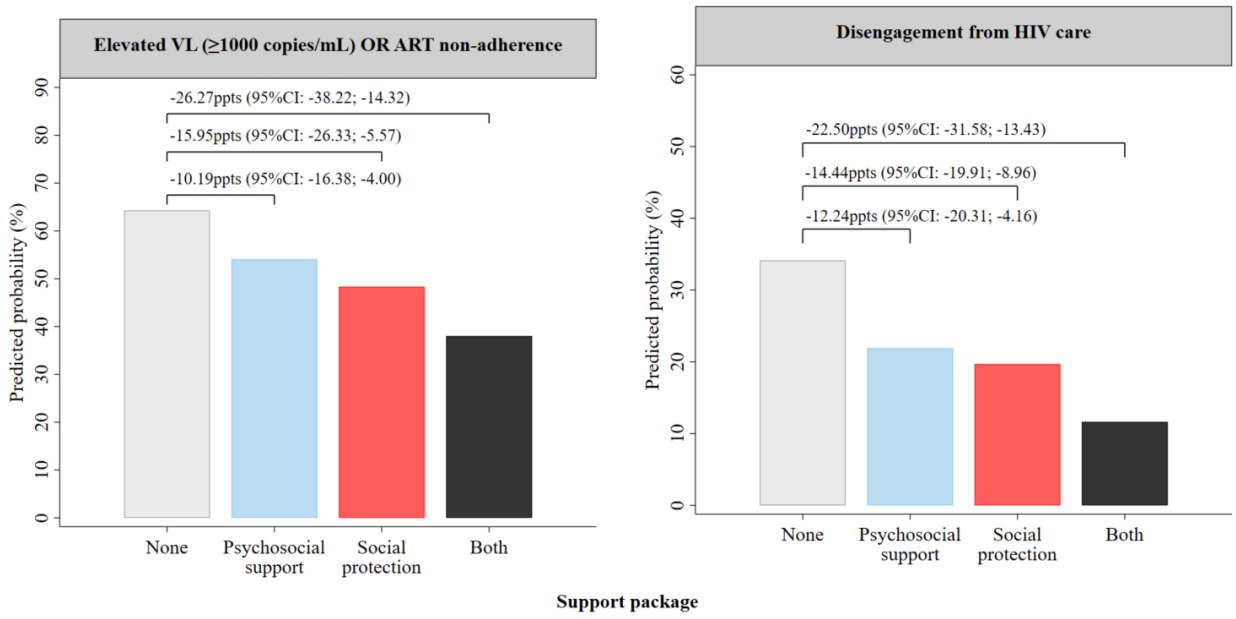
Table 8.3: Multivariable associations between psychosocial and economic support and HIV treatment outcomes (N=933)

Outcome	Elevated VL/non-adherence		Disengagement from HIV care	
Factors	**aOR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Psychosocial and economic support				
Social protection	**0.51 (0.32-0.81)**	**0.004**	**0.52 (0.36-0.77)**	**0.001**
Psychosocial support	**0.65 (0.49-0.85)**	**0.001**	**0.46 (0.35-0.59)**	**<0.001**
Covariates				
Age	**1.08 (1.02-1.14)**	**0.009**	1.03 (0.97-1.08)	0.326
Female	1.02 (0.78-1.34)	0.864	**1.35 (1.03-1.78)**	**0.032**
Rural	1.21 (0.90-1.63)	0.202	**0.72 (0.53-0.98)**	**0.038**
Informal housing	0.92 (0.65-1.28)	0.609	0.93 (0.66-1.33)	0.697
Sexually acquired HIV	**1.56 (1.05-2.31)**	**0.026**	**2.07 (1.44-2.98)**	**<0.001**

*All models adjust for the wave of the survey. aOR: adjusted odds ratio. CI: Confidence interval. Elevated VL is defined as viral load ≥1000 copies/ml.

Figure 8.1 shows the adjusted predicted probability of the main outcome comparing the impact of social protection and psychosocial support. The predicted probability of elevated VL/non-adherence for adolescents who had access to social protection and psychosocial support was 38.0% compared to 64.3% for those who did not access any support, thus a 26.3 percentage point difference (p<0.001).

Figure 8.1: Impact of psychosocial and economic support on elevated VL/non-adherence and disengagement from HIV care among 933 adolescents living with HIV (10–19-year-olds) in South Africa



Sensitivity analysis

A sensitivity analysis assessing the association between social protection and psychosocial support for the separate outcome measures (with VL measure imputed) showed similar results (Supplementary Table 8-3).

8.5. Discussion

There is an urgent need for more effective, evidence-based support to improve adolescent HIV treatment outcomes. This study extends the preceding work on ART adherence trajectories by examining the influence of social protection (government cash transfers) and psychosocial support on adherence trajectory membership. In this study, social protection and psychosocial support were predictive of adherence trajectory membership. Specifically, both support strategies were independently associated with lower odds of belonging in the trajectories that exhibit inconsistent adherence over time. In addition, the study showed that social protection and psychosocial support were associated with reductions in the odds of elevated VL/ART non-adherence, and disengagement from HIV care among ALHIV. Combining both social protection and psychosocial support maximised the reductions in the probability of elevated VL/ART non-adherence and disengagement from HIV care. Our study findings suggest that integrating social protection and psychosocial support into HIV care may optimise HIV treatment outcomes. These results show the potential of structural support, already embedded in the participants' lives, to enhance the global AIDS response in resource-poor settings.

These findings are similar to those from previous work in SSA, mostly from randomised control trials, which have demonstrated the potential of both social protection and psychosocial support in reducing HIV-risk behaviour. For example, a recent longitudinal cluster randomised trial in Uganda (2012-2017) found that family-based economic empowerment addressing economic insecurity improved ART adherence among vulnerable ALHIV [26, 27]. Another study among 35 ALHIV in Ghana found a reduction in non-adherence between baseline and 9-months of receiving conditional economic incentives [47]. However, they did not find any change in viral suppression during the study. Recent research has also demonstrated that NGO-led peer psychosocial support improves ART adherence and reduces viral load among adolescents [28]. Several reviews also underscore the potential of psychosocial interventions to support ALHIV to achieve better HIV treatment outcomes [5,

22]. Overall, our findings demonstrate the potential of bundled cash plus care support packages to improve HIV treatment outcomes among ALHIV [24, 48].

Our study is not without limitations. First, our findings come from a prospective cohort study rather than an experimental design hence causality cannot be inferred or proved. This study did, however, use longitudinal data with three waves of repeated measures, which has higher statistical power than cross-sectional designs [49]. Second, our measures of ART non-adherence were self-reported which is prone to social desirability and recall bias [8, 37, 50-52]. However, data for this study was collected by research interviewers who were trained to work with adolescents, lowering social desirability. Moreover, we used a recent (past week) measure of non-adherence to minimize recall bias. Third, the timing of the viral load testing was not always close to our study questionnaire dates but rather informed by the adolescent's viral load monitoring schedule, in line with the South African HIV treatment guidelines. Viral load was also missing for a number of participants which may have underestimated the extent of elevated VL. This may bias the relationship between the protective factors and outcomes. However, this study used a composite measure combining self-reported non-adherence and viral load data from national health records collected through standard procedures. Fourth, the social protection measure focused on government-provided cash transfers, and further research should examine other sources of social protection, such as NGOs. Last, this study is limited to a single country in SSA, so generalisability across the region is unknown. However, South Africa is a particularly valuable country for this investigation given the high coverage of HIV-affected populations and the world's largest population of adolescents living with HIV.

Despite these limitations, this study provides important evidence to inform the combination of effective psychosocial and economic support for ALHIV in low-resource settings. Our results show that mitigating socioeconomic stressors such as poverty through social protection programmes combined with psychosocial support may improve HIV treatment outcomes in ALHIV. This study further demonstrated substantial reductions in the risk of poor HIV treatment outcomes, associated with social protection plus psychosocial support provided by the government, schools, and families in communities where adolescents live. Therefore, there is a need for HIV programs to ensure the deliberate inclusion of ALHIV in social protection programmes and additional community-based support. Further research and interventions should focus on enhancing these natural support structures, identifying, and

addressing gaps, and exploring how these programs can be leveraged synergistically to optimize HIV treatment outcomes.

Conclusions

This study assessed whether social protection and psychosocial support are associated with ART adherence and viral load outcomes, proxies of the Global AIDS targets for ALHIV. Findings suggest that access to government cash transfers and family psychosocial support are independently and in combination, associated with reductions in long-term poor ART adherence and elevated VL as well as reductions in disengagement from HIV care. As ALHIV continue to experience multiple challenges, there is a need to prioritise access to ART medication as well as essential support resources that capacitate health and wellbeing. HIV programming may need to play a catalytic and linking role, by facilitating the inclusion of ALHIV in available structural support programmes. These findings are also important for national governments, donors, and service providers seeking scalable support strategies that can be delivered simultaneously- and ideally address multiple HIV treatment outcomes in ALHIV.

8.6. Supplementary Tables and Figures:

Supplementary Table 8-1: Comparison of baseline characteristics for complete cases and LFTU[¥] (Full sample)

	Total (N=1046)	Interviewed at all three rounds (N=933)	Loss-to-study-follow up (N=113)	
Baseline characteristics	**N (%)**	**N (%)**	**N (%)**	**P-value**
Age (15+ years)	394 (37.7)	337 (36.1)	57 (50.4)	**0.003**
Female	576 (55.1)	514 (55.1)	62 (54.9)	0.964
Rural residence	271 (25.9)	248 (26.6)	23 (20.4)	0.509
Informal housing	196 (18.7)	172 (18.4)	24 (21.2)	0.728
Orphanhood	616 (58.9)	545 (58.4)	71 (62.8)	0.367
Sexually acquired HIV	222 (21.2)	197 (21.1)	25 (22.1)	0.689

[¥] LFTU represents adolescents lost-to-study follow-up at least one-study round.
*At each successive study round, participants were actively followed up. Below is the breakdown of the (N=113) loss-to-study follow up between Round 1 and 3: (N=12) passed on between Round 1 and 2, and (N=22) passed on between Round 2 and 3, (N=55) were lost-to-follow-up for the following reasons between Round 1 and Round 2: - refusals, untraceable or avoidant. (N=24) were lost-to-follow-up between Round 2 and Round 3 either as refusals, untraceable or avoidant.

Supplementary Table 8-2: Baseline factors associated with missing VL at all three study rounds (N=933)

	Total (N=933)	Has at least one VL record (N=845)	Missing VL (N=88)	
Variables	**N (%)**	**N (%)**	**N (%)**	**p-value**
Age	13.56 (2.88)	13.48 (2.86)	14.33 (2.94)	**0.009**
Sex				0.210
Male	419 (45%)	385 (46%)	34 (39%)	
Female	514 (55%)	460 (54%)	54 (61%)	
Place of residence				0.520
Urban	684 (73%)	622 (74%)	62 (70%)	
Rural	249 (27%)	223 (26%)	26 (30%)	
Informal housing				0.190
Formal	760 (82%)	682 (81%)	78 (89%)	
Informal	172 (18%)	162 (19%)	10 (11%)	
Mode of HIV acquisition				**<0.001**
Vertically acquired HIV	729 (79%)	669 (79%)	60 (72%)	
Sexually acquired HIV	197 (21%)	174 (21%)	23 (28%)	

Supplementary Table 8-3: Impact of psychosocial and economic support on HIV treatment outcomes after VL missing data imputation.

Outcome	Past-week non-adherence		Elevated VL[¥]	
Factors	**aOR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Psychosocial and economic support				
Government-provided social protection	**0.47 (0.38-0.58)**	**<0.001**	**0.56 (0.37-0.84)**	**0.006**
Psychosocial support	**0.68 (0.49-0.95)**	**0.022**	**0.59 (0.47-0.76)**	**<0.001**
Covariates				
Age	1.01 (0.97-1.05)	0.567	**1.08 (1.03-1.14)**	**0.003**
Female	1.19 (0.97-1.47)	0.096	1.02 (0.79-1.33)	0.865
Rural	0.94 (0.75-1.18)	0.587	1.25 (0.95-1.65)	0.109
Informal housing	0.86 (0.65-1.12)	0.260	0.98 (0.71-1.36)	0.920
Sexually acquired HIV	**1.77 (1.34-2.35)**	**<0.001**	**1.62 (1.10-2.38)**	**0.015**

*All models adjust for the wave of the survey. [¥]Multiple imputations by chained equations were used to impute missing dichotomous elevated VL values. aOR: adjusted odds ratio; 95% CI – confidence interval.

8.7. References

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CHAPTER 9. DISCUSSION AND RECOMMENDATIONS

The main aim of the thesis was to contribute to the evidence gap on longitudinal ART adherence and HIV treatment outcomes among adolescents living with HIV (ALHIV) in sub-Saharan Africa (SSA). Specifically, this thesis sought to: (1) explore the longitudinal ART adherence trajectories among adolescents, (2) investigate the factors that determine distinct adherence trajectories among adolescents living with HIV, and (3) assess the association between longitudinal adherence trajectories and HIV treatment outcomes among adolescents living with HIV. The results included in this research come from a cohort of ALHIV and their HIV-negative peers in the Eastern Cape province of South Africa. This chapter brings the findings together and discusses their contribution to existing literature, pragmatic practices, and policy implications. It also includes reflections on the study's strengths and limitations and directions for future research.

9.1. Main contributions of this PhD and key recommendations

This research contributes to several critical gaps in adolescent health research in South Africa and SSA. The essential findings from the five results chapters included in this thesis are:

1. Self-reports are a potentially valuable tool for measuring ART adherence among ALHIV over time.
2. GBTM may be used to describe adolescents' longitudinal ART adherence and facilitate the identification of groups at risk of non-adherence.
3. Not all adolescents living with HIV are the same, adolescents were segmented into unique groups displaying distinct longitudinal adherence behaviour patterns with different levels of risk for poor HIV treatment outcomes.
4. HIV treatment outcomes, including long-term adherence to ART are poor among adolescents.
5. Promising strategies or forms of support for adolescents to achieve optimal HIV treatment outcomes.

9.1.1. Self-reports are a potentially valuable tool for measuring ART adherence among ALHIV over time.

There are many ways of measuring adherence to ART, although none provide a perfect measure (consistent across time and settings) [24, 189]. Many studies demonstrate that ART

adherence varies significantly by measure [192] and that self-reported adherence measures—which are more accessible in resource-constrained settings—are prone to bias and likely to overestimate adherence. Despite these issues, this thesis demonstrated that longitudinal self-reported measures may be useful in identifying adolescents at risk of non-adherence and potentially flag current or pending elevated viral load. This thesis further demonstrated that combining feasible multiple self-report measures, assessed longitudinally, significantly improves sensitivity to detect cases of elevated VL.

The five self-reported measures of adherence used in Chapters 4 and 5—adapted from the Patient Medication Adherence Questionnaire [217] —were associated with viral load and had high test accuracy (able to discriminate between adolescents with and without elevated VL). The measures included four items on missed doses *in the past 3 days, past week, past month,* and *any past-month days missed* and one item on *missed clinic appointments* [218, 219]. This is one of the first studies to evaluate multiple longitudinal self-reported measures against viral load, providing evidence of the value of self-reports measured over time. Although adherence measurement in this study was unique in that (i) the questionnaire was facilitated by staff trained to work with adolescents and (ii) outside the health care setting, these results provide a proof of concept for the use of self-reported measures (single item or in combination) to detect non-adherence in routine clinical care and research settings. Self-reported measures are simple, inexpensive, and relatively easy to administer [188]. In the absence of a perfect measure, self-reported measures will likely continue being used in research and clinical settings. Therefore, more efforts to refine and improve these for ALHIV are needed**.** These findings demonstrate that self-reported measures may be used widely, to develop adolescent-friendly methods to screen or identify adolescents at risk of poor adherence. Based on these findings, we recommend that research and clinical practice develop low-cost adolescent-specific adherence measurement tools, integrating the non-stigmatising self-reported measures identified in this thesis, for use in resource-limited settings. However, these tools may require some training to implement in and outside of healthcare settings.

9.1.2. Not all adolescents living with HIV are the same.

Applying the five self-reported measures identified in Chapter 4 and group-based multi-trajectory modelling, adolescents were segmented into unique groups displaying distinct longitudinal adherence behaviour trajectories over the four-year study period. Compared to traditional methods of assessing adherence—which divides adolescents into adherent and

non-adherent groups—results from Chapter 5 show that the adolescent population comprises four unique groups with distinct patterns of adherence to ART over time. Of the ALHIV in the study, 49.8% were classified into the (i) consistent adherence trajectory: a group of adolescents who start high and consistently report taking their ART over time, 23.5% into the (ii) gradually decreasing trajectory, 20.8% into the (iii) low start and increasing trajectory, and 5.9% were consistently non-adherent (iv) low start and decreasing trajectory. All four trajectory groups were distinct by age, sex, and mode of HIV acquisition which is essential for targeting. For example, older female adolescents (≥ 15 years) who acquired HIV sexually were more likely to be in the low start and decreasing trajectory. These findings suggest both heterogeneity and inconsistencies in long-term ART adherence, which is relevant to understanding differences in adolescents' medication-taking behaviour over time. This information can inform policy on the groups of the adolescent population who may need more support in navigating living with HIV. While prior research has focused on adults [71, 197] and/or women's [220] ART adherence trajectories, this research is one of the first to conduct an exhaustive assessment of ART adherence trajectories in adolescents from a natural setting followed up over four years.

Further exploration of the distinct groups in Chapter 7, showed that adolescents have unique experiences that shape, and help explain changes and inflexions in their ART adherence behaviour trajectories. This analysis identified clusters of barriers contributing to each adherence trajectory relative to the consistent adherence trajectory. ART medication side effects and mental health symptoms were directly associated with the low start and increasing adherence trajectory, while experiencing food insecurity and clinic travel time (>1 hour) were directly associated with the gradually decreasing adherence trajectory. ART medication side effects and mental health symptoms, internalised HIV stigma, clinic travel time (>1 hour), and witnessing domestic violence or conflict were directly associated with the low start and decreasing adherence trajectory. These findings corroborate the existing evidence on barriers to adherence among adolescents [23, 30, 147] and further provide insight into how different barriers or experiences at different strata of their ecological environment shape distinct adherence trajectories among ALHIV. Intervention efforts should consider multi-level adherence support strategies, customised for specific adolescent risk groups based on their life experiences and adherence behaviour, to maximise impact. The clusters of barriers identified above could be used to develop new screening tools for adolescent well-being or

refine existing checklists for use in resource-limited settings such as the WHO's HEADSS/HEADSS+ [221].

While most quantitative studies measure direct relationships [222], this thesis also explored indirect pathways linking barriers contributing to each of the adherence trajectory groups across multiple levels of the socio-ecological model namely: individual, household, community, and health care levels. We found that the gradually decreasing adherence trajectory had simpler pathways, and the two inconsistent adherence trajectories had more complex pathways. While adolescents following the gradually decreasing trajectory face food insecurity and clinic travel or proximity challenges which hinder sustaining adherence over time, the low start increasing/ decreasing trajectories are exposed to multiple interlinked challenges. Identifying these early (i.e., at diagnosis) for immediate support may be essential to interrupt pathways of risk to poor long-term ART adherence. Indirect pathways identified in this thesis point to existing multi-level mechanisms leading to distinct adherence trajectories among ALHIV. These findings call for the need to intensify multi-level intervention efforts, particularly for adolescent groups exhibiting complex pathways.

While evidence on the association between mental health and adherence has been established, there is a noticeable lack of evidence—specific to adolescents—on indirect pathways linking potential causes of mental health symptoms to long-term adherence. This thesis provides granular data on the association between mental health symptoms and adherence, which includes unique pathways linking co-occurring barriers and mental health symptoms to longitudinal adherence for different groups of adolescents. The unique pathways point to specific forms of trauma and violence exposure for different adolescent groups which may impact their mental health, leading to unique adherence trajectories. Addressing causes of common mental health symptoms such as bullying in schools, and violence in homes and communities may interrupt pathways of risk between mental health and adherence to lifelong ART [223-225]. These findings have implications for policy and practice. First, the role of mental health in adolescents' ART adherence calls for the need to integrate mental health support into adolescent HIV care. This includes investing in establishing and maintaining linkages between HIV care and mental health services. Second, we need to adapt current care models to incorporate trauma-informed approaches. The main goals of trauma-informed care are to (i) reduce repeated trauma, (ii) highlight adolescent (victim) strengths and resilience, (iii) promote healing and recovery from the experience, and (iv) support the development of

healthy coping mechanisms [226]. In practice, healthcare practitioners could identify causes of mental health symptoms, including different forms of trauma, and use these as entry points to intervention or supporting ALHIV. Third, there is a need to strengthen counselling support for mental health among ALHIV in routine clinical care, as well as preparing adolescents for transfer to adult care, treatment side effects, and adherence to life-long ART.

Together, these results highlight several important opportunities to support long-term adherence to lifelong ART and improve HIV treatment outcomes in adolescence. Along with efforts to reduce mental health symptoms among ALHIV, there is a need to implement or maintain targeted interventions to address food insecurity and healthcare-related barriers such as clinic proximity. The interventions may include scaling up existing social protection in the form of government cash grants and food parcels, to address food insecurity. Introducing mobile clinics to deliver care where ALHIV are or offering clinic transportation subsidies may address clinic proximity or travel issues. Broader efforts to reduce internalized HIV-related stigma among ALHIV are also needed, especially in schools, homes, or communities where adolescents spend most of their time. Together these findings suggest the need for multi-sectoral interventions to support adolescents to sustain adherence to lifelong ART. These findings have implications for designing adolescent-centered interventions, including how interventions may need to address multiple levels of the adolescent's socio-ecological environment to achieve success. This points to the need for a holistic and integrated suite of support mechanisms in HIV care to support adolescents and young people living with HIV [31, 137, 151, 153, 168, 173, 178, 227], with the potential for scaling up differentiated service delivery (DSD) models in resource-limited settings [228]. In particular, the findings support the implementation of DSD to support targeted HIV care for adolescents in SSA.

9.1.3. HIV treatment outcomes are poor among adolescents

Research on long-term sustained or consistent adherence to ART among ALHIV in low-resource settings remains scarce. Sustained adherence to ART is necessary to achieve long-term viral suppression and improve immunological and clinical outcomes, and survival [58]. The combined results of this thesis highlight substantial long-term inconsistent adherence, poor viral suppression rates, and high rates of mortality among ALHIV. In Chapter 5, only 49.8% of the ALHIV cohort displayed consistent adherence, and the remaining 50.1% displayed different forms of inconsistent adherence over the study period. These results show that few adolescents maintain adherence over time and are similar to those reported studies—

which predominantly used single self-reported measures to model adherence [56, 57]—indicating a significant challenge of not only immediate but sustained adherence over time among adolescents.

This may explain the observed poor, and declining rates of viral suppression over time illustrated in Chapter 5, mirroring the inconsistent trend in ART adherence over the study period. Results from Chapter 5 showed that rates of viral suppression (≤1000 copies/mL) decreased from 59.4% to 50.1% over the study period, among those with VL test measurements at two or more study visits. These rates are comparable with those reported in South Africa among adolescents on similar ART regimens [9, 19, 44] and those reported elsewhere in SSA [229-231], but lower than the UNAIDS target of 95% [232]. This aligns with recent survey estimates of the adolescent treatment cascade, which show that adolescents have lower attainment of each step of the treatment cascade target, with only 78% virally suppressed [21]. Results in Chapters 5 and 6 further revealed that viral suppression rates differ by adherence trajectory groups, demonstrating that variations in patterns of ART adherence over time influence HIV treatment outcomes of ALHIV. Adolescents categorised in trajectories displaying inconsistent adherence over time had significantly lower rates than those with sustained adherence over the study period. The rates ranged from 63.9% in the consistent adherence trajectory to 28.6% in the low start and decreasing trajectory, falling short of the 95% UNAIDS target [8]. These findings suggest that within the adolescent population, there are groups that experience lower levels of viral suppression than others. Despite ongoing challenges in viral load monitoring among adolescents in low-resource settings [81, 82], this thesis demonstrates that adolescents are at high risk of treatment failure [190, 233] and drug resistance [190].

Results from Chapter 6, further suggest differentials in all-cause mortality rates across different adolescent adherence trajectories. Most importantly, the findings in this chapter show that adolescents with sustained ART adherence—categorised in the consistent adherence trajectory—have significantly lower mortality rates compared to those displaying inconsistent adherence over time. The results of this thesis provide additional insight into all-cause mortality rates among adolescents in general. Chapter 6 showed considerable mortality among ALHIV compared to their HIV-negative peers (8.7% vs 0.4%). This may be partly due to disproportionately poor treatment outcomes [234] including poor adherence to ART. Poor adherence was highlighted as a risk factor for all-cause mortality among ALHIV in this

thesis. Moreover, there is limited disaggregated data on mortality among adolescents and this thesis further contributes to knowledge by giving all-cause mortality data disaggregated by sex, age, and mode of HIV acquisition. The findings suggest marked sex differences in all-cause mortality among ALHIV, with higher proportions of deaths among males than females. Adolescent-centred interventions, including efforts to improve adherence to life-long ART, may present an opportunity to reduce mortality among ALHIV. Careful consideration is required to prioritise adolescents' vulnerabilities and address inequities to improve survival.

The long-term success of ART requires consistent adherence, sustained through one's lifetime [235]. Inconsistent adherence to ART during adolescence observed in this thesis presents a risk for poor viral suppression, treatment failure, and mortality. To sustain the benefits of lifelong ART as adolescents grow older, it is essential for adherence support strategies to shift focus to sustained adherence and engagement in ART services. National HIV programmes should focus on strengthening routine viral load monitoring in public healthcare facilities where adolescents receive care, to facilitate timely access to tailored adherence support. Additional focus is needed on the South African adolescent HIV population, to develop systems for tracking mobile ALHIV—considering challenges around transition to adult care [212, 236]—to prepare the health care system to adapt to changing patients' circumstances. Current national guidelines for the management of HIV in adolescents [77] should be adapted to consider the heterogeneous nature of the adolescent population. Overall, adolescent-specific interventions to address long-term poor ART adherence and viral load suppression are urgently needed. Findings from this thesis contribute to filling the existing gap in understanding longitudinal adherence to ART and its impact on long-term HIV treatment outcomes among ALHIV in SSA.

9.1.4. GBTM is useful in describing ART adherence trajectories and may facilitate the identification of distinct non-adherence risk groups.

One of the primary objectives of this thesis was to explore the longitudinal ART adherence trajectories among adolescents. To achieve this, this research employed GBTM, an emerging methodology in the study of medication adherence [38, 237]. As demonstrated in Chapter 5, the application of multi-trajectory GBTM identified four distinct adherence trajectories within this population group; one consistent adherence trajectory that consistently reported adherence to ART, and three trajectory groups with varying patterns of inconsistent adherence over the observation period. When compared to the consistent adherence group,

there were statistically significant differences in viral suppression levels and all-cause mortality. This is one of the first applications of GBTM to model adolescents' longitudinal ART adherence in SSA, with the majority of prior applications examining trajectories of HIV-care retention [70, 238-240], ART adherence [62, 220, 241], and viral loads [65, 68] among adult populations. For example, a recent study in the United States applied GBTM to describe ART adherence trajectories among women aged 18 years or older [220]. This study identified four adherence trajectories namely: consistent high, moderate increasing, moderate decreasing, and consistently low adherence group. Compared to the consistently high adherence group, the risk of virologic failure was found to be significantly higher among the other three trajectories displaying varying degrees of inconsistent adherence. Another study conducted on African American adults living with HIV in the US identified three distinct ART adherence trajectories with statistically significant differences in perceived treatment effectiveness, substance use, and healthcare quality ratings [197]. Similar findings were observed in a study in Senegal, conducted among adults living with HIV [241]. These studies demonstrated that GBTM provides a strong statistical tool to summarise large datasets and discover hidden groups of people that follow unique trajectories.

The findings from this thesis show the utility of multi-trajectory GBTM in summarising longitudinal adherence patterns among adolescents, with the potential to:

i. *Reduce measurement bias resulting from the use of single self-reported adherence measures.*

An extension of GBTM, the multi-trajectory GBTM, allows the use of multiple measures or indicators of a behavioural phenomenon [237]. In particular, the use of multiple categorical indicators or measures of ART adherence to categorise trajectories may lead to a more comprehensive assessment of adherence compared to single measures. As demonstrated in Chapter 4, combining multiple indicators of adherence maximised test accuracy in predicting elevated viral load. This is particularly important in low-resource settings, where viral load testing is infrequent and there is limited consistent adherence monitoring.

ii. *Provide insights into the heterogeneous nature of the adherence behaviour, and how adherence among ALHIV changes over time.*

Although the application of GBTM in clinical research has grown in the past decade, its application in modelling adolescents' ART adherence remains limited. This study is one of

the first in South Africa to provide a more nuanced description of adolescents' ART longitudinal adherence, a group that is well-documented to have suboptimal adherence. In particular, this thesis demonstrated that dichotomising adolescents as adherent versus non-adherent and examining within-person patterns of adherence is insufficient to capture the heterogeneous nature of adherence [51, 242-244]. The application of GBTM is essential in ART adherence literature, particularly for adolescents (Chapter 5), as it captures the variability in their long-term adherence behaviour and describes its heterogeneous nature over time. Moreover, the use of longitudinal measures for categorising trajectories reduces the potential of making misleading conclusions based on cross-sectional assessments. The results from GBTM are essential and may inform tailoring and targeting adherence support interventions, and focusing on adolescents at risk of poor adherence and subsequent treatment failure rather than all ALHIV [245].

iii. Assist healthcare providers to identify individuals at increased risk of poor adherence or treatment failure.

Methodologically, the adherence trajectories in Chapter 5 reveal two important things: (1) adherence items or measures used in this analysis appropriately capture ALHIV adherence behaviour over time –trajectories align with adolescents' viral load, and (2) the trajectories give an approximate picture of the changes in adherence among adolescents and their effect on viral suppression. Given this, the multiple items or measures of adherence used in this study could be used as prompts in this setting to query patient adherence behaviour and anticipate their possible adherence trajectory. Trajectories based on these multiple self-reported measures—capturing multiple recall strategies and timelines—may also inform the development of adolescent-specific adherence measurement tools or scales [246] and construct better adherence metrics. The identification of socio-demographic characteristics unique to each trajectory group (Chapter 5) may facilitate the identification of individuals at most risk of poor adherence [62], and provide actionable insights to tailor interventions compared to traditional metrics of ART adherence.

iv. Facilitate the identification of the determinants of distinct adherence trajectories among adolescents.

Research shows that there exist few effective interventions to improve adolescent ART adherence [31], and hence a need to develop and test targeted intervention strategies to

improve adherence among this high-priority population. Trajectory groups identified using GBTM facilitate the identification of modifiable factors or determinants of each distinct trajectory [247] as demonstrated in Chapter 7. By examining the individual, household/family, community and healthcare factors researchers and clinicians can pinpoint key variables that influence adherence behaviour. This information can inform the development of tailored care and adherence support strategies for adolescents.

Overall, GBTM is valuable for understanding the dynamics of adherence over time, which is essential to track how adherence changes and identify when different groups of adolescents are most at risk. This approach also facilitates the identification of potential triggers for fluctuations in ART adherence over time, which may be unique for specific trajectories. This is crucial and offers insights into when and what interventions may be needed, allowing for more timely and tailored support to prevent viral non-suppression. GBTM can also uncover subtle differences in the type of support needed by groups of adolescents following unique adherence trajectories, and the intensity and approach of interventions may differ, which is valuable for clinical practice.

9.1.5. Promising strategies or forms of support for adolescents to achieve optimal HIV treatment outcomes.

The role of poverty and inequality in impeding progress towards achieving the UNAIDS 95-95-95 treatment targets has been widely recognised [248]. Consequently, social protection has gained traction as a key programmatic area in the recently adopted Global AIDS Strategy 2012-2026. The results from Chapter 8, provide evidence for the impact of social protection HIV treatment outcomes among ALHIV. Using access to direct government social grants as an indicator of social protection, this thesis found a strong positive association with improvements in ART adherence and viral load outcomes over time. Over 90% of the cohort accessed this form of social protection over time. These findings provide real-life longitudinal evidence for the impact of social protection on HIV treatment outcomes for adolescents.

In the thinking on social protection, psychosocial support has largely been missing and recent evidence shows that psychosocial support interventions—broad-based or targeted—offer potential pathways to improve health and behavioural outcomes [170, 178]. However, there is little evidence on the nature and impact of psychosocial support for ALHIV [249]. The findings from Chapter 8 demonstrate that family-provided psychosocial support plays a

significant role in improving ART adherence and viral suppression among ALHIV in resource-limited settings. Literature shows that psychosocial support promotes mental health and well-being [170], which was highlighted as one of the barriers to sustained ART adherence among ALHIV in this thesis. Psychosocial support has also been shown to have the potential to reduce HIV-related stigma in South Africa [250]. Therefore, efforts to foster family psychosocial support are crucial for adolescents and young people. ART programmes and interventions should seek to promote family-centred programming [251] and encourage family-oriented psychosocial support to improve the health and psychosocial well-being of ALHIV.

Furthermore, the effects of integrated intersectoral interventions—combining social protection and psychosocial support—have not been synthesized among adolescents. This thesis demonstrates that adding psychosocial support programs to social protection may maximise the impact on HIV treatment outcomes. These findings have important implications for national governments, non-governmental organisations, and service providers seeking scalable support services that can be delivered simultaneously- and ideally address multiple HIV outcomes in ALHIV. For the governments, this may mean sustaining the social grant system and ensuring that it is HIV-sensitive [252]. There is a need to promote economic empowerment activities [174]—at both household and community levels—and expand on existing targeted psychosocial interventions for adolescents and young people [178].

9.2. Implications for clinical providers and program implementation

The findings emphasise a need for adolescent-sensitive approaches in HIV care, tailored for different adolescent risk groups, to address adherence challenges and improve overall health outcomes. Clinical providers can use the findings to develop self-reported adherence measurement tools, specifically designed for adolescents. These tools can serve as quick and effective interim screening mechanisms to identify those at risk of non-adherence early. By leveraging insights from ART adherence trajectories, program implementation should focus on developing multi-level, tailored support strategies that address the diverse socio-ecological barriers faced by adolescents, to promote long-term adherence to ART and improve their long-term treatment outcomes. Targeted support strategies and interventions such as social protection programs, that help address some of the structural challenges facing ALHIV, should be integral to the comprehensive care strategy. Moreover, programming should integrate mental health support into adolescent HIV care. This could be done through

strengthening counselling in HIV care, incorporating trauma-informed care principles and family-centred programming.

9.3. Limitations and Strengths

The overarching limitations and strengths of the thesis should be considered. The focus on adolescents 10 to 19 years of age at recruitment, is a limitation, which results in a survivor bias, as individuals with vertically acquired HIV would have had to survive childhood to be eligible for inclusion in the study. The age of the data (2014-18) may impact the relevance of these findings to current practice, which has transitioned from NNRTI-based ART regimens to newer ART drug regimens that include dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI) [253]. This has implications on the well-documented ART adherence-viral suppression relationship, with recent evidence from randomised control trials showing that this relationship is likely to be different with the availability of new drug regimens [254] . The prevalence of mortality in this cohort may also mean that those adolescents who died were more vulnerable, potentially risking underestimation of effects. Another limitation is the use of self-reported measures which are prone to social desirability and recall bias [24, 26, 192, 255, 256]. Additionally, the tool used to measure adherence in this study was unique in that it was facilitated by adolescent-trained staff, and it was conducted outside of the healthcare system, which may limit generalisability of our results in routine clinical settings. Furthermore, our VL measure was missing for several participants—15.8% of the analytic sample had no VL measure at all three waves—which may have underestimated the extent of elevated VL and virological treatment failure. This may also bias the relationship between the protective factors and outcomes. Lastly, this study is limited to a single country in SSA. However, South Africa is a particularly valuable country for this investigation, and the issues discussed in this thesis are relevant beyond this setting.

The strengths of this research include that the cohort of ALHIV was large and that a cohort of age-matched HIV-negative adolescents from the same communities was included as a comparator. The inclusion of HIV-negative peers as a comparison group makes these findings generalisable to other countries or similar contexts in sub-Saharan Africa, as well as other resource-constrained settings. All adolescents were followed longitudinally—three times over four years—which is sufficient to examine the short- and mid-term effects. The longitudinal design strengthens the precision of the associations between our exposures and outcomes, via temporal ordering and has higher statistical power than cross-sectional designs

[257]. Moreover, this study actively traced adolescents over multiple waves, allowing the inclusion of adolescents who have moved between healthcare facilities or disengaged from care. Cohort retention was high, and for the objectives that required longitudinal viral load outcomes, routine data were accessed from the National Health Laboratory Services (NHLS) data warehouse to strengthen this study data. Combining longitudinal self-report data and routine data can help offset the limitations of the respective data type [258] and can generate evidence with a high level of external validity. Self-reported data in this study was based on standardised questionnaires which were administered by research assistants trained to work with adolescents, and outside of routine HIV care. The use of multiple self-reported adherence items with varying item content and recall timeframes—validated against viral load outcomes—to describe longitudinal adherence is more robust and corrects for measurement bias to construct better adherence metrics [259]. Furthermore, the use of longitudinal statistical methods such as GBTM provides timely relevant insights into challenges faced by ALHIV over time. Another strength of this study is that it provides evidence from a sample of ALHIV accessing care through government services in South Africa's Eastern Cape Province, a province affected by poor health infrastructure and high rates of HIV [260].

9.4. Directions for future research

Continuous assessment and monitoring of adherence and subsequent HIV treatment outcomes among adolescents is essential. However, there is a potential for 'research fatigue' in this population as the current generation of ALHIV may have been participating in research for most of their childhood. Given the large population of over 300,000 ALHIV in South Africa, future research should prioritize strategies to adequately reach and engage underrepresented groups, ensuring broad and equitable participation in research. There is also a need for innovative ways of engaging ALHIV to sustain follow-up as they transition to adult care. These may include accessing electronic records such as through NHLS to reduce the need for face-to-face visits.

This thesis provides a proof of concept for the use of longitudinal self-reported adherence to detect the risk of elevated VL. Further research is needed to validate the feasibility and potential use of self-reports to measure adherence in routine care. Viral load monitoring alone may not differentiate between poor ART adherence and drug resistance. The value of self-

reports and other measures of adherence including drug concentrations, in combination with routine viral load, to flag potential ART resistance requires further investigation.

There is also a growing recognition of the dynamic nature of ART adherence, emphasising changes in medication-taking behaviour over time on ART. Therefore, more evidence on adherence trajectories among ALHIV is needed, given the increased availability of longitudinal administrative data for adherence measurement as well as identifying opportunities to support adherence. Additional research is also needed to establish at what point in the care of an adolescent trajectories can be assigned. Future studies can also apply GBTM methodologies to describe other outcome patterns such as HIV risk and VL suppression among ALHIV.

The role of caregivers in the lives of ALHIV, for example, as part of the psychosocial support system was not explored in detail in this thesis. Further research could explore this more comprehensively, to gain a deeper understanding of the essential role caregivers play in the lives of ALHIV and develop effective strategies for supporting both caregivers and the adolescents they care for.

More evidence on HIV treatment outcomes including granular data on which factors are associated with higher risk of mortality is also needed. Further studies could investigate the causes of death among adolescents, which was not possible in this study.

9.5. Conclusion

The combined findings of this thesis highlight substantial inconsistent ART adherence through multiple adherence trajectories, low viral suppression rates and high all-cause mortality among ALHIV, posing a threat to the potential benefits of lifelong ART. Efforts to end AIDS as a public health threat will yield limited long-term success if adolescents and young people cannot sustain adherence to ART over their life course. Adolescence is a critical developmental stage, and the challenges of HIV care in this group are complex, thus the price of failure is extremely high. Therefore, any evidence that can directly inform the development of tailored support interventions for improving HIV treatment outcomes among adolescents is critical [32]. The findings from this thesis provide insight into potential intervention foci among adolescents including an opportunity to identify and target specific sub-groups of ALHIV in need of support.

This thesis demonstrates that the adolescent population is composed of distinct groups with different adherence trajectories highlighting the need for differentiated HIV care delivery among adolescents. This thesis further established unique plausible pathways between socio-ecological factors and different trajectories of ART adherence among adolescents presenting an opportunity to tailor care to specific groups of ALHIV. Mental health symptoms were linked to several pathways leading to inconsistent adherence, among other barriers, hence there is a need to address underlying issues leading to poor mental health. These findings call for the need to integrate mental health support into HIV care and to incorporate trauma-informed care into support for adolescents living with HIV [261]. Protective factors, such as government-provided social protection and psychosocial support may inform interventions designed to safeguard adolescents from contextual realities of poverty and mental health challenges. These may also act as key add-on support to enhance the effectiveness of ART and reduce disparities in HIV treatment outcomes among adolescents from low-resource settings. Recommendations include the need to empower or encourage family-oriented psychosocial support to facilitate psychological well-being which is detrimental to long-term adherence to ART.

Lastly, this thesis contributes results comparing longitudinal self-reported adherence measures to predict viral load among an African cohort of adolescents living with HIV. Self-reported adherence shows promise for low-cost and relatively easy-to-administer alternative measures to ensure timely identification of poor adherence to ART among adolescents, particularly in settings where virologic monitoring is limited. The value of using non-stigmatising longitudinal self-reported measures for adherence assessment in routine care warrants further investigation.

In conclusion, there is a need to focus on long-term sustained adherence in HIV care for adolescents in order to realise the benefits of lifelong ART. Current strategies need to shift from a one-size-fits-all model of care to customised HIV care, combining biomedical with psychosocial and structural interventions to address the needs of distinct groups of ALHIV. Customised care may guarantee better allocation of HIV care resources to improve adolescents' HIV treatment outcomes.

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CHAPTER 10. Appendices

10.1. Supplementary material for Chapters 1-3

Appendix 10-1: Mzantsi Wakho - Measures and Scales Summary

OUTCOME MEASURES
Adherence to Antiretroviral Therapy (ART)
ART adherence was measured by adolescent self-report (Evans et al, 2015), using the standardized Patient Medication Adherence Questionnaire (Duong et al, 2001), and measures developed in Botswana for adolescent ART adherence in the past week, past 3 days, and past weekend (Lowenthal et al. 2014). The following questions were included on adherence to ART (Giraffes)/ medication (Elephants/ Bears): 1. How many pills? 2. How many times a day? 3. When in the day? (worded as do you need to take your ARVs in the: morning, day, evening) 4. Missed doses over past three days? (worded as correct number of doses: yesterday, day before, and two days ago) 5. How many days participants took all ARVs at the right time in last week? 6. Last missed dose? (worded as did you ever miss doses in: past week, past month, past year, never)
Reasons for ART non-adherence were measured using: **i.** The Adult AIDS Clinical Trials Group Adherence Instruments: Adherence Follow-up Questionnaire, and Adherence Barriers Follow-up Questionnaire (Chesney et al., 2000; Murphy, 2003) **ii.** Section 2 of the Adolescent Adherence Questionnaire developed by the Pediatric AIDS Clinical Trials Group, which measures 21 reasons for missing medications over the past month (e.g. didn't have medication with self, fell asleep or slept through dose time, simply forgot, etc.) (Naar-King, 2006). The scale of was adapted to HIV-positive adolescents in the South African setting, based on consultations with experts and the Teen Advisory Group. The adapted scale showed internal consistency (α) 0.60 at baseline. Defaulters were asked an adapted list of 42 questions related to when they were last taking ART/ long-term medication.
COMPLEX MULTI-LEVEL HIV-SPECIFIC FACTORS
Sexual and Reproductive Health
High-risk sexual behaviour was measured through a combination of questions. Items from the PREPARE trial (Mathews, 2013), and the National survey of HIV and risk behaviour amongst young South Africans (RHRU, 2005) were used to measure sexual activity (screening item), HIV risk knowledge, age of sexual debut, concurrent sexual partners, self-efficacy/agency in relation to condom use, frequency of condom use, transactional sex, sexual activity under the influence of alcohol or drugs. Items from this survey were also be used to measure pregnancy, and sex with older partners.
Most recent sexual experience was measured with 2 items: partner age, and condom use at last intercourse.
Sexual practices over the last year were documented through 8 items: number of sexual partners, frequency of condom use, contraception use, reasons for contraception use, location where adolescent obtained contraception, and transactional sex (in the last year). Reasons for contraception use in the last year were recorded through a multiple-response question, adapted from the only other study among HIV positive adolescents in Southern Africa to record these motivations quantitatively (Birungi 2009). Transactional sex in the last year was measured through a Yes/No question for receipt of a present in exchange for sex. Any previous experience of transactional sex was also measured in the "High-risk sexual behaviors subsection" detailed above. In this question adolescents were asked if they have ever had sex in exchange for a list of items including food, airtime, cell phones, transport, etc.

Medication-Related Factors – Individual level
General medication: 1. Are you currently taking: Any pills? Any liquids or syrups? Any injections? Any other form? 2. Do you know why you are taking these medicines? Are you taking them for your: chest, diarrhea, TB, prevent getting pregnant, for HIV/AIDS, epilepsy, prevent child getting HIV/AIDS, ears, for one month to prevent HIV infection, unsure why taking.
ARV Medication: 1. Ever taken ARVs, currently taking ARVs? 2. Age started taking ARVs? 3. Changes to treatment? 4. How many changes to treatment? Further questions on ARVs are included in the "ART adherence" subsection (e.g. Pill burden, Frequency of pill taking).
Treatment and Health Literacy: was measured through 10 items developed based on the work of Treatment Action Campaign (TAC) and Medecins Sans Frontiers (MSF) in South Africa (Coetzee et al., 2004; Skhosana, Struthers, Gray, & McIntyre, 2006; TAC, 2012). Items explored the knowledge of participants on the following topics: (i) understanding of treatment regimen at initiation (1 item) (ii) understanding of recent blood test results (q. 118) (iii) most recent CD4 count (q. 120) (iv) most recent viral load (q. 122) (v) treatment adherence literacy (3 items) with a scale adapted from the Baylor clinic adolescent support groups treatment adherence game (BIPAI, 2009).
Family and Community Level Factors included the type of adherence support the adolescents receive. Based on items from the Adolescent Adherence Questionnaire (Naar-King, 2006), 5 items (internal validity (α) 0.64 at baseline) were added to the medication-related factors scale described above, to measure community level factors that might affect adherence including the use of alarms, cellphone reminders, boyfriend/girlfriend, a TV programme, or a normal activity of daily life to remind participants to take their medication,. 3 items measured whether participants received support from treatment adherence buddies, 5 items measured participant attendance to clinic support groups.
ARV access/supply will be assessed through a tool adapted from TAC's Road to Good Adherence on participants' experiences of obtaining ARVs: time, frequency, whether medication is delivered (and by whom) or collected (whether accompanied and by whom) and frequency of stock-outs (TAC, 2011).
HIV disclosure
Adolescent knowledge of HIV-status was assessed in steps: first through healthcare worker report, then with primary caregivers during the consent process. Discrepancies between healthcare worker and caregiver reports requited that interviewers check whether adolescents understood their status while obtaining consent, to prevent recent disclosure. Adolescents were screened on their recent history of illness and medication-taking. Those who did not know their status were asked about "illness" and "medication" instead of "HIV" and "ART" respectively.
Stigma
Primary stigma among HIV-positive adolescents was measured through the 10-item ALHIV stigma scale (ALHIV-SS) measuring internalized (7 items), anticipated (2 items) and enacted HIV stigma (4 items). The scale was cross-culturally adapted from a stigma scale previously used with HIV-positive adolescents in the US (Wright, Naar-king, Lam, Templin, & Frey, 2007). We adapted the scale through cognitive interviews with 9 South African adolescents and validated it within the present study, using the baseline sub-sample of HIV-positive adolescents who were aware of their status (n=721). ALHIV-SS demonstrated good psychometric properties, with internal consistency (α) of 0.70, 0.57 and 0.75 for anticipated, enacted and internalized stigma respectively at baseline (Pantelic et al., under preparation).
Secondary stigma due to HIV in the family or household was measured through the Stigma-By-Association (SBA) scale. SBA was used in our two previous studies with HIV/AIDS-affected youth in South Africa. The scale has been validated for use in South Africa (Mark E. Boyes, Mason, & Cluver, 2012) and demonstrated good reliability (6 items). In this population it demonstrated reliability of 0.60 for HIV+ individuals and 0.63 across the whole baseline sample.
INDIVIDUAL-LEVEL RISK AND PROTECTIVE FACTORS

Mental health
Depressive symptoms. The Child Depression Inventory (short form) (Kovacs, 1992) (10 items). This form was used in our previous studies examining AIDS-affected children in South Africa with good acceptability. The CDI is a widely-used and well-validated measure with strong psychometric properties, and has been used in multiple other South African populations (Suliman, 2002). Here it demonstrated reliability at baseline; 0.64 among the HIV+ individuals and 0.68 across the whole sample.
Anxiety symptoms was measured using the Children's Manifest Anxiety Scale – Revised (RCMAS) (Reynolds & Richmond, 1978). The RCMAS is a widely-used scale that has been standardized in US populations, shows good internal consistency and test-retest reliability (Gerard & Reynolds, 1999; Reynolds & Richmond, 1978). An abbreviated version with 14 items has been validated with good internal consistency in our previous South African studies of AIDS-affected children (M. Boyes & Cluver, 2012). In the baseline sample α=0.80 for both the entire sample and HIV+ individuals.
Post-traumatic stress symptoms was measured using the The Child PTSD Checklist (Amaya-Jackson, McCarthy, Newman & Cherney, 1995), which has been widely used in Black African youth in South Africa (Seedat, Nyamai, Njenga, Vythilingum, & Stein, 2004; Seedat, Van Nood, Vythilingum, Stein, & Kamlner, 2000). The checklist was restructured using the new DSM-V criteria and factor analysis from previous studies of familial AIDS, in which it was validated and demonstrated excellent validity (M. E. Boyes, Cluver, Gardner, & Seedat, 2012). The included scale was formed of 19 items with α of 0.90 and 0.89 for the full sample and HIV+ individuals respectively at baseline.
Suicidality/self-harm was measured using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) suicidality and self-harm subscale (D. Sheehan, Shytle, & Milo, 2004) (5 items). The MINI-KID has been extensively validated in developed world populations, and shows strong internal consistency and test-retest reliability (Lecrubier et al., 1997; D. V. Sheehan et al., 1997). In this population α=0.87 and 0.88 for the full sample and HIV+ individuals, respectively, at baseline.
Neurocognitive development and learning capacity
Neurocognitive development and learning capacity was measured through a memory sub-test derived from the WISC-IV and WAIS-III tools (Wechsler, 2004) which have been validated among Xhosa speakers (Van der Merwe 2008): *Immediate and delayed recall* of 5 words was tested.
Hyperactivity was measured using a subscale (5 items, at baseline α=0.53 for all and 0.54 for HIV+) from a version of the Strength and Difficulties Questionnaire adapted and validated in the Xhosa language (Goodman 2004).
Physical health
Physical health was measured through a combination of tools. First, 1 item on self-reported health over the past 12 months and a 2 item scale on physical and cognitive disability adapted from The International Classification of Functioning, Disability and Health (ICF) (WHO, 2001). Severity of health issues was assessed using 26 items based on the Verbal Autopsy questionnaire (Lopman et al., 2006) adapted into a verbal symptomology checklist in consultation with HIV-positive youth, clinicians and our qualitative team. The revised 26-item verbal symptomology scale included 8 items on TB symptoms, 17 items linked to AIDS-related opportunistic infections (including epilepsy and asthma) and antiretroviral treatment side-effects, and 5 items on STI symptoms (burning whilst urinating, genital itching/ redness, anal itching/ soreness/ bleeding, genital discharge) in the last 6 months, following WHO guidelines for symptomatic diagnosis of STIs (WHO, 2004). The TB symptomology items were adapted from the South African Demographic and Health Survey (2003) (Department of Health, Medical Research Council, & OrcMacro, 2007) the World Health Organization Stop Tuberculosis Team, and the Kwa-Zulu Natal Department of Health TB symptom guidelines, to assess symptoms of active pulmonary TB. Items were also included on types of diagnositic testing for TB in the previous year, their results, and whether the participant has ever been treated for TB.
Risk taking behaviour and conduct problems

Behaviour problems and peer relationships were measured by combining the Child Behaviour Checklist (CBCL) (Achenbach 1992, Achenbach, 2000) and the Strengths and Difficulties Questionnaire (SDQ) (Goodman,2004). Rule-breaking was measured with a 10 item subscale from CBCL. The CBCL-YSR has been normed on a mixed-ethnicity US population, and was used in the Family Health Project study of orphan well-being in the USA (Forehand et al., 2002) and in South Africa (Barbarin, Richter, & DeWet, 2001) as well as in our two studies among HIV/AIDS-affected youth in South Africa. The CBCL-YSR is commonly used as a 'gold standard' measure of child behaviour. A small adaptation is necessary - replacing the item 'I set fires' (included in the CBCL as a sign of destructive tendencies but commonly a task undertaken by children in South Africa in order to cook). 5 items from the conduct problems and pro-social subscales of SDQ were added. Two devised items on carrying of weapons are also added – these were adapted from the National Primary Schools Violence Survey (Burton, 2008), to include carrying of weapons both inside and outside school (2 items). A final 2 items were developed to measure gang membership and gambling.

Alcohol and substance use

Screening for **hazardous alcohol use** (1 item) was based on an item adapted from the Alcohol Use Disorders Identification Test (AUDIT), a 10-item, self-rating questionnaire that assesses hazardous drinking. The AUDIT was developed and validated by the World Health Organisation for international use and has been validated for a variety of community and primary healthcare settings (Cohen et al., 2011; Jaspan, Mueller, Myer, Bekker, & Orrell, 2011). The scale showed very high sensitivity and specificity among HIV-positive people in South Africa (Myer et al., 2008).

Demographic information

Child age, gender, and other basic demographic information was asked using items from the South African Census (2001) (SSA, 2001).

Community involvement and Migration

Community involvement was measured with1 item asking participants to indicate all community groups that they are involved with, 1 item asked for frequency of nightclub/ tavern/ shebeen use, and 1 item asked about family use of a school or community garden to grow food.

FAMILY AND COMMUNITY-LEVEL FACTORS

Caregiver Status

Existence of primary caregiver, and relationship the adolescents to primary caregiver, was identified using items from the National survey of HIV and risk behaviour amongst young South Africans (RHRU 2005). Primary caregiver was identified as the person who 'stays with you and takes care of you at home'. Relationships of caregiver to children was categorized as the following: biological parent, grandparent, other extended family member (aunts, uncles, cousins, adult siblings etc), non-family member (social worker/ careworker, foster carer), living in a child-headed or youth-headed households.

Education and School Experiences

Education items were developed with the South African Department of Education. Some items from the 'Young Lives' study (Boyden & Dercon, 2008) were used to determine some education outcomes, others were identified by the National Action Committee for Children Affected by AIDS (NACCA) and NGOs. Items include: age of school enrolment, current grade, repetition of grades and reasons for repetition, failure of grades and reasons for failure, school dropout and reasons, number of different schools attended, ability to pay school fees, free schools, and access to school fees exemption. An item documented access to school feeding by asking which meals participants received for free at school (breakfast, lunch, other or combination). Six items on school experience were developed by adapting a scale of the PREPARE trial (Mathews, 2013) and items from qualitative research in the Young Carers study including experience of school violence, safety, and positive expectations of schooling.

Parental and caregiver morbidity and mortality

Caregiver morbidity was assessed using an adapted version of the verbal autopsy questionnaire (Lopman et al., 2006) (13 items), as used in our previous studies. Further questions measured general health and knowledge of caregiver ARV use (6 items).

When children identified parental death, cause of death was recorded, a verbal autopsy questionnaire completed and any ARV use prior to death noted. These items were developed as part of a South African national survey of AIDS-affected children (Cluver et al., 2013). 21 items for each caregiver.

Bullying

Bullying was measured with the 9-item, standardized 'Social and Health Assessment Peer Victimization Scale' (Ruchkin, Schwab-Stone, & Vermeiren, 2004), used in research with vulnerable children in Cape Town (Ward, Martin, Theron, & Distiller, 2007) and in our previous studies of AIDS-affected children. This scale was adapted from the Multidimensional Peer Victimization Scale, which was validated in the US (Mynard & Joseph, 2000). Items include; being called names, being hit or threatened and having possessions broken or stolen. This measure generates a total global score of exposure to bullying. It demonstrated good internal consistency at baseline (α) of 0.81 for the entire sample and 0.79 for the HIV+ sample.

Peer norms

Peer norms were measured through 4 items adapted from a study of adolescents living with HIV in the United States (Bauermeister, Elkington, Brackis-Cott, Dolezal, & Mellins, 2009). The scale assesses how many peers within participants' social networks perceived being-sexually active makes someone "cool" or "popular". Items were derived from two sub-scales: norms about expected sexual activity of peers (2 item) and perceived peer sexual behaviour (2 items), adapted to the South African context. One of the items on expected sexual activity of peers: "How many of your friends think that using condoms is like eating sweets in their wrapper?," while one of the items on perceived peer sexual behaviour was "Do you have friends who have had sex because they were drunk or high on drugs?" (α=0.73 for all, 0.76 for HIV+, both at baseline).

Parenting and Home Environment

Positive parenting (6 items, α=0.89 for all, 0.90 for HIV+ at baseline) – including items on praise, positive reinforcement and support from caregiver and *good parental supervision* (10 items, α=0.92 for all, 0.93 for HIV+ at baseline) – including monitoring of adolescent social activities and home rule setting – were measured using the positive parenting and parental supervision sub-scales of the Alabama Parenting Questionnaire (Elgar, Waschbusch,Dadds & Sigvaldason, 2007).

5 items form the Child-Parent Communication Apprehension Scale for use with Young adults (Lucchetti, Powers, & Love, 2002) were adapted to measure communication between adolescents and their caregiver. The revised scale showed strong reliability in the full sample (α=0.93), but poor reliability among the HIV+ sub-sample (α=0.45).

Negative Family Processes and Child Trauma

Exposure to family conflict and domestic violence was measured using physical abuse (2 items) and emotional abuse (10 items) were measured using items from the UNICEF Measures for National-level Monitoring of Orphans and Other Vulnerable Children (Snider & Dawes, 2006) which have been successfully used previously in two other studies of HIV/AIDS affected adolescents in South Africa (Meinck, Cluver, Boyes, & Loening-Voysey, 2016; Meinck, Cluver, Boyes, & Ndhlovu, 2015).

Exposure to sexual abuse was measured using 3 items from the Juvenile Victimization Questionnaire (JVQ) (Finkelhor, Hamby, Ormrod, & Turner, 2005) and used in our previous studies in South Africa.

Access to help and reactions to disclosure of abuse were measured using 3 items from the ISPCAN International Child Abuse Screening Tool (Zolotor et al., 2009).

Community-level trauma was measured using 4 items from the Child Exposure to Community Violence (CECV) Checklist (Martinez & Richters, 1993), adapted to reflect commonest community traumas in South Africa, as identified by national police statistics (SAPS, 2005).

STRUCTURAL / SOCIETAL HYPOTHESISED RISK AND PROTECTIVE FACTORS

Experiences with Health Care Services

Health care utilization was measured with 1 item on the type of health care accessed by participants (chemist, pharmacy, public clinic, private doctor, traditional healer, church, traditional herbalist, public hospital or private hospital). Barriers to access were assessed with questions on accessibility (2 items - distance to clinic, mode of transport), affordability (2 items – cost of transport, frequency of not having enough money to attend), and acceptability (5 items – member of staff spoken to at the clinic, length of wait,

whether accompanied and frequency of there being no one available to accompany or lack of safety preventing attendance).
Household poverty
Poverty was measured using a range of tools. Items from the South African Census (SSA 2001) will determine whether children live in formal, informal (i.e. shacks), or traditional structures.
Food insecurity will be measured using 1 item from the South African National Food Consumption Survey (1999) (Labadarios et al., 2003).
Poverty will also be measured by access to the top 8 socially-perceived necessities for children, as identified by the Centre for South African Social Policy in the 'Indicators of poverty and social exclusion project' (Wright, 2008), and endorsed by over 80% of the South African population in a nationally-representative survey (the South African Social Attitudes Survey 2006) (Pillay, Roberts, & Rule, 2007). These include items such as 'enough clothes to keep you warm and dry' and '3 meals a day' (8 items α=0.74 for all, 0.72 for HIV+ at baseline). Household employment was measured as number of people cohabiting with the child who are employed (part-time or full-time).
Social Support
Social support was measured using 7 items from the Medical Outcomes Study (MOS) Social Support Survey Instrument (Sherbourne & Stewart, 1991), with a mixture of 3 items from the material support subscale and 4 from the psychological support subscale. This scale has been widely used in the developing world, including in South Africa (Casale 2015) 1 item was added to measure the relationship of the person from whom the child receives the most support. The scale demonstrated good reliability of α=0.86 for the whole sample and 0.85 for the HIV+ sample, at baseline.
Support from state and NGOs
Receipt within the household of the major forms of *social security transfers* (Child Support Grant, Foster Care Grant, Pension, Disability Grant and Care Dependency Grant) were measured. 5 items asked if the participants receive foster care, child support, pensions, disability and care dependency grants. 1 item measured if participants receive food parcels or free meals and 1 item measured the receipt of any home-based care. Items described above in the education section will determine whether their school is a no-fees school or whether they have fees exemption and whether their school provides food, including during the holiday.

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Appendix 10-2: Summary of measures from the NHLS data linkage process

NHLS VARIABLE NAMES	CONTENTS	ADDITIONAL COMMENTS
EPISODE_NO	NHLS episode numbers for each test result	The number is not unique and can be shared between tests, e.g., several formats of TB tests can have the same episode number
SN	Participant study serial number	The new format used, obtained from study roster
YEAR_TESTED	The Year in which the test was conducted	Created based on DATE_TESTED
TEST_TYPE	Type of test	e.g., CD4 ARV, HIV Viral Load, HIV-1/2 AG/AB, and TB test
TEST_CLASS	Broad category/class test belongs to	HIV-related (CD4 ARV, HIV Viral Load, HIV-1/2 AG/AB, and TB test) or non-HIV-related tests
TESTED_DATE	NHLS date sample tested	Complete
REVIEWED_DATE	NHLS date test reviewed	Complete
SPECIMEN_GROUP	Group test specimens belonging to	e.g., blood, sputum, urine, biopsy etc
SPECIMEN_TYPE	More detailed group specimens belong to	e.g., EDTA blood, Fine needle aspirate
RESULT_NUMERIC	The numeric value of the result	Relevant for tests with numeric results, however, will exclude results such as "lower than detectable limit"
RESULT_VALUE	Both the numeric and text values of the results	Excludes text values for TB and ELISA results
RESULT_TEXT	Result in text format	Includes TB results and HIV ELISA results
RESULT_TYPE	Result type for HIV ELISA	Only available for HIV ELISA (HIV - 1/2 AG/AB) e.g., SCREENING or CONFIRMATORY TEST

Appendix 10-3: Self-reported adherence items in the Mzantsi Wakho study

Measure	Questions as per the questionnaire	Study definition
Missed dose measured using positive framing of pill intake		
Any past 3-days missed dose	5. How many times did you take your ARVs or HIV medicine yesterday? 6. How many times did you take your ARVs or HIV medicine the day before yesterday? 7. How many times did you take your ARVs or HIV medicine three days ago? 8. How many times a day do you have to take your ARVs or HIV medicine?	Calculated the total number of times the adolescent took all their ARVs in the past three days. If the reported pill intake did not equal the expected prescribed number of pills for the three days, then we assigned them to the non-adherent group.
Any past-week missed timing of dose	How many days did you take all of your ARVs or HIV medicine at the right time last week?	The responses ranged from 0 to 7 days. Missed dose timing any was defined as a binary indicator for missing dose timing (did not take their ARVs at the right time) at least one day in the past week.
Any past-month days missed	How many days in the last month did you want to take your ARVs but you couldn't?	The responses ranged from 0 to 31 days. Missed dose days any was defined as a binary indicator for failing to take ARVs for at least one day in the last month.
Missed dose measure using negative framing of pill intake		
Any weekend missed dose	How many times did you not take your medication last weekend (Friday night, Saturday, and Sunday)?	Defined as 1 if the participant did not take their medication at least once in the last weekend and 0 otherwise.
Any past-week missed dose	Did you miss taking any of your ARV pills or HIV medicine in the last week?	Defined as a binary indicator of missing ARV pills at least once in the last week.
Any past-month missed dose	Did you miss taking any of your ARV pills or HIV medicine in the last month?	Defined as a binary indicator of participants missing ARV pills at least once in the last month.
Missed dose measure as delayed refill		
Any past-year missed Clinic appointment	How many times in the last year were you not able to get to your clinic appointment?	Dichotomised to 1 if the participant reported missing clinic appointments at least once in the last year and 0 otherwise.

Appendix 10-4: Summary of key variables for the study

Variable	Description	Data source
Age	Age was measured in years at the time of the interview	Self-reported data
Sex	Categorised as boy or girl.	Self-reported data
Geographic location (urban/rural)	The geographic location of the adolescent's residence at the time of the interview was categorised as urban vs rural.	Self-reported data
Adherence indicators	• Did you miss taking your pills or medicine in the past weekend? • In the last year, were you always able to get to your clinic appointment? • Did you miss taking any of your ARV pills or HIV medicine in the last (week/month/year)? • How many days did you take all of your ARVs or HIV medicine at the right time last week? • Took the right number of pills 3 days ago • Took the right number of pills 2 days ago • Took the right number of pills yesterday? • How many days in the last month did you want to take your ARVs but you couldn't?	Self-reported data (see Table 2 for categorisation)
Mode of HIV transmission	Mode of HIV acquisition categorised as vertical or horizontal	Self-reported data
Viral load	Will be defined as any VL≥200 copies/ml.	Clinic patient files, NHLS linkage data
CD4 count	CD4 count/percent will be defined as the CD4 count/percent observed annually.	Clinic patient files, NHLS linkage data
TB infection	Based on TB test results among ALHIV (categorised as YES or NO)	Self-reported data NHLS linkage data
LFTU	LFTU was defined as (>12 months) from the last HIV test i.e. without any record of other outcomes (categorised as YES or NO)	Self-reported data NHLS linkage data
Mortality	Mortality is defined as any reported death at the time of the interview.	Self-reported data

10.2. Ethics approval

Appendix 10-5: CSSR UCT Ethics approval: Mzantsi Wakho study (2013/14)

CENTRE FOR SOCIAL SCIENCE RESEARCH
University of Cape Town • Private Bag Rondebosch 7701 • South Africa
Tel: 021 650 4656 • Fax: 021 650 4657 • Web: www.cssr.uct.ac.za

TO: Dr Rebecca Hodes

FROM: Jeremy Seekings
Professor and Director, Centre for Social Science Research, UCT

SUBJECT: Ethics Review CSSR 2013/4.

RESEARCH: Promoting Adolescent Antiretroviral Adherence …

DATE: 17th April 2013

Dr Hodes, a Research Associate in the Centre for Social Science Research, submitted for review relevant documents relating to research that she intends doing, with colleagues from the UCT and Oxford University, on adherence to antiretroviral treatment among adolescent men and women in the Eastern Cape. The documents were scrutinised by the CSSR Research Ethics Review Committee, which included (by invitation) a member of UCT's Health Sciences Faculty Research Ethics Committee.

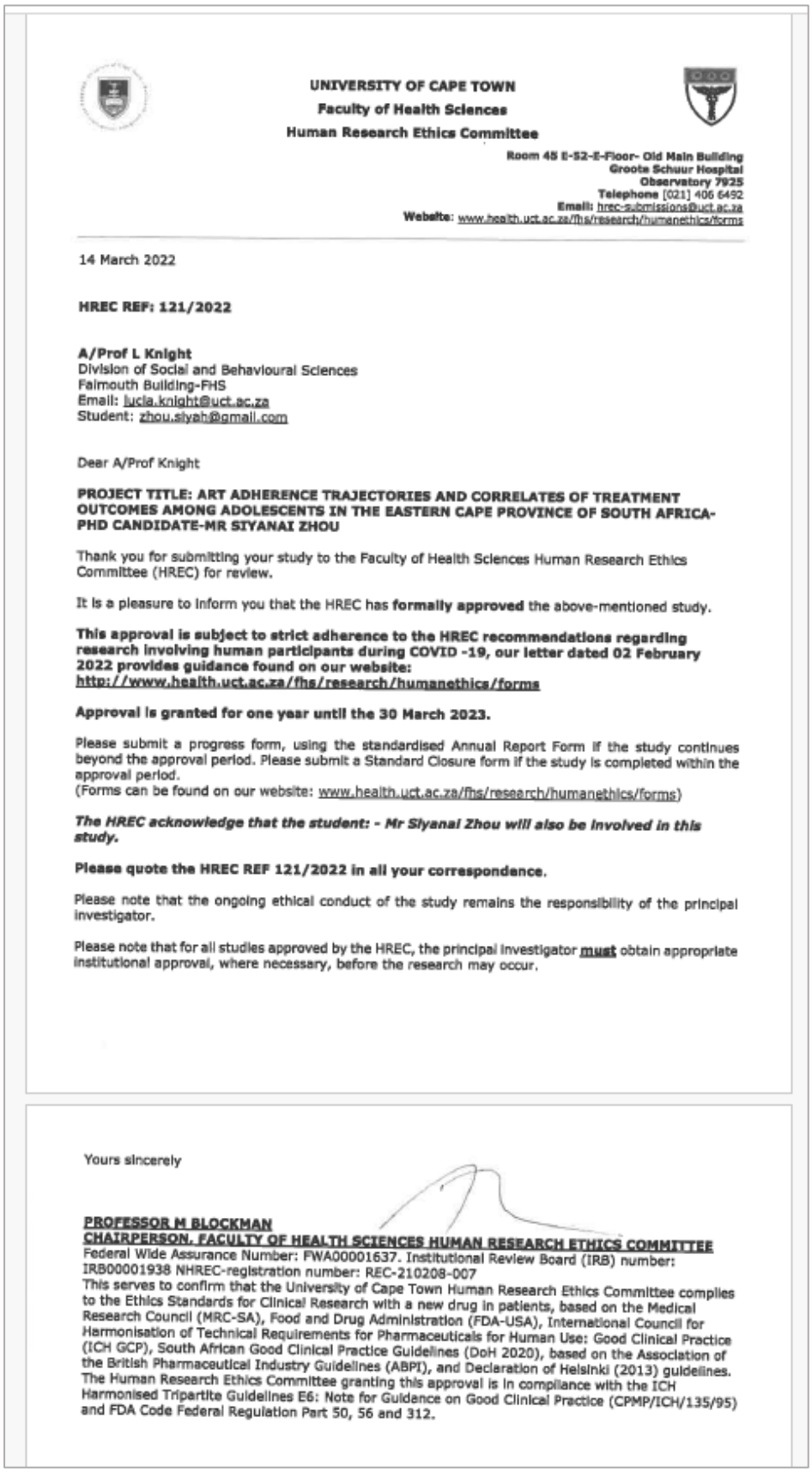
The Review Committee raised a number of concerns, primarily with respect to the issue of involuntary disclosure of personal information by other participants in discussion groups. The relevant documentation has been reworded, and the researchers have made a clear commitment to pay close attention to this issue. With these changes, the review panel is satisfied that the research will be conducted in a manner that meets the standards of the University of Cape Town.

The proposed research is therefore approved.

Jeremy Seekings.

Jeremy Seekings
Professor and Director, Centre for Social Science Research

Appendix 10-6: University of Cape Town Human Research Ethics Committee ethics approval:



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

14 March 2022

HREC REF: 121/2022

A/Prof L Knight
Division of Social and Behavioural Sciences
Falmouth Building-FHS
Email: lucia.knight@uct.ac.za
Student: zhou.siyah@gmail.com

Dear A/Prof Knight

PROJECT TITLE: ART ADHERENCE TRAJECTORIES AND CORRELATES OF TREATMENT OUTCOMES AMONG ADOLESCENTS IN THE EASTERN CAPE PROVINCE OF SOUTH AFRICA-PHD CANDIDATE-MR SIYANAI ZHOU

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, our letter dated 02 February 2022 provides guidance found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Approval is granted for one year until the 30 March 2023.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Mr Siyanai Zhou will also be involved in this study.

Please quote the HREC REF 121/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.04.2025
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	4/4/24

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	03/04/2024		
HREC REF Number	121/2022	Current Ethics Approval was granted until	30/03/2024
Protocol title	ART adherence trajectories and correlates of treatment outcomes among adolescents in the Eastern Cape Province of South Africa		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?		☐ Yes	☒No
If yes, could you please provide the HREC Reference number for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Assoc. Prof. Lucia Knight		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)