From Protocol to Practice: Evaluating the Real-World Effects of Decentralising HIV Care on Adolescents' Care Outcomes and Experiences in South Africa

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soundless, it crosses a line, quiets into a seed
& then whatever makes a seed. almost like gone
but not gone. the air kept its shape. not antimatter
but the memory of matter. or of it mattering. it doesn't
cross my mind now that it whispers so soft it's almost
silence. but it's not. someone dragged the screaming boy
so deep into the woods he sounds like the trees now.
gone enough. almost never here. daily, swallowed
within a certain window, a pale-green trail on the tongue
the pale-green pill makes before it's divvied among
the ghettos of blood, dissolves & absolves
my scarlet brand. ritual & proof. surely science
& witchcraft have the same face. my mother
praises god for this & surely it is his face too.
regimen, you are my miracle. this swallowing
my muscular cult. i am not faithful to much.
i am less a genius of worship than i let on.
but the pill, emerald dialect singing the malady
away. not away. far enough. for now.
i am the most important species in my body.
but one dead boy makes the whole forest
a grave. & he's in there, in me, in the middle
of all that green. you probably thought
he was fruit.

—Danez Smith, "undetectable," *Homie*

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This thesis was written across three continents, through quarantines in each one. Over the past four years, it has been an incredible privilege not only to be able to travel across these borders but also to have a home and supportive network in each setting. For all the reasons the world is a strange place to live right now, it is an even more important time to elevate the voices of the unheard.

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Thesis Abstract

Background: To rapidly scale up HIV care, several sub-Saharan African countries have decentralised antiretroviral therapy (ART) and HIV care delivery. Decentralisation triages patients by intensity of care need, with clinically "stable" patients being down-referred to primary care clinics from secondary or tertiary hospital settings. Compared to other age groups, adolescents demonstrate both high rates of new HIV infections and the worst care outcomes once initiated on ART. However, the effects of decentralising HIV care remain poorly characterised for adolescents, despite its extensive and continuing rollout. Therefore, this thesis aims to characterise the current reality of HIV care delivery for adolescents in South Africa's decentralised HIV care system, in order to identify potential ways to tailor services for improving care outcomes in this vulnerable population.

Objectives: (1) Summarise current evidence for effects of decentralising ART delivery for youth health outcomes; (2) Assess adolescent attainment of HIV care targets in South Africa's decentralised healthcare system; (3) Characterise adolescent experiences of transition out of paediatric HIV care in South Africa's decentralised healthcare system

Methodology: This thesis consists of a systematic review of decentralising HIV care for youth in low- and middle-income countries (Paper 1), and an epidemiological study of HIV care outcomes and experiences for ART-initiated adolescents (n=1080) in South Africa's decentralised HIV care system (Papers 2-3). Primary data analyses for Papers 2-3 were based on a community-traced cohort (2014-2018) of all adolescents who had ever initiated ART in 52 public healthcare facilities of a health sub-district of the Eastern Cape. This candidate was a lead Co-Investigator of this longitudinal cohort study. At each of the three study waves, adolescents completed questionnaires about their health on digital tablets, administered by research assistants. In parallel, participants' clinical records were extracted in two waves (2014-2015 and 2016-2017) from electronic and paper-based patient files in healthcare facilities. At each facility, healthcare staff completed a semi-structured interview that provided a facility "profile" of available services.

Results:
Paper 1: A systematic review was conducted in accordance with PRISMA guidelines to critically appraise evidence on the effects of decentralising ART delivery on health outcomes for adolescents and young people (10-24 years old) in low- and middle-income countries. An extensive search was conducted through 12 electronic databases, contacting relevant experts, and hand-searching references. Implementation fidelity, study quality, and risk of bias were assessed using the TIDieR checklist, CASP checklists, and ROBINS-I tool, respectively. Of 5302 records identified, 11 studies were potentially eligible but required age disaggregation. Only 2 studies could provide age-disaggregated data, but meta-analysis was not possible due to limited data availability and heterogeneity in implementing decentralisation. Results from these 2 studies suggest the potential for at least equivalent attrition outcomes within decentralised care, but both studies faced significant selection and allocation bias. This review highlighted three key limitations in the current evidence base: (1) a general paucity of evidence on decentralisation for adolescents and youth in resource-limited settings, (2) a critical gap in recent evidence (post-2011) on decentralising HIV care, and (3) the focus of evidence on highly resourced models of HIV care delivery, rather than public care models. This paper is published in *Global Health Action*.

Paper 2: Using clinical records through 2017, this study evaluated adolescent progression along an extended HIV care cascade in South Africa's decentralised public HIV care system, including operational and care-terminating outcomes. Mortality and loss to follow-up recorded in clinical records were adjusted for unreported deaths and "silent" care transfers. Sociodemographic and treatment-related predictors were tested through sequential multivariable logistic regressions. Predicted probabilities for the effects of predictors were estimated by sex and mode of infection. Rates of mortality and loss to follow-up in the total cohort were 3.3% and 16.9%, respectively. Although almost all participants with available clinical records had at least one recorded viral load, only 51.1% of these adolescents had viral loads from the past 12 months. Having a recent viral load was associated with experiencing decentralised care and longer time on ART. The protective effect of decentralised care was greater for female and sexually infected adolescents. At most recent available viral load, 58.4% of adolescents were fully virally suppressed. Among the total cohort, only 23.2% of adolescents were fully virally suppressed in the past 12 months. Younger age and longer time on ART were associated with full viral suppression. Thus, although overall rates of viral load coverage are high, adherence to routine testing guidelines and viral suppression remain low for adolescents living with HIV in South Africa. This paper is under review at *BMC Infectious Diseases.*

Paper 3: This study identified adolescents' pathways in HIV care across facility care types and levels in South Africa's decentralised HIV care system, including transitions out of paediatric care. Associations between transition pathways and care outcomes were tested in sequential multivariable regressions. Thematic analysis of clinic-level questionnaires identified transition support available at facilities. In the total cohort, 57.8% had initiated ART in paediatric care, and 20.4% had transitioned out of paediatric care, with median age at first transition of 14 years. Among those who transitioned, two main pathways were identified: *down-referral transition* to generalised primary care clinics (56.7%) and *classical transition* to specialised adult HIV care (43.3%). Across pathways, 27.3% experienced *cyclical transition*, with repeated movement between paediatric and non-paediatric care. Experiencing *down-referral transition* was protective against viral failure, and median post-transition viral load change was not clinically significant. Healthcare providers at hospitals and community health centres described informal "protocols" used to mitigate risk of negative post-transition care outcomes for adolescents. This study suggests a new, contextually relevant model for adolescent transitions out of paediatric HIV care, beyond models found in high-income countries. This paper is published in the *Journal of Acquired Immune Deficiency Syndromes*.

Conclusions: This thesis provides new and urgently required evidence on the reality of HIV care outcomes and experiences for ART-initiated adolescents in sub-Saharan Africa. This thesis highlights adolescents' high level of inter-facility mobility in South Africa's decentralised HIV care system, as well as low rates of recent viral load availability and viral suppression in clinical records. Further, this thesis identifies multiple pathways of transition out of paediatric HIV care in South Africa. Down-referral transition to generalised primary care clinics, a result of decentralising HIV care, was associated with viral suppression and facilitated by informal protocols developed by healthcare providers. Findings suggest that decentralising HIV care has substantially transformed HIV care experiences for adolescents, including greater agency in their care-seeking. This unique context requires a shift in understanding sub-Saharan adolescent HIV care beyond current models from high-resource settings. With increased mobility across facilities and care levels, it is crucial to ensure that health information systems accurately reflect adolescents' current clinical status. Thus, this thesis highlights both the need for structural interventions to improve clinical data monitoring and the potential for feasible protocols to

mitigate risk of negative care outcomes for adolescents as they approach adulthood. Still, further studies with greater longitudinal coverage are required to confirm the dynamic and long-term effects of decentralising HIV care.

1. Thesis Overview

1. Publications and Presentations from this Thesis

Peer-Reviewed Publications

1. **Haghighat R,** Toska E, Cluver L, Gulaid L, Mark D, Bains A. (2019). Transition Pathways out of Paediatric Care and Associated HIV Outcomes for Adolescents Living with HIV in South Africa. *Journal of Acquired Immune Deficiency Syndromes*; 82 (2): 166-174.

2. **Haghighat R**, Steinert J, Cluver L. (2019). The Effects of Decentralizing Antiretroviral Therapy Care Delivery on Health Outcomes for Adolescents and Young Adults in Low- and Middle-income Countries: A Systematic Review. *Global Health Action;* 12 (1): 1668596.

3. Toska E, Pantelic M, Cluver L, Meinck F, Keck K, **Haghighat R**, Cluver L. (2017). Sex in the Shadow of HIV: A Systematic Review of Prevalence, Risk Factors, and Interventions to Reduce Sexual Risk-taking among HIV-positive Adolescents and Youth in sub-Saharan Africa. *PLoS One;* 12 (6): e0178106.

Publications Under Review

1. **Haghighat R**, Toska E, Bungane N, Cluver L. (Under review). The Extended HIV Care Cascade for Adolescents Initiated on Antiretroviral Therapy in a Health District of South Africa: An Observational Cohort Study. *BMC Infectious Diseases.*

Policy Documents

1. Elizabeth Glaser Paediatric AIDS Foundation, Technical Working Group: "Adolescent and Youth Transition of Care Toolkit." (2020). New Horizons Advancing Paediatric HIV Care Collaborative.

2. **Haghighat R**, Cluver L, Toska E, Armstrong A, Gulaid L, Bains A. UNICEF Policy Brief: "New Evidence on Adolescent Transition in HIV Care in sub-Saharan Africa." UNICEF Eastern and Southern Africa Regional Office HIV/AIDS Programme. *Forthcoming.*

Academic and Policy Presentations

1. **Haghighat R.** (30 October 2019). "Adolescent HIV care and experiences and outcomes: Evidence from South Africa's decentralized healthcare system." Centre for Evidence-Based Intervention Research Group, Department of Social Policy and Intervention, University of Oxford.

2. **Haghighat R** and Casale M. (10 September 2019). “Beyond the Third 90: Supporting Adolescents Living with HIV to Remain Engaged in Care as They Transition to Adulthood.” UNICEF. Webinar series on Evidence & Solutions for Adolescents in Eastern & Southern Africa.

3. **Haghighat R.** (17 April 2019). “Modelling longitudinal patient stability among ART-initiated adolescents living with HIV in a South African public healthcare setting.” Implementation Science Working Group, Centre for AIDS Research, University of California San Francisco.

4. Cluver L, **Haghighat R**, and Toska E. (14 February 2019). “From Clinics to Community: Supporting Adolescents Living with HIV.” Elizabeth Glaser Paediatric AIDS Foundation. Webinar series for the New Horizons Adolescent Learning Collaborative.

5. **Haghighat R.** (13 February 2019). “Decentralisation of Adolescent ART in South Africa: Complexity of HIV care experiences and effects on longitudinal health outcomes among adolescents living with HIV.” Implementation Science Working Group, Centre for AIDS Research, University of California San Francisco.

6. **Haghighat R** and Toska E. (30 October 2018). “Organized Chaos? Patterns of Transition to Adult Care for Adolescents Living with HIV in South Africa.” *New Horizons Collaborative Workshop*, Johannesburg, South Africa.

7. **Haghighat R**, Toska E, Gulaid L, Bains A, Cluver L. (10-12 October 2018). “Organized Chaos? Patterns of Transition to Adult Care for Adolescents Living with HIV in South Africa.” Poster presentation, *2nd International Workshop on HIV & Adolescence*, Cape Town, South Africa.

8. **Haghighat R.** (5 September 2018). “Decentralised Antiretroviral Therapy Care Delivery for HIV+ Adolescents in the Eastern Cape, South Africa.” Implementation Science Working Group, Centre for AIDS Research, University of California San Francisco.

9. **Haghighat R**, Cluver L, Bungane N, and Toska E. (26 July 2018). “90-90-48: The reality of viral suppression among ART-initiated adolescents in South Africa.” Oral poster presentation, *22nd International AIDS Conference*, Amsterdam, Netherlands.

10. **Haghighat R**, Cluver L, Bungane N, and Toska E. (20-21 July 2018). “90-90-48: The reality of viral suppression among ART-initiated adolescents in South Africa.” Poster presentation, *10th International Workshop on HIV Paediatrics*, Amsterdam, Netherlands.

11. **Haghighat R**, Cluver L, Bungane N, Toska E. (6 September 2017). “HIV treatment cascade among ART-initiated adolescents in South Africa.” Oral

presentation, *Public Health Association of South Africa Conference*, Johannesburg, South Africa.

12. **Haghighat R,** Cluver L, Bungane N, Toska E. (13-15 June 2017). "HIV treatment cascade among ART-initiated adolescents in South Africa." Poster presentation, *8th South African AIDS Conference*, Durban, South Africa.

13. **Haghighat R.** (24 November 2016). "Decentralisation of antiretroviral therapy care: the effects of down-referring HIV treatment and service-related predictors on health outcomes for HIV+ adolescents in South Africa." Centre for Evidence-Based Intervention Research Group, Department of Social Policy and Intervention, University of Oxford.

2. Note on Candidate's Role and Contribution to Research Project

This candidate is a Co-Investigator and Quantitative Project Manager of the Mzantsi Wakho research project, with which she has been involved since commencing her MSc at the University of Oxford in 2015. As a Co-Investigator of Mzantsi Wakho, this candidate has been directly involved with the design, data collection, analysis, and dissemination of findings from this research project. In particular, this candidate's role has largely centred on developing the clinic-based component of this longitudinal cohort study, including extraction of participants' clinical records and clinic-level questionnaires with healthcare staff. This candidate provided academic and programmatic leadership for this clinical arm of the study: from conceptualisation of the overall study arm to design of data collection tools, implementation of data collection strategy in field, and creation and analyses of datasets.

From August to September 2016, this candidate conducted consultations in the Eastern Cape with research assistants on the clinic team and nurses and operational managers at healthcare facilities. This pre-DPhil preliminary exploratory work expanded her knowledge of practical aspects of HIV care provision within the Eastern Cape as well as the availability of different types of data. During this time, she piloted the follow-up clinical record data extraction form, which she amended based on feedback from the clinic team. She then established a protocol for follow-up collections of clinical records, informed by the structure of patient files in included facilities.

In 2016, this candidate co-developed the clinic-based data collection tools (clinical record data extraction form and clinic-level questionnaire) with the quantitative Principal Investigators (Prof. Lucie Cluver and Dr. Elona Toska). This

candidate also reviewed and edited the adolescent questionnaire for the second and third waves of data collection. Additionally, she worked on amending ethics approval documents for Years 2 and 3 of the research project.

From January to December 2017, this candidate directly managed the full Mzantsi Wakho research team in the Eastern Cape, South Africa. During this time, she managed all modes of the project's quantitative data collection for Years 2 and 3: follow-up participant interviews, clinical record data extraction, and clinic-level questionnaires. Responsibilities during this time included day-to-day management of the field team (~50 research assistants and fieldwork coordinators), including problem solving of data collection issues for both adolescent questionnaires and clinic-based data. This candidate developed and helped implement the clinic-based data collection strategy, which required searching for both paper- and electronic-based patient files for *all* included participants at *all* included healthcare facilities. During her year of fieldwork as Project Manager, this candidate also gained a more nuanced understanding of decentralisation and the realities of HIV care provision, which she has incorporated into the study design of her dissertation. Given this candidate's research focus on clinical outcomes, she provided particularly close guidance and on-going consultation with the clinic-based team of research assistants.

Upon the completion of data collection, this candidate cleaned data from participants' clinical records and created the clinical record dataset in R software. Additionally, this candidate oversaw the cleaning of data from clinic-level questionnaires and created the clinic-level questionnaire dataset in SPSS. The study design, data analysis, and writing for all papers presented in this

dissertation were conceptualised and led by this candidate. During her ESRC Overseas Institutional Visit with the Implementation Science Working Group at the UCSF Centre for AIDS Research, this candidate also gained several conceptual and methodological insights that have been incorporated into this research and study design.

3. List of Tables

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5. List of Supplementary Tables

6. List of Appendices

Appendices to this dissertation are presented in a separate document.

Appendix 1. Research Ethics Approvals
Appendix 2. Additional Systematic Review Materials
Appendix 3. Information Sheet and Consent Form for Recruiting Participants
Appendix 4. Data Collection Tools

2. Introduction

As South Africa's HIV care system has expanded to provide antiretroviral therapy (ART) for all persons living with HIV, its healthcare system has undergone critical and significant changes in patient populations, care needs, and care delivery systems. A crucial structural change to rapidly scale up HIV care has been the decentralisation of HIV care from centralised tertiary hospitals to primary care clinics. This thesis evaluates the effects of decentralising HIV care on the health outcomes and experiences of adolescents initiated on ART in South Africa. In particular, this thesis investigates (1) what evidence already exists on the effects of decentralising HIV care for adolescents in resource-limited countries, (2) current estimates of adolescent HIV care outcomes after ART initiation in South Africa's decentralised healthcare system, and (3) how adolescents experience transitions out of paediatric HIV care within South Africa's decentralised system. Primary data from a large, longitudinal, community-traced cohort of adolescents living with HIV (Mzantsi Wakho) were used to investigate the second and third research questions .

This DPhil consists of eight chapters, including three stand-alone papers (Chapters 4, 6, and 7) as required by the DPhil-by-publication track at the Department of Social Policy and Intervention. Two of these papers (Chapters 4 and 7) have already been published in peer-reviewed journals, and the third (Chapter 6) is currently under review.

Chapter 3 (Background and Study Rationale): This chapter contextualises this thesis by summarising extant literature on adolescent HIV care

in sub-Saharan Africa, describing the context of South Africa's public HIV care system, and illustrating what decentralisation of HIV care entails in South Africa. This chapter also includes a description of the theory of change for how decentralising HIV care delivery may improve patients' care outcomes and concludes with the specific research aims of this thesis.

Chapter 4 (DPhil Paper 1): *Objective: To synthesise and critically assess the evidence base for the effects of decentralising ART delivery on health outcomes for adolescents and young adults living in low- and middle-income countries.*

This chapter is a systematic review that was published in *Global Health Action*. This chapter provides the literature review required for a dissertation within the Department of Social Policy and Intervention, and it includes an additional narrative review of studies excluded from the systematic review. This chapter concludes by discussing the implications of the systematic review findings for this DPhil.

This study found very limited data for this age group, with available studies reflecting outdated healthcare contexts. Although the included studies suggested that at least equivalent care outcomes were possible in decentralised HIV care, meta-analysis was not possible due to the small number and heterogeneity of included studies. This systematic review highlights a critical lack of recent—and therefore relevant—evidence about adolescents' health outcomes in decentralised HIV care systems within resource-limited contexts. Therefore, the empirical papers of this DPhil aim to address that knowledge gap through primarily quantitative analyses.

Chapter 5 (Methodology): This chapter describes the research design and methodology of the Mzantsi Wakho cohort study, within which the empirical studies of this DPhil were nested (DPhil Papers 2 and 3). The Mzantsi Wakho cohort comprised adolescents initiated on ART in public healthcare facilities of the Eastern Cape, South Africa. This chapter provides a detailed overview of the research setting, sampling strategies, data collection procedures, dataset structure, and ethical considerations.

Chapter 6 (DPhil Paper 2): *Objectives: (1) To evaluate progression through an extended HIV care cascade across public healthcare facilities in South Africa for a large cohort of ART-initiated adolescents and (2) to identify predictors of attaining cascade steps.*

This chapter aims to provide current estimates for adolescent HIV care outcomes after ART initiation in the context of decentralisation. This study evaluates adolescent progression along the HIV care cascade to viral suppression within South Africa's decentralised HIV care system, using clinical records from the Mzantsi Wakho cohort (n=1080). This analysis highlights remaining gaps in adolescent HIV care after treatment initiation, including the coverage and recency of viral load testing as well as rates of viral suppression, loss to follow-up in care, and mortality. Findings highlight the limited availability of recent viral loads in adolescents' clinical records, with recorded rates of past-year viral suppression far below national targets. This paper is under review at *BMC Infectious Diseases.*

Chapter 7 (DPhil Paper 3): *Objectives: (1) To characterise pathways of transition out of paediatric HIV care for ART-initiated adolescents in South Africa's*

decentralised public care setting and (2) to identify associations between transition pathways and HIV outcomes.

This chapter investigates how decentralising HIV care may affect adolescents' experiences of HIV care transitions. This study applies a mixed-methods approach to characterise pathways for transition out of paediatric HIV care for adolescents in the Mzantsi Wakho cohort. Within the context of South Africa's decentralised HIV care system, this study identifies the most common mode of transition out of paediatric care to be movement from specialised paediatric care to decentralised primary care clinics. This down-referral transition was also found to be protective against viral failure. Semi-structured interviews with healthcare staff illustrate informal protocols used to mitigate risk of adverse post-transition outcomes. This paper was published in the *Journal of Acquired Immune Deficiency Syndromes.*

Chapter 8 (Discussion): This chapter provides a summary of key findings from this dissertation, highlights limitations and strengths of the presented research, discusses implications for policy and programming arising from this DPhil, describes dissemination efforts undertaken by this candidate, and suggests future directions for further research. Dissemination efforts, aiming to generate impact, included direct engagement with policy and programming partners, including the development of a policy brief and toolkit for care providers, as well as local capacity building of the research team. This chapter ends with a brief conclusion of the overall dissertation.

Further details about ethical approvals and study methodologies are provided in the Appendices document.

3. Background and Study Rationale

1. Adolescents living with HIV in sub-Saharan Africa: current context

The expansion of access to antiretroviral therapy (ART) in sub-Saharan Africa has averted the deaths of nearly 5 million people since the mid-1990s (UNAIDS, 2014a). ART is vital to not only reducing mortality and enabling the long-term management of HIV among people living with the virus, but also reducing rates of HIV transmission to HIV-negative sexual partners (UNAIDS, 2015a). Access to this life-saving treatment through prevention of mother-to-child transmission (PMTCT) has also enabled more children vertically infected with HIV to survive into adolescence and subsequently adulthood (Mofenson and Cotton, 2013). However, adolescents have demonstrated persistently high rates of new HIV infections, representing roughly 11% of new HIV infections in 2018 (UNAIDS, 2019).

Together, the growing populations of both vertically and sexually infected adolescents are resulting in an increasing HIV burden among adolescents, who face a unique set of challenges to ART uptake, retention in care, and positive care outcomes (Hazra et al., 2010). According to the most recent UNAIDS estimates there were 1.7 million [1.1-2.4 million] adolescents living with HIV (ALHIV) globally in 2019, 90% of whom were living in sub-Saharan Africa (UNAIDS, 2020a). The World Health Organization (WHO) classifies adolescents as individuals aged 10-19 years old, while young people refers to those aged 15-24 years (World Health Organization, 2016a). Young people accounted for approximately one third of new HIV infections globally in 2019, with 5500 young women becoming infected every

week (UNAIDS, 2020b). In sub-Saharan Africa, adolescent girls and young women accounted for 24% of all new HIV infections, despite comprising only 10% of the population (UNAIDS, 2020c). This combination of high prevalence and incidence rates has led adolescents and youth to be described as the "centre of the epidemic," but this key population also represents a critical opportunity to turn the tide against the epidemic (United Nations Inter-Agency Network on Youth Development, 2012; Davies and Hamlyn, 2018).

ALHIV demonstrate the worst health outcomes in care compared to all other age groups, with the lowest rates of retention in care, ART adherence, and viral suppression (Adejumo et al., 2015; Nglazi et al., 2012; UNAIDS, 2017b). A meta-analysis of adolescents and young people aged 12-24 years found that only 62% were adherent to ART (Kim et al., 2014). Longitudinal studies have estimated that adolescent rates of virological suppression in sub-Saharan Africa range from 28-78%, compared to rates as high as 90% in adults (Fairlie et al., 2014; Agwu and Fairlie, 2013). AIDS remains the leading cause of death for adolescents in Africa, despite the availability of ART (World Health Organization, 2019a). This growing population of adolescents living with HIV also translates into a rapidly increasing number of adolescents requiring life-long ART. Thus, understanding the specific HIV care needs and challenges for this population is crucial for properly tailoring care to improve health outcomes in the present and to prevent onwards transmission in the future, particularly in the context of global HIV care scale-up (Davies and Hamlyn, 2018; Slogrove and Sohn, 2018).

Given the far-reaching implications of early and continual ART, the United Nations have called for massive efforts to scale up ART, including

recommendations for a universal “treat all” strategy, with the goal of enrolling all persons living with HIV on ART and ending the AIDS epidemic by 2030 (Millennium Development Goal 6 and Sustainable Development Goal 3) (UNAIDS, 2015a; World Health Organization, 2016b). A key strategy towards these scale-up goals has been the UNAIDS 90-90-90 treatment targets, which were introduced in 2014 to highlight the ultimate goal of viral suppression among people living with HIV. These treatment targets call for the following by 2020: 90% of all people living with HIV to be aware of their status; 90% of people aware of their HIV-positive status to be on ART; and 90% of people on ART to be virally suppressed (UNAIDS, 2017b). The subsequent steps in UNAIDS’s Fast-Track Strategy to end the AIDS epidemic aim to raise these 90-90-90 targets to 95-95-95 by 2030 (UNAIDS, 2014b).

The most recent global estimates indicate that, by 2019, of all people living with HIV, 81% [68-95%] were aware of their status, 82% [66-97%] of whom had accessed ART, and a further 88% [71-100%] of whom were virally suppressed (UNAIDS, 2020a). In total, 59% of all people living with HIV were virally suppressed. In sub-Saharan Africa, for the 25.6 million people living with HIV, these estimates were 81% aware of status, 83% of whom were initiated on ART, and 88% of these virally suppressed (UNAIDS, 2020a). However, official regional and global estimates for adolescent attainment of these targets are unavailable, due to the lack of age-disaggregated data in most countries’ national monitoring tools (Slogrove et al., 2017). Yet, existing studies suggest that adolescents and young people lag far behind these whole population figures, with rates particularly lower than adults. Surveys from Malawi, Zambia, and Zimbabwe in 2016 found

that the 90-90-90 target attainment rates for people aged 15-24 years were only 46-82-79, compared to older adults with rates of 78-90-90 (Justman et al., 2017; Wong et al., 2017).

These critical gaps indicate the significant progress required for ALHIV to achieve and sustain positive health outcomes and to attain the 2030 targets for ending the AIDS epidemic. Additionally, these gaps reflect the numerous challenges to accessing and remaining on HIV care that are faced by ALHIV, particularly in sub-Saharan Africa.

2. Barriers to accessing and remaining in care for adolescents living with HIV

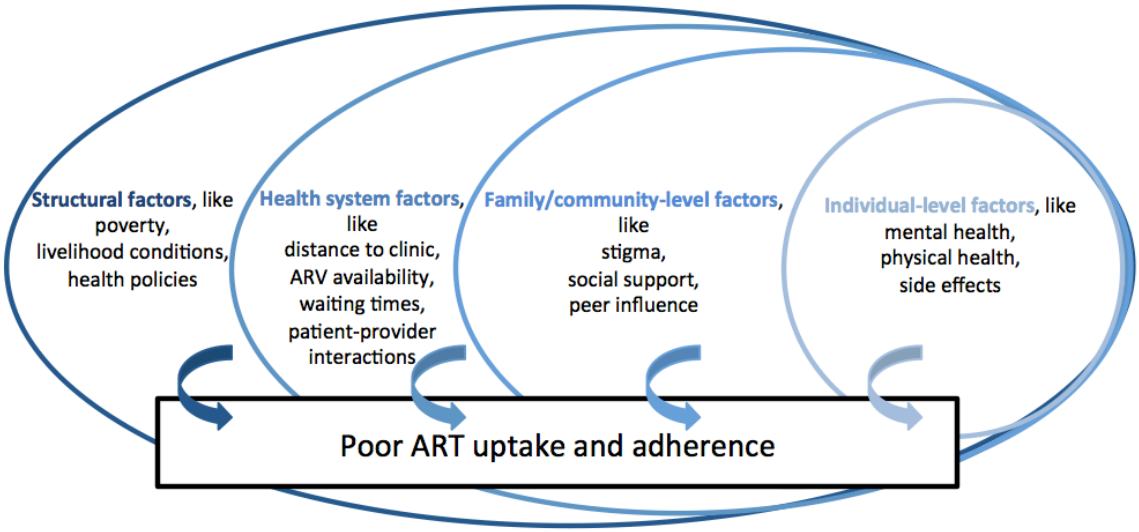
In the context of HIV, adolescents are particularly vulnerable because adolescence is a critical period for physical, sexual, emotional, and psychological maturation during which individuals commonly experience impulsivity, risk-taking, difficult decision-making, and sexual and behavioural experimentation (Kim et al., 2014; Reisner et al., 2009). During adolescence, increased peer influence and reduced parental control can significantly accelerate these behavioural changes (Fairlie et al., 2014). Consideration of these unique characteristics of adolescence is critical for determining whether HIV care systems are truly accessible and acceptable for ALHIV.

Generally, adolescents are also characterised by low levels of communication and openness and lack of financial autonomy. Consequently, adolescents often experience limited *actual* access to care (i.e. due to temporal, financial, and logistical constraints) and *perceived* access to care at facilities (i.e. fear or mistrust of service delivery, temporal and financial inconveniences, and

low self-efficacy) (Napierala Mavedzenge et al., 2011; Persson and Newman, 2012; Fortney et al., 2011). Thus, adolescents face specific challenges at the individual, family and community, and structural levels that are distinct from those faced by adult and paediatric cohorts and that merit careful consideration (Hudelson and Cluver, 2015). Particularly in resource-limited settings, barriers can intersect across these different levels, as shown in Figure 1, and generate cumulative effects. ALHIV who experience a combination of barriers at different levels are less likely to be adherent to medication than those facing single barriers (Lall et al., 2015). These critical challenges present significant implications for initiation and retention on ART.

The focus of this thesis is not to further investigate barriers to ART uptake and adherence for ALHIV. However, in order to examine the effects of decentralising HIV care on their outcomes and care experiences, it is essential to first understand what factors influence their engagement with HIV care. This section provides an overview of the complex network of factors that impact adolescents' access to care, medication use, and health in the context of HIV. Effectively, this section highlights the lived context for ALHIV in sub-Saharan Africa—both beyond and within the clinic.

Figure 1. Nested relationships of factors from the individual to structural level that can affect ART uptake and adherence (adapted from Musheke et al. 2013)



Individual-level factors

Individual-level barriers to sustained care include mental health issues and difficulty with lifestyle challenges, such as incorporating ART dosing schedules into busy school and work schedules (Fairlie et al., 2014). Mental health issues such as depression, low self-esteem, and neurocognitive delays can result from HIV-related neurocognitive complications as well as exposure to adverse environmental influences, including HIV-related stigma and illness in the family (Adejumo et al., 2015; Mellins and Malee, 2013; Laughton et al., 2013). One study of an urban cohort of adolescents in South Africa (92% vertically infected) found that 12% screened positive for symptoms of depression, anxiety, or post-traumatic stress disorder, with lower likelihood of mental health symptoms found among those with greater social support (West et al., 2019). Additionally, a survey among adolescents attending urban and rural clinics in Uganda found that 46% reported depressive symptoms, indicating a large range in prevalence of mental health challenges across settings for ALHIV (Kemigisha et al., 2019).

Furthermore, high rates of HIV burden have been reported among families of ALHIV: a case series of 32 ALHIV in Zimbabwe reported that over 50% of the cohort had lost both parents, and chronic ill health was found among 44% of the surviving family members (Ferrand et al., 2007). In the US, the coping mechanisms used by some ALHIV to handle the loss of family members have also been linked to non-adherence, such as withdrawal and passive emotional regulation (Agwu and Fairlie, 2013). However, few studies have examined these psychosocial problems among ALHIV in resource-limited settings, including sub-Saharan Africa. One study of South African ALHIV found that internalised beliefs about uncleanliness related to HIV and antiretroviral (ARV) side effects can worsen adolescents' understanding of their own bodies and result in neglect, denial, and difficulty with health management (Campbell et al., 2007). Similarly, a cross-sectional survey of ALHIV in Uganda found that psychological distress was associated with ART non-adherence, across 3 different self-reported measures (Mutumba et al., 2016).

Medication-related barriers present a key challenge for ALHIV in sub-Saharan Africa, where options for alternative ART regimens are extremely limited. ARV side effects range from the inconvenient (such as diarrhoea and flatulence) to the more severe, including lipoatrophy, gynaecomastia, and long-term toxicity (Agwu and Fairlie, 2013). Qualitative and quantitative findings have demonstrated that these side effects can discourage sustained adherence due to both discomfort and increased stigmatisation resulting from the visibility of ARV-related side effects that can signal one's HIV status to peers (Dawood, 2015). For example, lipoatrophy resulting in unusual fat distribution can worsen body image

issues, which is a particular concern for adolescents entering an increasingly sexual social context.

Surveys of ALHIV in the US found that the most commonly cited barrier to ART adherence was high pill burden, a challenge also relevant to adolescents in resource-limited settings (Adejumo et al., 2015). In sub-Saharan Africa, the complexity of ART regimens (pill burden and dosing frequency) can be exacerbated by common comorbidities like tuberculosis (TB), which require further daily medications. ART regimens can be simplified through fixed-dose combinations. However, when adolescents age and become more treatment-experienced, simplified regimens become less feasible due to the development of resistance and treatment failure (Agwu and Fairlie, 2013). This challenge is likely to intensify over time because the successful scale up of PMTCT has resulted in ART initiation beginning at earlier ages for young children and longer exposure to ARVs, alongside the increasing number of people infected in adolescence (Elizabeth Glaser Pediatric AIDS Foundation, 2015).

Family- and community-level factors

Family- and community-level barriers to sustained ART adherence among ALHIV largely involve relationships with caregivers and peers. Adolescence, particularly in sub-Saharan Africa, is marked by greater autonomy and reduced caregiver support, especially if an AIDS-affected caregiver is ill or deceased (Adejumo et al., 2015). In qualitative interviews with children living with HIV aged 8-17 in the Democratic Republic of the Congo, stigmatisation from family members was cited as a key barrier to adherence. Some children reported throwing away medications to avoid shaming by relatives or unintended disclosure

of their status to relatives or neighbours (Fetzer et al., 2011). Conversely, qualitative studies of children and adolescents living with HIV in Uganda, Kenya, and South Africa reported the positive impact of social support networks among family and peers on improved ART adherence (Petersen et al., 2010; Adejumo et al., 2015). By reducing HIV-related stigma and encouraging continued treatment maintenance, these social networks can enable individuals to better cope with psychosocial challenges surrounding medication-taking. Without caregiver support, adolescents must assume responsibility for treatment, while on-going developmental, psychological, economic, and social challenges—including the desire for peer approval—threaten consistency of care-seeking behaviours (Martin et al., 2007; Fetzer et al., 2011; Adejumo et al., 2015).

A review of quantitative and qualitative studies among ALHIV in sub-Saharan Africa highlighted the complexity of factors influencing HIV care-seeking behaviours among this key population. Having to assume daily responsibilities for HIV treatment, unlike their HIV-negative peers, conflicts with the desire for peer approval and is compounded by issues of stigma, treatment fatigue, and socioeconomic challenges (Adejumo et al., 2015). HIV-related stigma may discourage adolescents from taking medications or attending routine clinic visits for fear of being seen at the clinic, resulting in unintended status disclosure. Indeed, stigmatising behaviour from peers and school teachers, such as name-calling and social isolation, have been associated with depression, poor ART adherence, attrition from HIV care, and suicidal ideation (Adejumo et al., 2015). Paradoxically, a study in 5 sub-Saharan African countries found ART adherence to be a source of self-stigmatisation, as regular dosing reminded individuals of

being dissimilar to their peers (Makoae et al., 2009). However, improvements in physical and mental health resulting from ART adherence are also associated with reduced internalised stigma, which suggests that the positive effects of adherence may eventually offset the stigma barrier (Tsai et al., 2013).

Health system-level factors

Even when adolescents do seek treatment, some of the largest barriers to ART adherence stem from the HIV healthcare system, ranging from healthcare delivery to healthcare policy. These healthcare system factors are closely intertwined with structural barriers, including poverty and poor healthcare infrastructure for this age group (UNAIDS, 2015a). Notably, vertically infected adolescents face heightened economic difficulties due to HIV-related loss of family members, often requiring them to assume greater responsibilities within the family (World Health Organization, 2013b; MacPherson et al., 2015). Such economic challenges render the financial and temporal costs of transportation to clinics significant barriers to ART adherence (Biadgilign et al., 2008; Adejumo et al., 2015). Thus, in a cyclical process, already stigmatised ALHIV face further socioeconomic and cultural barriers to accessing healthcare and social support services (Lall et al., 2015).

Studies in Uganda, Malawi, and Kenya found that distance to facilities and cost of transportation were among the most commonly cited barriers to ART initiation and retention in HIV care for adults (Geng et al., 2010b). Furthermore, in an analysis across Western, Eastern, and Southern Africa, if travel time to clinic exceeded 2 hours, the risk of loss to follow-up among mothers living with HIV doubled (Rabkin et al., 2010). Similarly, a study among ALHIV in Uganda reported

that reduced distance to a clinic was significantly associated with greater self-reported ART adherence (Bermudez et al., 2016).

Qualitative studies have underscored the link between poverty and transportation-related issues in HIV care provision, particularly for patients living in rural areas generally far from healthcare facilities (Duff et al., 2010). Patients relying on public transportation are often forced to decide on whether to spend limited money on travelling to clinics or purchasing food, including for other family members. In quantitative studies among children and youth living with HIV, limited food accessibility was also found to challenge ART adherence in Malawi, Ethiopia, and the Democratic Republic of the Congo, because available funds were prioritised for obtaining food, rather than accessing medication or clinical care (Fetzer et al., 2011; Jimmy-Gama et al., 2011; Biadgilign et al., 2009). This doubled financial burden is compounded by the medical recommendation of taking ARVs with nutritious foods. In response to these transportation-related challenges, international health organisations have endorsed policies such as decentralisation that aim to make HIV care services more physically and financially accessible (Davis et al., 2018).

Beyond transportation *to* facilities, temporal costs *within* facilities remain a significant barrier to HIV care, as patients of all ages regularly encounter prohibitively long clinic waiting times in sub-Saharan Africa (Govindasamy et al., 2012). Qualitative and quantitative studies in sub-Saharan Africa have reported average waiting times of 2 to 4 hours in HIV clinics, with some ranging to over one day (Musheke et al., 2013b; Duff et al., 2010). For older adolescents and their caregivers in Uganda, the opportunity cost of these clinic waiting times was often

cited in in-depth interviews as a barrier to care-seeking, due to conflicts with family and work commitments (Geng et al., 2010b). Hence, the most vulnerable adolescents are frequently unable to wait long hours for appointments, such as those taking care of ill family members or providing incomes for their households. An explanation from one participant in a study of Zambian people living with HIV is particularly illustrative: "[I]t is not that we do not know the good things that ARVs can do to us. The problem is because of the services…The process is so long" (Musheke et al., 2013a).

Closely tied to the issue of long waiting times is the challenge of shortages of healthcare staff. With the dual expansion of ART eligibility to all persons living with HIV and global scale-up of care, patient volumes at healthcare facilities have increased exponentially. These larger patients populations can overwhelm healthcare providers and pharmacy staff, which not only prolongs waiting times but also may reduce the quality of care received by patients (Waldrop et al., 2016). In a Zambian qualitative study, both adult patients and healthcare staff expressed the belief that higher patient burden resulted in lower quality of care (Musheke et al., 2013a). Indeed, a cohort study of adults living with HIV in Mozambique (n=11,793) found that patients in facilities with medium to high pharmacy patient burden demonstrated higher risk of attrition from care, compared to those in facilities with low patient burden (Lambdin et al., 2011). Findings from these adult cohorts could be reasonably expected to apply for ALHIV as well.

Several studies have noted that the shortage of healthcare workers—relative to the volume of patients—has impeded the expansion of and retention in

care (McGuire et al., 2013; Kipp et al., 2012; Rasschaert et al., 2011). Clinical staff in these overcrowded settings take on significant, stressful workloads that can negatively affect patient interactions, particularly in resource-limited healthcare settings. These encounters can act as major deterrents to continued care, particularly for adolescents who are sensitive to criticism and judgment from peers and authority figures. Indeed, in a Ugandan study, 33% of PMTCT patients reported very negative interactions with healthcare staff that discouraged continued care, including rude comments and shouting (Duff et al., 2010). By distributing the patient population across more facilities, decentralising HIV care has been proposed as a solution to this service-level barrier as well (Kredo et al., 2013).

Increased patient volumes have also placed strain on the supply of healthcare resources, including ARVs and other medications. Notably, stock-outs of ARVs have been cited as a frequent bottleneck to care for HIV patients (Pasquet et al., 2010; Schouten et al., 2011). A survey of facilities across Malawi, Uganda, and Zimbabwe found that stock-outs were significantly more common in paediatric facilities than adult ones, indicating that adolescents may be especially vulnerable to this challenge (Chan et al., 2014). Due to ARV shortages, patients presenting for ART initiation may be triaged out of care. Others may experience forced interruptions of medication-taking, which can both limit ARV effectiveness and encourage further non-adherence. Studies among adult patients reported that drug stock-outs led to between 10-28% and 52% of ART discontinuations in Côte d'Ivoire and Rwanda, respectively (Pasquet et al., 2010). Qualitative reports from adults in Zambia have shown that patients' uncertainty about the long-term

availability of ARVs and concerns about consequent treatment interruptions can discourage ART initiation and adherence (Musheke et al., 2013a). Concerns about ARV availability also intersect with the challenge of long waiting times. Patients may wait several hours for clinical appointments—setting aside family and financial obligations—only to be told that the ARV supply has finished and that they must return for another appointment (Duff et al., 2010).

Furthermore, because adolescents have historically not been prioritised in national HIV plans, health systems have failed to provide accessible and acceptable treatment services that facilitate retention in care (World Health Organization, 2013b). In February 2015, UNAIDS and UNICEF launched the All In to #EndAdolescentAIDS strategy to accelerate adolescent progress towards the global Fast Track treatment goals (UNAIDS, 2015a). This agenda marked the beginning of increased global programmatic and research attention to this vulnerable population. However, even with this recent priority shift, adolescents often fall into the gap between paediatric and adult HIV care in sub-Saharan Africa, due to the limited provision of adolescent-specific health services. One key factor has been the lack of available data specifically on adolescents in national and global HIV care monitoring and evaluation tools (UNAIDS, 2015a). In part, this is because the WHO and many other organisations summarise adult and paediatric data as ≥15 years and <15 years categories, respectively. Consequently, the lack of evidence specific to this age group has hindered efforts to tailor HIV care for this vulnerable population, with robust estimates of their HIV outcomes unavailable (Slogrove et al., 2017). In recent years, some sub-Saharan African countries, including South Africa, have made progress towards

disaggregating national health surveillance data specifically for adolescents (Human Sciences Research Council, 2019).

In most South African healthcare facilities, the shift of HIV care management from paediatric to adult services begins at age 15 (Southern African HIV Clinicians Society, 2017). This transition from paediatric to adult HIV care in mid-adolescence can present a major challenge for ALHIV. They must adjust to new clinical settings and interactions, and this transition may be disruptive for patients who have been receiving care from the same paediatric providers and facilities since early childhood (Dahourou et al., 2017). Studies in high-income countries have found that the transition to adult healthcare services negatively impacts ART adherence, which can be worsened for adolescents experiencing emotional or cognitive delays resulting from HIV infection (Adejumo et al., 2015). This transition remains very under-researched in the sub-Saharan African context (Judd and Davies, 2018). Healthcare facilities across sub-Saharan Africa also face a severe shortage of healthcare workers experienced in adolescent health who can tailor HIV care to the needs of ALHIV, which would facilitate improved adherence and care outcomes (Agwu and Fairlie, 2013).

Therefore, to encourage sustained adolescent engagement with HIV care, healthcare delivery models must take into account these wide-ranging barriers—from the individual to structural levels within each country's context. Considerations of the future of adolescent HIV care in South Africa must be grounded in an understanding of how the South African healthcare system is structured, particularly with regards to HIV care delivery. This context also demonstrates the extent to which adolescents have not yet been considered in

South Africa's response to the epidemic, including in its decentralisation policies. Given its large population of ALHIV and early implementation of decentralisation, South Africa's HIV care system can offer unique insights for the future of decentralised adolescent HIV care delivery in similar settings across sub-Saharan Africa.

3. The care context: HIV care in South Africa's public healthcare system

South Africa houses the world's largest population of people living with HIV, estimated at 7.5 million people (UNAIDS, 2020a). Accordingly, South Africa's National ART Programme is also the world's largest ART programme, accounting for 21% of the global population on ART in 2016 (UNAIDS, 2020a). For its total population across all ages in 2019, South Africa achieved the following rates towards the UNAIDS Fast-Track targets: 92% of people living with HIV were aware of their status, 75% of those aware of their HIV-positive status had initiated ART, and 92% of those on ART were virally suppressed (UNAIDS, 2020a).

Public healthcare sector of South Africa

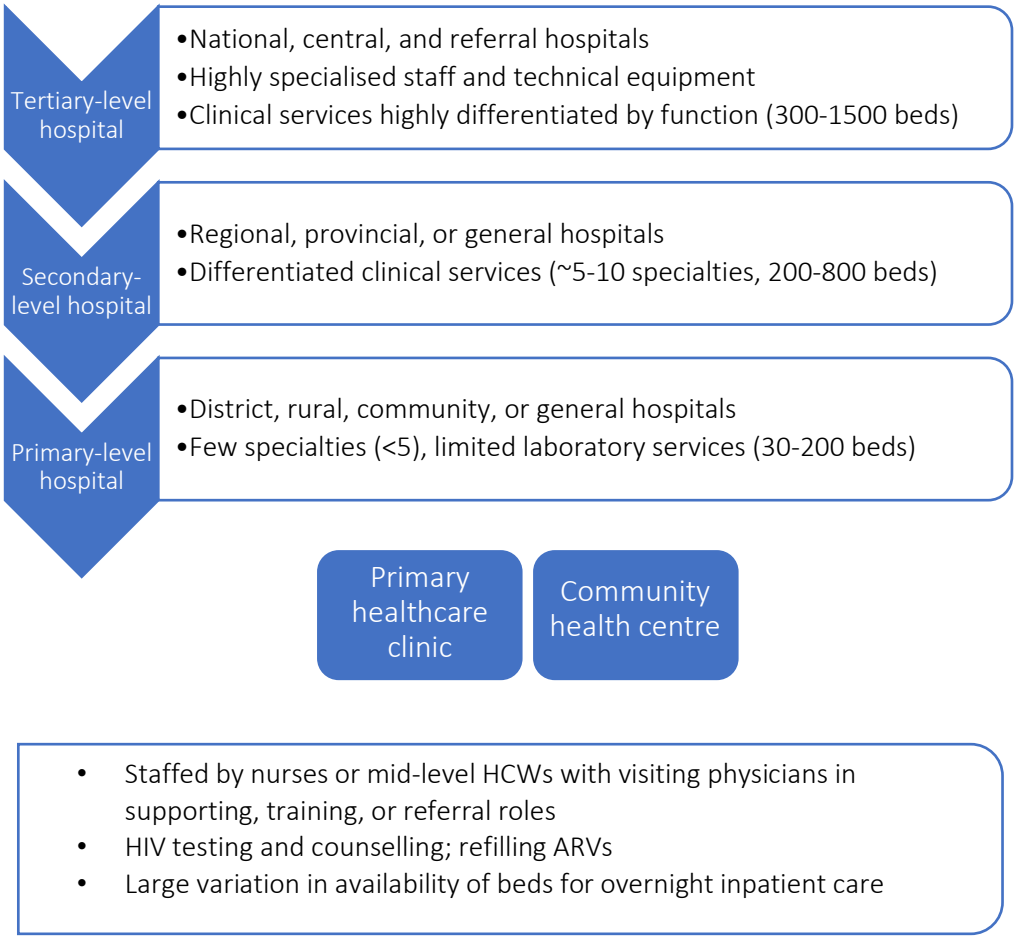
South Africa's public healthcare system serves approximately 84% of the population, and it is comprised of approximately 3920 healthcare facilities, of which 81% are primary care clinics (Jobson, 2015; Day and Gray, 2016). On average, these clinics provide care for 13,718 persons each, well in excess of the WHO guideline of 10,000 patients per clinic, with 1 doctor for every 4219 persons (Jobson, 2015).

Primary healthcare comprises the foundation of the public health sector, as the first line of care for most South Africans through primary care clinics,

community health centres, and primary-level hospitals (district hospitals) (Jobson, 2015). The next tier in the healthcare system are secondary-level hospitals, which receive patients who have been referred from primary clinics for more intensive clinical care. Subsequently, the tertiary-level hospital system consists of national, academic, and referral hospitals that offer advanced treatment, diagnostic procedures, and training for healthcare providers (Hensher et al., 2006). Also, referral hospitals often provide managerial and administrative support for other parts of the healthcare system, including the management of laboratory services and distribution of medications and medical supplies (Hensher et al., 2006). An overview of the different types of healthcare services available at these three tiers in South Africa is provided in Figure 2.

In practice, distinctions between the tiers of healthcare in South Africa are more fluid—especially between primary care clinics and district hospitals. However, general classifications can be made based on the consideration of three factors for the diagnosis and treatment of medical conditions: 1. Availability of specialised personnel 2. More sophisticated diagnostic technologies 3. More advanced therapeutic technologies (Hensher et al., 2006).

Figure 2. Tiers of South African healthcare facilities and services available at each level



HIV/AIDS and the South African healthcare response

Although South Africa has the largest HIV burden in the world, the rollout of ART remained slow until the mid- to late-2000s, resulting in heavy criticism from the international community (Ojikutu et al., 2007). In 2003, after significant international and local pressure, the South African Department of Health announced its Operational Plan to begin public sector ART rollout, with plans to expand treatment up to 450,000 persons by March 2006 (Kavanagh, 2014). Simultaneously, the WHO launched its "3 x 5" initiative in 2003 to increase ART provision in resource-limited settings. The initiative called for enrolling 3 million people on ART by 2005. Through this initiative, the number of ART-initiated

people in sub-Saharan Africa increased 10-fold between 2003 and 2006, from 100,000 to over 1 million persons (Ojikutu et al., 2007).

ART provision and HIV care only began in most provinces of South Africa by mid-2004 (Nattrass, 2006). By the end of 2005, the number of people on ART in the public sector was less than 30% of the year's target for the "3x5." This delay in effective implementation of a public ART programme resulted in the loss of an estimated 330,000 lives, or 2.2 million person-years (Chigwedere et al., 2008).

Although the Department of Health determines eligibility criteria and policies for ART initiation, ART programmes in South Africa were supported by external funding for many years (Patel et al., 2012). In 2004, the US government launched the President's Emergency Plan for AIDS Relief (PEPFAR), which assisted primarily African governments to establish HIV prevention, care, and treatment programmes in public and private clinics (Patel et al., 2012). By 2009, PEPFAR was providing support for the treatment of 75% of all children on ART in South Africa (Patel et al., 2012). However, in 2010, PEPFAR began shifting its emphasis to capacity building for countries to manage their own ART programmes in public health facilities. Through this transition, the South African Department of Health committed to supplying first-line ART for its population of people living with HIV (Kavanagh, 2014).

In order to scale up HIV care, the Department of Health began decentralising care from hospitals to primary care facilities and task-shifting treatment from physicians to nurses. For example, in April 2010, the Department of Health prioritised nurse-initiated management of ART (NIMART) for adult ART programmes, and from 2003 to 2012 the number of nurses increased by over

40% (Patel et al., 2012; Mayosi and Benatar, 2014). South Africa's National Strategic Plan for HIV, TB, and STIs (2012-2016) outlined the government's approach to scaling up HIV testing and treatment, which included decentralisation of HIV care to direct more patient care to primary care facilities. Through efforts guided by the National Strategic Plan, South Africa's ART programme is currently the largest in the world (Statistics South Africa, 2016; UNAIDS, 2020a). From 2012-2016, South Africa made significant gains in responding to the HIV epidemic. By 2016, life expectancy rose to 62.4 years from 58.3 years in 2011, while the national TB treatment success rate rose to 83% (South African National AIDS Council, 2017).

However, to reach international and national public health goals, South Africa must accelerate its national response to the HIV epidemic. Today, HIV/AIDS is still the leading cause of premature and adolescent death in South Africa (Mayosi and Benatar, 2014). Additionally, to provide adequate care for the country's growing HIV patient population, estimates indicate the need for triple the current size of the healthcare workforce (Mayosi and Benatar, 2014).

In acknowledgement of these remaining challenges, the National Strategic Plan was renewed for 2017-2022 with a new set of goals, centred on a strategy of "focus[ing] for impact" (South African National AIDS Council, 2017). These eight goals, outlined in Table 1, are addressed through a focus on decentralising care at the provincial, district, and ward levels. Through a multi-sectoral and community-centred approach, the new Plan aims to address structural drivers like poverty while developing differentiated care models that allow for the tailoring of

interventions to each patient's specific needs (South African National AIDS Council, 2017).

Table 1. Goals of the South African National Strategic Plan (2017-2022)

Goal	Approach (2017-2022)
Accelerate prevention to reduce new HIV and TB infections and STIs	Reduce new HIV infections by over 60%; TB incidence by at least 30%; and new gonorrhoea, chlamydia, and syphilis infections
Reduce morbidity and mortality by providing HIV, TB, and STI treatment, care, and adherence support for all	Achieve 90-90-90 target for HIV and TB by 2020 • Provide 90% of PLHIV with ART • Ensure that 90% of patients on ART achieve viral suppression • Attain 90% treatment success rate for drug-sensitive and 75% for multi-drug resistant TB
Reach all key and vulnerable populations with customised and targeted interventions	Build capacity of community-based service providers and community- and peer-led programming to create environments for accessing hard-to-reach groups and increasing the uptake of life-saving services
Address the social and structural drivers of HIV, TB, and STIs, and link these efforts to the NSP	Apply a multi-sector approach to addressing social and structural drivers of the epidemics • Implement socio-behavioural change programmes • Increase access to services and social protection for vulnerable groups
Ground the response to HIV, TB, and STIs in human rights principles and approaches	Reduce internalised and externalised stigma among PLHIV and TB by at least 50% • Facilitate access to justice for PLHIV and those vulnerable to HIV • Promote an environment that ensures human and legal rights
Promote leadership and shared accountability for sustainable response to HIV, TB, and STIs	Strengthen decentralised approach to centre quality services at the district level • Improve collaboration between government, civil society, development partners, and the private sector
Mobilise resources to support the achievement of NSP goals and ensure a sustainable response	Improve efficiency and mobilise sufficient resources to achieve the NSP goals
Strengthen strategic information to drive progress towards achievement of the NSP goals	Build capacity for and coordinate the collection of routine health information, monitoring and evaluation of implementing the NSP, estimates of epidemic measures in the general population and key populations • Strengthen research activities for the creation of strong evidence for greater impact

ART: Antiretroviral therapy; PLHIV: People living with HIV; NSP: National Strategic Plan; STI: Sexually transmitted infection; TB: Tuberculosis

However, efforts to expand ART provision while maintaining quality of care have been limited by the lack of adequate facilities and an insufficient number of

healthcare workers with expertise in ART provision (Ojikutu et al., 2007). These challenges are particularly acute for vulnerable key populations, including ALHIV, whose specific HIV care needs have been largely overlooked, even in decentralised healthcare systems.

Adolescent HIV care guidelines in South Africa

South Africa houses the world's largest population of ALHIV, estimated at 360,000 adolescents in 2019 (UNAIDS, 2020a). In alignment with updates to WHO recommendations for ART delivery, South African national guidelines for ART initiation expanded significant between 2010 and 2016 (Meyer-Rath et al., 2017). An overview of the changes in ART initiation criteria is provided in Table 2, including the current guidelines for universal treatment that were implemented in 2016 in South Africa.

Table 2. Summary of changes to WHO and South African national guidelines for ART initiation among adolescents living with HIV (2010-2016)

WHO guidelines		**South African national guidelines**	
Date	Recommendations	Date	Guidelines
July 2010	Eligible at CD4 ≤350 cells/mm^3; universal treatment for patients co-infected with active TB or hepatitis B	April 2010	Eligible at CD4 ≤350 cells/mm^3 for patients co-infected with TB and pregnant patients; universal treatment for patients with CD4 ≤200 cells/mm^3
		August 2011	Eligible at CD4 ≤350 cells/mm^3
June 2013	Eligible CD4 ≤500 cells/mm^3; universal treatment for patients co-infected with active TB or hepatitis B, pregnant and breastfeeding women, or HIV-positive partners in serodiscordant couples	January 2015	Eligible at CD4 ≤500 cells/mm^3; universal treatment for patients co-infected with TB or hepatitis B and pregnant or breastfeeding women
September 2015	Universal treatment for all persons living with HIV	September 2016	Universal treatment for all persons living with HIV

TB: Tuberculosis; WHO: World Health Organization
Note: Across all years listed in the table, patients in WHO Clinical Stage III or IV have been eligible for ART initiation regardless of CD4 cell count.

A global assessment of facility-level data for adult patients indicated that universal ART initiation has been successfully implemented across sub-Saharan Africa, including in rural primary care facilities (Brazier et al., 2019). However, data were unavailable for both the uptake of universal ART for adolescents and the implementation of post-initiation clinical monitoring guidelines.

Once adolescents have initiated first-line ART, their healthcare providers' goal is to maintain effective treatment on the first-line regimen for as long as possible, because second- and third-line treatments in South Africa are more complicated to manage, less available, and more costly (Boyd et al., 2009). During the first year after ART initiation, all patients are considered clinically unstable and required to present for more frequent clinical appointments, including clinical examinations as well as viral load and CD4 cell count testing (Southern African HIV Clinicians Society, 2017). From the second year on ART onwards, ALHIV in South Africa generally undergo less frequent clinical review—focusing on routine health maintenance—unless patients exhibit clinical instability, which requires more frequent and intensive clinical management. Table 3 summarises the frequency and types of services officially required for ART maintenance among clinically stable and unstable patients in South Africa.

Table 3. South African national guidelines for clinical monitoring of adult and adolescent patients on ART from second year after initiation (adapted from Southern African HIV Clinicians Society, 2017)

	Clinically Stable		Clinically unstable
	Clinical review	**ART refill**	**Clinical review and ART refill**
Visit frequency	6-monthly	3-monthly	1-3 monthly, at clinician's discretion
Services delivered	Annually: • Full clinical examination • Viral load testing • CD4 cell count At each visit: • Viral load and CD4 count review • TB screening • Sexual and reproductive health screening • Mental health screening • Additional support as needed	• ART refill • Adherence evaluation • Review of referrals to auxiliary services (e.g. social worker, psychologist, counsellor)	All services provided for clinically stable patients **plus:** • Monthly clinical examinations until clinically stable (e.g. resolved opportunistic infections) • If viral load >1000 copies/mL, increased adherence monitoring and repeated viral load test after 3 months • Additional blood tests as indicated (e.g. tests of liver or kidney function) • Evaluation of pharmacy refill records and appointment attendance • Psychological assessment, if applicable • Assessment of readiness to move to clinically stable management

ART: Antiretroviral therapy; TB: Tuberculosis

These official guidelines represent the minimum requirements for clinical ART maintenance that ALHIV patients in South Africa's public health sector should theoretically be receiving, across all modes of healthcare delivery—including the most decentralised care models. However, the global assessment of universal treatment uptake found that viral load monitoring was available in only 45% of facilities in low- and middle-income countries by the end of 2017 (Brazier et al., 2019). In sub-Saharan Africa, limited human and physical resource capacity in healthcare facilities—such as the lack of capacity for routine viral load monitoring—often generates sub-optimal adherence to guidelines for routine

clinical care (Musa et al., 2018). Several studies across sub-Saharan Africa have highlighted this critical implementation gap between care guidelines recommended by the WHO and national Departments of Health and the reality of HIV care, particularly in primary care clinics (Musa et al., 2018; Ambia et al., 2017).

4. Decentralisation of ART delivery in South Africa

The size of South Africa's ART programme reflects both the high demand for HIV care within the country and the National Department of Health's efforts to rapidly scale up care (UNAIDS, 2013). In 2010, to meet the HIV care needs for the population, the Department of Health began decentralising HIV care within a broader strategy for re-engineering primary healthcare (Pillay and Barron, 2011; Mayosi and Benatar, 2014). With the adoption of a universal "test and treat" policy in 2016, the scale up and decentralisation of HIV care are continuing to expand in South Africa, looking towards UNAIDS goals for ending the AIDS epidemic by 2030.

Decentralisation aims to expand healthcare access by shifting the majority of care provision from tertiary and secondary facilities (i.e. hospitals) to lower-level healthcare facilities such as primary care clinics, which are generally closer to patients' homes (Kredo et al., 2013). Although decentralisation theoretically allows a greater number of people to access HIV care, it also requires patients to engage with a new form of care delivery. This new mode of care generally entails different, lower-resourced facilities and different care providers, who usually have lower levels of training (Duncombe et al., 2015). Additionally, effective decentralisation requires the scale-up of human resources to staff these facilities

and ensure sufficient quality of care, through training a larger number of personnel (Gilks et al., 2006).

Through the incorporation of decentralisation into its National Strategic Plans for HIV, TB, and STIs (2012-2016 and 2017-2022), South Africa has been one of the earliest sub-Saharan African countries to roll out decentralisation nationally. Furthermore, given the size of the national ART programme, South Africa represents a "stress test" for the ability to manage HIV care through a decentralised health system while maintaining quality of care for vulnerable populations like ALHIV (South African National AIDS Council, 2017; National Department of Health, 2010). Thus, as other sub-Saharan African countries adopt decentralisation into strategies for scaling up care, South Africa provides a unique opportunity to gain insights on how to provide and improve decentralised care.

Defining decentralisation of HIV care delivery in South Africa

The primary mode of decentralising HIV care delivery within the South African National Strategic Plan has been the decentralised facility-based model for ART delivery. An overview of this intervention using the TIDieR framework (Template for Intervention Description and Replication) is presented in Table 4 (Hoffmann et al., 2014). Through this model, ART-initiated patients who have met eligibility criteria for clinical stability are down-referred from more specialised health facilities, such as hospitals, to lower level facilities like primary care clinics (Duncombe et al., 2015). More recently, decentralisation has expanded to allow for the initiation *and* management of patients at decentralised sites led by trained nurses.

Table 4. Description of decentralisation of HIV care delivery based on items included in the Template for Intervention Description and Replication (TIDieR) checklist

Item	Description
1. Brief name	Decentralisation of HIV care delivery
2. Why Describe any rationale, theory, or goal of the elements essential to the intervention	To increase access to and retention in care to improve health outcomes. Proposed mechanism of change includes reducing workload (higher provider-to-patient ratio) and time and financial costs to patients due to transportation.
3. Materials Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers.	Creation of peripheral health centres with the capacity to provide HIV testing and counselling and to dispense antiretroviral medication; training of healthcare providers in ART initiation and maintenance.
4. Procedures Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Relocation of services from centralised sites (i.e. hospitals) to lower levels of healthcare, or peripheral health centres. Patients meeting nationally determined eligibility criteria for down-referral are provided with the option of treatment at a peripheral facility. However, in practice, the only choice most patients are given, if ever, is *which* peripheral facility they would prefer to attend—not whether or not to down-refer.
5. Who provided For each category of intervention provider, describe their expertise, background, and any specific training given.	Available levels of peripheral health centres and healthcare providers vary by country, but general guidelines for distinguishing training levels at each site category are as follows: Advanced or referral hospital—specialist doctor Hospital—doctor Health centre or community health centre—nurse or clinical officer (≥2 years training) Community care or primary care clinic—nurse or nurse aide (min. few months training)
6. How Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Face-to-face care at healthcare facilities. The two major forms of decentralisation are as follows: Partial decentralisation—ART initiation at hospital but follow-up care (maintenance) at health centre or clinic Full decentralisation—ART initiation and follow-up care at health centre or clinic
7. Where Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	Peripheral health centres that are typically closer to patients' homes. Typically, services available at healthcare facilities are as follows: Advanced or referral hospital—viral load testing and full care (HIV- and non-HIV-related) Hospital—CD4 count and medicine (HIV- and non-HIV-related)

	Health centre or community health centre—HIV testing, point-of-care laboratories, ARVs, opportunistic infection medicines Community care or primary care clinic—HIV testing and counselling, refilling ARVs
8. When and How Much Describe the number of times the intervention as delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose.	Frequency of clinic visits varies by severity of symptoms and facility. WHO guidelines recommend clinical visits and medication pickups every 3-6 months for patients stable on ART (World Health Organization, 2013a).
9. Tailoring If the intervention was planned to be personalised, titrated, or adapted, then describe what, why, when, and how.	Levels of minimum required training for healthcare providers and eligibility criteria for patients are determined by national guidelines.

ART: Antiretroviral therapy; ARVs: Antiretrovirals; WHO: World Health Organization

According to South African national guidelines, all ART-initiated patients are eligible for down-referral to a decentralised facility if they meet the following criteria, regardless of age:

- On ART for >12 months, to allow for two sets of laboratory tests (at 4 and 10 months on ART);
- Viral suppression (<400 copies/mL) at most recent test;
- Stable weight (<5% weight loss between last three visits);
- No opportunistic infections;
- Not currently pregnant or breastfeeding;
- No recent change in ARV regimen (Brennan et al., 2011; Southern African HIV Clinicians Society, 2017)

However, in practice, eligibility for down-referral is often determined based on clinicians' global assessments of which patients are "clinically well" (Copelyn et al., 2018). After being deemed eligible, patients are theoretically provided with the *option* of transferring care to a decentralised healthcare facility. The process and guidelines surrounding obtaining consent for decentralising adolescent patients in

South Africa have not been formalised. In Thailand, decentralisation of HIV care for younger paediatric patients requires caregiver consent, although increasing agency during adolescence makes this age group a particularly unique clinical population, especially for older adolescents (Hansudewechakul et al., 2012).

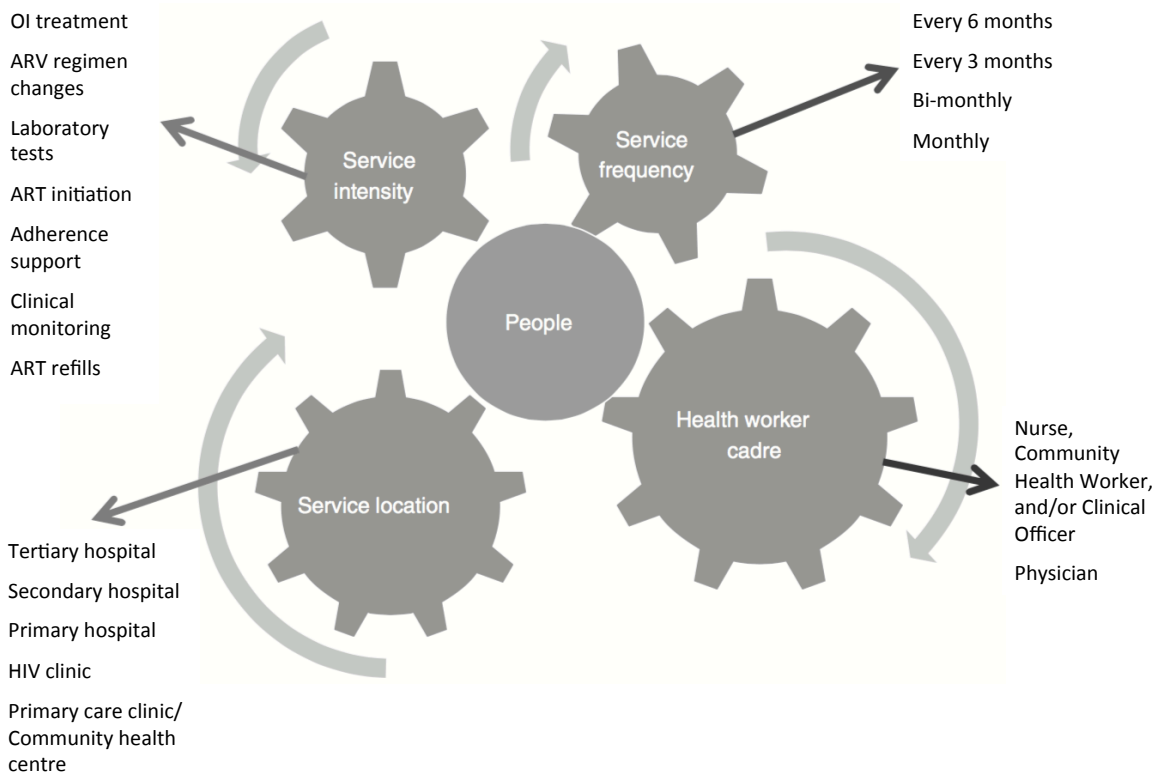
Even after down-referral to a decentralised facility, patients remain eligible for up-referral to centralised sites with physician-led care in the event of clinical instability (i.e. treatment complications, emergencies, co-morbidities, or pregnancy) (National AIDS & STI Control Program, 2009). Thus, the patient's current health status should determine whether the patient should be treated at a decentralised or centralised site, with room for mobility between the two levels (Duncombe et al., 2015).

Alongside the physical relocation of services from higher to lower tier facilities, care management is also transferred from more specialised providers (physicians) to non-physician providers through task-shifting (Kredo et al., 2014). Task-shifting transfers clinical management responsibilities to lower cadres of healthcare workers (i.e. nurses or clinical officers) so that the increased patient load can be distributed across available healthcare providers. Non-physician providers are trained to provide less intensive clinical care at decentralised sites, such as refilling ARVs and on-going clinical monitoring to identify worsening symptoms (Kredo et al., 2014). Additionally, task-shifting entails the transfer of more responsibilities to the patients themselves. In particular, patients are more actively involved in managing their illness through treatment adherence, seeking help when experiencing side effects or complications, and enacting behaviours to prevent onward transmission (Gilks et al., 2006). However, the actual increase in

patients' care ownership as a result of task-shifting remains understudied for adolescents and young people (Kredo et al., 2014; Murray et al., 2017). While task-shifting is an important component of decentralisation, this distribution of clinical responsibilities does not constitute decentralisation in itself. Decentralisation also entails the physical relocation of care, typically closer to patients' homes, and increased frequency of visits to decentralised facilities (Kredo et al., 2013).

Thus, decentralisation tailors HIV care delivery to patients through the dynamic interplay of four factors of HIV care delivery: location of service delivery, service intensity, service frequency, and cadre of healthcare provider. As Figure 3 suggests, as the intensity of required services decreases (e.g. ART refills), the location of care delivery shifts to a lower-tier facility like a primary care clinic. In turn, the cadre of healthcare provider at this site also shifts from physicians to nurses, clinical officers, or community health workers; and the frequency of visits to this site increases. Effectively, stable patients have more frequent visits to lower-level facilities for routine, low-intensity care administered by nurses. Conversely, as the intensity of required services increases—such as switching to second-line ART regimens—the service location shifts to more centralised sites, such as hospitals, where physicians can provide specialised care. However, the frequency of visits to a hospital will also decrease, as hospital-based care is only intended to treat conditions acutely, allowing for down-referral to a decentralised site once the patient has stabilised.

Figure 3. Four levels for tailoring HIV care to patients in a decentralised framework *(adapted from Duncombe et al. 2015)*



ART: Antiretroviral therapy; ARV: Antiretroviral; OI: Opportunistic infection

5. Theory of change for decentralisation of HIV care delivery to improve patient outcomes

As proposed in the current literature, the theory of change for how decentralising HIV care may improve patients' health outcomes addresses three major structural barriers to retention in care (Kaufman et al., 2014; Kredo et al., 2013). Briefly, these components of the theory of change are as follows:

1. Increasing the availability of care through a greater number of facilities and providers delivering HIV care, thereby reducing the patient burden in facilities that are already stretched for human and physical resources;
2. Bringing HIV care services closer to patients' homes, increasing the accessibility of care; and

3. Delegating more decision making to local authorities, which enables HIV care services to be tailored to the local population and thus increase acceptability of care.

First, in resource-limited settings with high HIV disease burden, hospitals' low provider-to-patient ratios make the expansion of high-quality care practically infeasible (Kredo et al., 2014). Although significant progress has been made throughout sub-Saharan Africa to scale up HIV care provision, the shortage of healthcare workers has limited further expansion in many settings (Ross et al., 2012). Furthermore, quality of care is frequently compromised by high levels of burnout among healthcare staff, which can translate into poor bedside manner, resulting in low patient satisfaction and disengagement from care (Ross et al., 2012).

Through decentralisation, clinically stable patients are down-referred from the small number of hospitals to numerous primary care clinics. These down-referrals distribute the patient population over a larger number of facilities and, therefore, care providers. Thus, decentralisation reduces the number of clinically stable patients in hospitals, so that more specialised healthcare providers can focus on care for complicated cases (Nyasulu et al., 2013). In parallel with decentralisation, task-shifting of care from doctors to other healthcare workers can mitigate burnout by increasing the number of qualified providers and reducing the patient burden per provider (Schneider et al., 2006; Reidy et al., 2014). Studies in South Africa, Rwanda, and Mozambique found that the quality of nurse-led HIV care was non-inferior to that of physician-led care for adult patients, although quality of care for adolescents was not evaluated (Sanne et al., 2010; Sherr et al.,

2010; Shumbusho et al., 2009). Distributing patient burden across sites should also reduce waiting times at facilities and the likelihood of ARV stockouts (Brennan et al., 2011; Lambdin et al., 2011).

Second, decentralisation relocates care for the majority of patients from centralised hospitals to smaller healthcare facilities that are often closer to patients' homes. Thus, decentralisation can reduce financial and temporal costs associated with transportation to seek HIV care (Jaffar et al., 2010; van Dijk et al., 2014; Kredo et al., 2013; Humphreys et al., 2010). As discussed in Chapter 3.2, longer travel times and associated expenditures (i.e. public transportation costs) have been associated with lower retention in care and ART adherence in sub-Saharan Africa (Geng et al., 2011; Posse et al., 2008; Tuller et al., 2010; Weiser et al., 2010). By reducing the temporal and financial burdens of transportation to healthcare facilities, decentralising care should increase the accessibility of health services.

Third, by relocating healthcare decision-making and management to local authorities, decentralisation allows for the tailoring of services to the needs and cultures of clients (Bossert, 1996). Due to greater physical and socio-political proximity to their clients, healthcare providers and management at decentralised sites can address healthcare issues in a manner that is more likely to be acceptable by the community (Loubiere et al., 2009). For instance, nurses providing HIV care to adolescents at a primary care clinic in a rural village are more likely to understand the realities and challenges experienced by ALHIV in that village. Consequently, they may be better equipped to tailor HIV care recommendations for their ALHIV clients, compared to healthcare providers based

in urban centres. Thus, decentralisation should theoretically increase the acceptability of care and patient satisfaction, which should improve sustained engagement in HIV care.

As the proposed theory of change demonstrates, decentralisation of HIV care delivery aims to address several key service-related barriers to care experienced by ALHIV. Thus, decentralisation of HIV care delivery has the potential to improve retention in care and health outcomes for adolescents in resource-limited settings. However, very few studies have actually evaluated *how* this structural intervention affects adolescents in sub-Saharan Africa, even though it has already impacted the lives of millions. As the rollout of decentralised HIV care continues globally, it is imperative to understand its implications for adolescents, a particularly vulnerable key population.

Figure 4. Entrance to the Dimbaza Community Health Centre in the Eastern Cape, South Africa

Source: Lucie Cluver

6. Thesis Aims and Questions

This thesis does not aim to determine whether or not decentralisation should be implemented as a model of HIV care for adolescents. Decentralisation is already underway and is necessary for resource-limited, high-burden settings. Rather, this research aims to characterise how decentralised HIV care is actually being implemented on the ground for ART-initiated ALHIV and to identify potential ways to optimise HIV care within a decentralised healthcare system. By focusing on the South African context, this dissertation evaluates decentralised HIV care in the public healthcare system treating the largest patient population of ALHIV.

These research aims are addressed through three sets of specific research objectives. Each objective set has resulted in a separate manuscript, ultimately producing three stand-alone publications and therefore adhering to the requirements for the DPhil by publication track. The three overall sets of objectives are as follows:

Objective, Paper 1: To synthesise and critically assess the evidence base for the effects of decentralising ART delivery on health outcomes for adolescents and young adults living in low- and middle-income countries

Objective 1 entailed a systematic review of evidence of the effects of decentralising facility-based ART delivery and HIV care on health outcomes for young people aged 10-24 living with HIV in low- and middle-income countries (LMICs). Given the lack of quantitative evidence on decentralising HIV care for adolescents in LMICs, this review's scope was expanded beyond adolescents to also include young adults aged 20-24 years. Health-related outcomes included

mortality, loss to follow-up in care, ART adherence, viral load, CD4 count, switches to second-line ART regimens, and morbidity measures. This paper aims to both identify the extant knowledge of how decentralising HIV care affects adolescents' health and to determine which critical gaps persist in our understanding of decentralised ART delivery for ALHIV. Thus, this paper helps establish the foundation for subsequent analyses in this dissertation, which aim to fill those research gaps.

The manuscript for this paper (Chapter 4) has been published in *Global Health Action* (DOI 10.1080/16549716.2019.1668596).

Objectives, Paper 2: Objectives: (1) To evaluate progression through an extended HIV care cascade across public healthcare facilities in South Africa for a large cohort of ART-initiated adolescents and (2) to identify predictors of attaining cascade steps.

The HIV care cascade is a tool used to track engagement with HIV care for a range of patient populations. This tool estimates the proportion of people living with HIV who have achieved specific stages of care, from HIV testing through the ultimate goal of viral suppression. Hence, this monitoring tool also provides an opportunity to assess patients' progress towards the UNAIDS 90-90-90 HIV treatment targets for 2020.

The vast majority of studies on adolescent HIV care outcomes in sub-Saharan Africa have drawn from clinical cohorts in well-resourced care centres or a single healthcare facility. The few studies that have examined adolescents'

health outcomes across multiple care facilities have been unable to distinguish between loss to follow-up and undocumented transfers to a different facility (Slogrove et al., 2018). As a result, the extant profiles of adolescents' HIV care outcomes do not reflect the "real-world" setting experienced by most adolescents in sub-Saharan Africa, where care is typically delivered in public care facilities, with high degrees of patient mobility across sites (Adejumo et al., 2015; Davies et al., 2017).

Therefore, this paper characterises adolescent progression across the HIV care cascade in a public care setting, using individually linked clinical records from routine data from ALHIV in a health district of the Eastern Cape, South Africa. This objective comprises the first of two empirical papers using primary data from the Mzantsi Wakho cohort study, collected across 52 healthcare facilities for 1080 adolescents living with HIV (further described in Chapter 5).

This paper extends the HIV care cascade to include operational outcomes that represent intermediate stages where patients may disengage from the HIV continuum of care, as well as adjusted estimates for care-terminating outcomes like loss to follow-up and mortality. It also tests associations between sociodemographic and treatment-related characteristics and attainment of cascade steps.

The manuscript for this paper (Chapter 6) is currently under review at *BMC Infectious Diseases.*

Objectives, Paper 3: (1) To characterise pathways of transition out of paediatric HIV care for ART-initiated adolescents in South Africa's decentralised public care

setting and (2) to identify associations between transition pathways and HIV outcomes

As adolescents living with HIV age from childhood into young adulthood, they simultaneously experience a shift from paediatric to adult HIV care. Previous studies have documented that this period of transition increases adolescents' vulnerability to disengage from care, as they may fall into the "gap" between these two modes of care (Dahourou et al., 2017). However, the majority of research on adolescent transitions out of paediatric HIV care has focused on transitions in high-income settings or on highly specialised, well-resourced transition programmes. Decentralisation of HIV care has introduced new pathways of mobility within and across healthcare facilities, facility levels, and degrees of specialised care, including the provision of paediatric HIV care.

Using real-world data from the Mzantsi Wakho cohort of adolescents living with HIV in South Africa, this study provides a new and contextually relevant model for adolescent HIV transitions, beyond the existing framework built on Western models of care. Based on an intensive data collection approach of both clinical record review and community tracing, this study first identifies the main pathways for transition out of paediatric HIV care and subsequently evaluates HIV care outcomes for adolescents who have experienced these pathways.

This analysis was co-conceived with the UNICEF Eastern and Southern Africa Regional Office HIV/AIDS Programme. This paper (Chapter 7) has been published in the *Journal of Acquired Immune Deficiency Syndromes* (DOI 10.1097/QAI.0000000000002125).

3. DPhil Paper 1: The effects of decentralising antiretroviral therapy care delivery on health outcomes for adolescents and young adults in low- and middle-income countries: a systematic review

The first paper of this dissertation is a systematic review and is therefore based on secondary data. This paper provides a comprehensive literature review of the effect of decentralising HIV care on youth health outcomes in low- and middle-income countries. This paper was published in Global Health Action in September 2019.

Objective: To synthesise and critically assess the evidence base for the effects of decentralising ART delivery on health outcomes for adolescents and young adults living in low- and middle-income countries

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Statement of Authorship
I confirm that I completed the majority of the work in this study (>70%). I conceptualised the study and led the study from title registration through final write-up and publication. After finalising the research question with input from Lucie Cluver, I wrote the review protocol, created and implemented the search strategy, conducted the analysis of included studies, and drafted the manuscript for this paper. Janina Steinert assisted in the screening of studies for inclusion in the review in order to satisfy the double screening criterion. All review authors further contributed to the write-up and interpretation of findings for the final manuscript. I also led the submission of this paper to *Global Health Action*.

Citation: Haghighat R, Steinert J, Cluver L. (2019) The effects of decentralising antiretroviral therapy care delivery on health outcomes for adolescents and young adults in low- and middle-income countries: a systematic review. *Global Health Action* 12:1. DOI: 10.1080/16549716.2019.1668596

Abstract

Background: Decentralisation of antiretroviral therapy has been implemented to scale up HIV care provision for patients in resource-limited countries. Youth living with HIV demonstrate the poorest care outcomes, compared to other age groups.

Objectives: To systematically evaluate evidence on the effects of decentralising facility-based HIV care on care outcomes for youth living with HIV in low- and middle-income countries.

Methods: A systematic review was conducted through 12 electronic databases of peer-reviewed articles, conference abstracts, and grey literature; contacting relevant experts; and hand-searching references. Records were included if they were published after 1 January 1996 (advent of triple-drug ART) and reported health outcomes for decentralised and centralised care, separately, or evaluated the effect of decentralised care on care outcomes. Two authors independently screened search results. When age-disaggregated data (10-24 years old) was required for inclusion, we contacted study authors for data abstraction. Implementation fidelity of decentralisation, study quality, and risk of bias were assessed using the TIDieR checklist, CASP checklists, and ROBINS-I tool, respectively.

Results: Of 11 potentially eligible studies, two studies from sub-Saharan Africa met inclusion criteria after data disaggregation by age. The studies and abstracted data were insufficiently homogenous in implementation and study design to justify meta-analysis. However, evidence suggests the potential for decentralised care to result in at least equivalent attrition-related outcomes (retention in care and mortality) for youth within decentralised HIV care. Limited sample size and

significant selection and allocation bias confound clear, generalisable conclusions for youth living with HIV in resource-limited settings.

Conclusions: There is a paucity of evidence for the effects of decentralising HIV care for youth living in resource-limited settings, particularly recent evidence reflective of the current HIV care landscape. Further work is required to rigorously analyse the effects of decentralising HIV care to inform policymakers and care providers, particularly as demand for HIV care in this population grows.

Registration: PROSPERO Registration #CRD42016051907, 21 November 2016

Background

The expansion of access to life-saving antiretroviral therapy (ART) has averted the deaths of over 7.6 million people since the mid-1990s, including nearly 5 million in sub-Saharan Africa (UNAIDS, 2014c). In the third decade of the HIV/AIDS epidemic, the disease burden has shifted to low- and middle-income countries (LMICs), which currently house 90% of the world's HIV-infected population (UNAIDS, 2015b; Scanlon and Vreeman, 2013). The efficacy of ART has also turned HIV infection into a manageable, long-term illness, such that perinatally infected children are able to survive through to adolescence and adulthood (Beck and Walensky, 2009).

Adolescents and youth represent 37% of new global infections and have consequently been described as the "centre of the epidemic" (United Nations Inter-Agency Network on Youth Development, 2012; Govender et al., 2018; UNAIDS, 2019). As children survive to adolescence and youth, they experience increasing ownership of their health and medicine-taking practices, in a crucial transition phase. Yet, compared to other age groups, adolescents and youths living with HIV demonstrate the lowest rates of ART adherence, poorest health outcomes under care, and lowest access to and utilisation of healthcare services (UNAIDS, 2017b; UNAIDS, 2015a). Adolescents are the only age group for which AIDS-related deaths are not decreasing (IANYD, 2012; UNICEF, 2011). AIDS remains the leading cause of death among adolescents in Africa, and the number of AIDS-related deaths has tripled since 2000 (UNAIDS, 2015a).

Even when enrolled in care, HIV-positive adolescents in sub-Saharan Africa demonstrate particularly poor health outcomes, as compared to adults

(World Health Organization, 2014b; Evans et al., 2013; Nachega et al., 2009; Slogrove et al., 2018; Nglazi et al., 2012). In a cohort study using routinely collected data from 160 HIV clinics in Kenya, Mozambique, Tanzania, and Rwanda, youths aged 15-24 had the highest attrition in care rates (31.1%) compared to all other age groups, including early adolescents and adults (Lamb et al., 2014). Longitudinal cohort studies have confirmed these findings: a study using data from 1999-2006 in southern Africa reported lower adherence rates for adolescents compared to adults after 12 months on ART (14.3% vs. 27.6%) (Nachega et al., 2009). Similarly, a study from rural Uganda reported that only 65% of adolescents on ART were retained in care from 2006-2011 (Okoboi et al., 2016). Further, longitudinal studies in South Africa and southern Africa have reported that adolescents (11-19 years old) are less likely to achieve viral suppression and more likely to experience shorter time to viral rebound, compared to adults (Nachega et al., 2009; Nglazi et al., 2012).

In LMICs, improved survival of HIV-positive children, combined with high new HIV infection rates among youth, have created a large, growing population of youth requiring ART (Scanlon and Vreeman, 2013). In parallel, UN guidelines have called for massive efforts to scale up ART initiation and treatment maintenance globally. Guidelines also call for ART initiation at increasingly earlier stages of infection, such as the enrolment of all HIV-infected persons on ART by 2030 (UNAIDS, 2015a). To achieve such levels of scaled-up care with limited resources, LMICs began decentralising HIV care in the mid-to-late 2000s, in alignment with recommendations from the World Health Organisation (South African National AIDS Council, 2017; World Bank, 2008; Reidy et al., 2014).

The primary goals of decentralisation are to expand healthcare accessibility and availability by shifting the majority of care from centralised hospitals to primary care clinics (World Health Organization, 2008). Thereby, decentralisation increases the number of facilities and healthcare professionals within them that can provide basic care—such as monthly antiretroviral provision (Peters et al., 2008; Duncombe et al., 2015). Additionally, decentralisation brings care closer to patients for whom hospitals in urban centres may be inaccessible. Although decentralisation theoretically allows for a greater number of people to access HIV care, it also requires patients to engage with a new type of healthcare—including different facilities with fewer resources and different care providers, generally with lower levels of training.

Decentralisation of HIV care is a mode of differentiating HIV care, wherein stable patients are down-referred to lower-level healthcare facilities such as community health centres or primary care clinics (Kredo et al., 2013). Alongside the scale-up of ART initiation, WHO guidelines have emphasised the need to scale up differentiated service delivery (World Health Organization, 2015). Hence, decentralising facility-based HIV care is both a form of differentiating care, and further differentiated care can be delivered within decentralised care, considering the particular care needs for specific patient populations (Southern African HIV Clinicians Society, 2017). For instance, in South Africa, even patients adopting further decentralised adherence strategies such as central chronic medicine dispensing and distribution (CMDD) programmes must engage with facility-based decentralised care through regular clinical appointments for examinations and blood tests at primary care clinics (Southern African HIV Clinicians Society, 2017).

One systematic review of decentralising HIV treatment among adult and paediatric populations in LMICs suggested the non-inferiority of this care delivery model (Kredo et al., 2013). Similarly, two systematic reviews reported at least comparable outcomes when comparing routine care to task-shifted ART delivery for adults and children from physicians to non-physician healthcare workers in sub-Saharan Africa (Kredo et al., 2014; Penazzato et al., 2014). Task-shifting care is often a key component of decentralisation, but these two interventions can be implemented separately or together. However, none of these reviews specifically examined outcomes among adolescents or youth as a distinct category, so their findings may not apply to young people.

To date, there have been no systematic reviews published in English that evaluate the effects of facility-based decentralisation of ART care among HIV-positive adolescents and youths in LMICs. This gap in evidence is particularly concerning given that facility-based decentralisation is currently being scaled up throughout LMICs as a strategy for improving ART coverage and maintenance. Evidence on the efficacy of this mode of delivery for youths living with HIV is required to understand how best to optimise care delivery and outcomes. The importance of this research is further underscored by the fact that HIV-positive youth continue to demonstrate the greatest difficulty in accessing and maintaining HIV care.

Therefore, it is imperative to evaluate the effects of decentralising HIV care on health outcomes for adolescents and youths living with HIV in LMICs, compared to those receiving centralised care. This review systematically

assesses evidence for the effectiveness of decentralising ART care delivery on health outcomes of HIV-positive adolescents and youth in LMICs.

Methods

We conducted a systematic review of the evidence following Cochrane Collaboration guidelines, according to a registered protocol (PROSPERO Registration #CRD42016051907) (Higgins and Green, 2011).

Inclusion Criteria

Inclusion criteria for the review were the following:

- Comparative study design (pre-/post- or multi-arm comparison groups) evaluating the decentralisation of ART delivery (ART initiation, follow-up care, or both) from centralised facilities to lower-level health centres and clinics, compared to routine care in a centralised facility (i.e. hospital) at the same time and province as the intervention arm.
- Study population includes HIV-positive adolescents and youth (10-24 years old) who were initiating or already enrolled on ART in an LMIC. Adolescents are defined as 10-19 years old and youths as 15-24 years old by the World Health Organisation (World Health Organization, 2014a).
- Measures health-related outcomes: mortality, loss to follow-up, attrition from care, ART adherence, viral load, CD4 count, WHO disease stage, morbidity, or changes to second- or third-line ART regimens.

Interventions comparing facility-based to home-based care were not included within this review, as this review focuses on decentralisation within facility-based

care. Studies that evaluated task-shifting of care from physicians to non-medical practitioners or lower-level health practitioners, such as nurses, were not included if they did not also evaluate the decentralisation of care across facility levels.

Search Strategy

We searched 12 electronic databases and conference archives for publications within the period of 1 January 1996 (the advent of triple-drug ART) to the initial date of search (11 October 2016). We searched from 1 January 1996 because 1996 marked the advent of triple-drug ART, which has been the standard of care for HIV since its development. In a subsequent search, we updated all 12 searches for publications between October 2016 and the new search date (15 February 2019). The 12 databases, which include grey literature, were as follows: PubMed, EMBASE (1996-present), Cochrane Central Register of Controlled Trials, CINAHL, Web of Science, WHO African Index Medicus, OpenGrey, Grey Literature Report, Clinicaltrials.gov, WHO International Clinical Trials Registry Platform, International AIDS Conference abstract archive (2001-2017), and Conference on Retroviruses and Opportunistic Infections (CROI) abstract archive (2014-2017). Searches were limited to the English language, and terms were entered only in English. A sample of the search strategies used for these databases is provided in Supplementary Table 1A.

Further, we contacted selected experts in the field, including staff members of relevant international organisations and leading researchers in the field, in order to identify additional completed or on-going studies as well as any unpublished or internal reports. The following key journals were hand-searched

for relevant articles in the original and updated searches: *Journal of Acquired Immune Deficiency Syndromes* (1996-2018), *The Lancet* (1996-2018), *The Lancet HIV* (2014-2018), *PLoS One* (2006-2018), *Journal of the International AIDS Society* (2000-2018), *Current Opinion in HIV and AIDS* (2006-2018), and *AIDS and Behaviour* (1997-2018). Reference lists of all studies selected for full-text screening were reviewed for additional relevant studies.

Screening

Two reviewers (RH and JS) independently reviewed the records identified by the search strategy to determine inclusion. Full-text articles of selected abstracts were examined by both reviewers for final determination of potential study inclusion. Disagreements about inclusion were resolved by consensus.

Data Extraction and Analysis

One reviewer (RH) abstracted data using a standardised data extraction form developed in consultation with the Effective Practice and Organisation of Care (EPOC) data collection form. Extracted study information included the following: study author, location, year, study and analytic designs, patient population, sample size, follow-up period, type of ART care, intervention details, comparison groups, and outcomes (EPOC, 2013). When studies reported at least 50 youth living with HIV in their sample but age-disaggregated data were not available within the publication, authors were contacted for age-disaggregated data. If age-disaggregated data were provided, studies were included in the review.

For non-randomised controlled trials, quality of evidence was assessed

using the Critical Appraisal Skills Programme (CASP) Checklist (Critical Appraisal Skills Programme, 2018). To determine implementation fidelity, the Template for Intervention Description and Replication (TIDieR) checklist was completed and compared between included studies (Hoffmann et al., 2014). Risk of bias for non-randomised studies was assessed using the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) Assessment Tool (Sterne et al., 2016).

Meta-analysis was deemed inappropriate due to the small number of included studies, significant differences in intervention implementation across included studies, and low quality of evidence. Instead, we present a descriptive summary of findings from included studies.

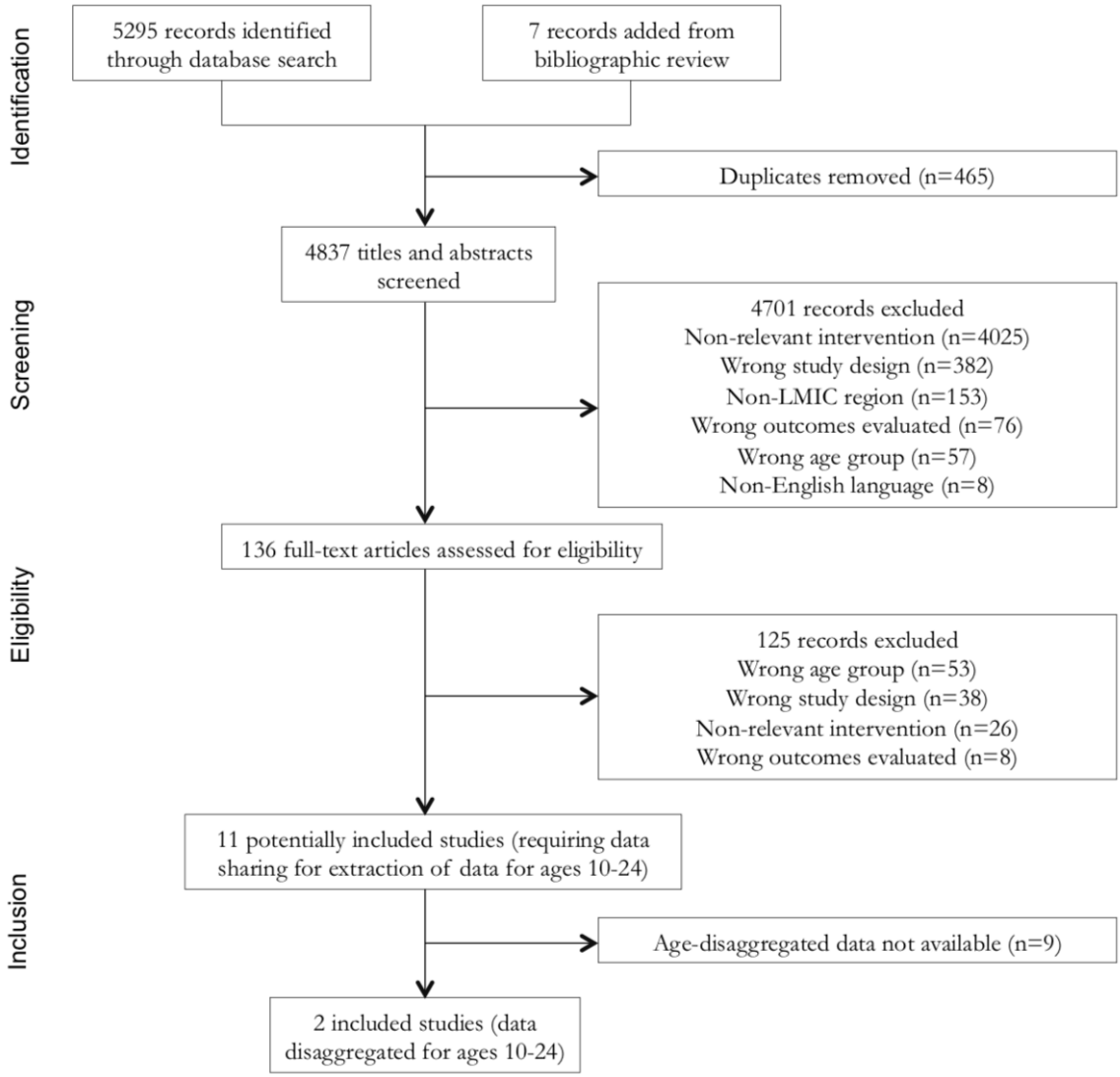
Results

The systematic literature search yielded 5295 records, including grey literature, and 7 records were added from bibliographic review of key articles (Figure 5). After an initial removal of duplicates, 4701 records were excluded by screening titles and/or abstracts. Full-text articles of 136 publications were reviewed to determine eligibility for inclusion. At this stage, 125 records were excluded, the majority of which were studies in the wrong age group. We identified 11 studies that were potentially eligible. All 11 studies' samples were not limited to youths and required data to be age-disaggregated for inclusion in the review (Reidy et al., 2014; Scheibe et al., 2013; Chan et al., 2010; McGuire et al., 2012; Auld et al., 2016; Nuwagaba-Biribonwoha et al., 2013; Massaquoi et al., 2009; Megerso and Garoma, 2016; Mutenda et al., 2016; McNairy et al., 2017; Long et al., 2016). The lead author contacted study authors for all 11 studies at the end of each record

screening round, and only studies whose authors provided age-disaggregated data were included in the review.

Ultimately, we identified two studies that met the inclusion criteria because age-disaggregated data for adolescents and youth (10-24 years old) were available (Chan et al., 2010; Scheibe et al., 2013).

Figure 5. PRISMA flowchart of studies screened and selected for systematic review



LMIC: low- and middle-income country

Study Descriptions

Table 6 provides a descriptive overview of the included studies. Both studies were conducted among mixed paediatric and adult populations residing in rural sub-

Saharan Africa, one in Uganda (Scheibe et al., 2013) and one in Malawi (Chan et al., 2010). Within this review, study outcomes and sample characteristics are described only for adolescent and youth participants aged 10-24 at baseline in the study.

Both studies were designed as retrospective cohort analyses of decentralising ART initiation and management, with task-shifting of care integrated into both interventions. Significant differences in the implementation of decentralisation—and any co-interventions—are further discussed below. Both studies recruited participants using registration records from included facilities, including all HIV-positive patients enrolled in care from facility inception. Analysed data were comprised of clinical records extracted from patient records and HIV registers. Data coverage for both studies began in 2004, but collection ended in December 2008 for the Malawian study (Chan et al., 2010) and September 2009 for the Ugandan study (Scheibe et al., 2013). For adolescents and youths, available outcomes for analysis were attrition in care (including mortality) for the Ugandan study (Scheibe et al., 2013) and retention in care and mortality, separately, for the study in Malawi (Chan et al., 2010).

In the Iganga District of eastern Uganda, decentralisation of ART maintenance began by shifting care from the public general hospital in town to 4 rural health centres between December 2005 and May 2007 (Scheibe et al., 2013). In February 2007, both ART initiation and management were decentralised to these health centres, with provision of the necessary physical resources and care provider training. These health centres were open once or twice a week and outfitted to provide HIV-positive patients with 30-day supplies of ARVs. Health

centres also provided HIV testing, one ART register per facility, and equipment for routinely weighing patients, although no CD4 counting equipment was available in the district. Drug supplies at health centres were delivered by the National Medical Store under the Ugandan Ministry of Health. At the health centres, care was provided by clinical officers, nurses, or midwives who had undergone the standardised national training course for comprehensive HIV care and ART provision. Study authors evaluated clinical records retrospectively in an observational study, without involvement in the delivery of decentralised care (Scheibe et al., 2013).

In southern Malawi's Zomba District, the decentralisation and scale-up of ART care was facilitated through the Malawian Department of HIV and AIDS, with assistance from Dignitas International, a Canadian humanitarian non-governmental organisation (NGO) (Chan et al., 2010). In the district, decentralised ART management beyond the single tertiary hospital began in March 2007. Decentralisation of ART initiation began in April 2008. At the 16 decentralised rural health centres in the study, ART care was delivered with the co-intervention of an integrated primary care model unique within Malawi, such that HIV services were integrated into routine outpatient services. To facilitate both scale-up and integrated care, Dignitas International provided intensive physical and human resources, including staffing at facilities as well as biweekly supervision, monthly mentorship, and training support for lower-cadre Ministry of Health healthcare workers. Across the 16 decentralised health centre sites, care was provided by 2 physicians visiting on a monthly basis, 5 clinical officers, 20 medical assistants, 70 nurses, 16 ART clerks, and 16 ART counsellors (Chan et al., 2010). Further

details about the implementation of decentralisation in the two studies, including the breakdown of staffing across the 16 facilities, are provided in Supplementary Table 1B.

Overall, considerable heterogeneity was observed in the design and implementation of decentralisation between the two studies. Notably, the study in Malawi delivered decentralised care alongside an integrated primary care model with intensive support from Dignitas International. Furthermore, age-disaggregated data from both studies was significantly limited in scope and depth. Age-disaggregated data for the Uganda study only provided comparative findings on one of the three outcomes in the full study—attrition. Age-disaggregated data provided for the Malawi study was only uncontrolled summary data for outcomes in the two study arms. Without individual-level data for covariates, adjusted analyses or meta-analysis between studies was not possible.

Assessment of Study Quality and Risk of Bias

Following assessments via checklist for cohort studies, both studies were judged to have fair methodological quality. The study in Malawi by Chan et al. had a large sample of adolescents and youths aged 10-24 that allowed for precise estimates (n=1062) (Chan et al., 2010). However, the study in Uganda by Scheibe et al. had limited data available for the same age group (n=56), resulting in low precision of youth-specific outcomes (Scheibe et al., 2013). The two cohort studies provided limited controls for baseline differences between the decentralised and centralised patient arms—such as baseline viral load or CD4 count, which would have reflected differences in immunovirological function at the study onset. Chan et al.

adjusted analyses only using WHO stage at ART initiation (Chan et al., 2010). Scheibe et al. controlled analyses for most recent WHO stage, which most likely reflects a morbidity outcome, rather than a baseline characteristic for adjustment (Scheibe et al., 2013). Additionally, the latter study applied complete-case analysis, excluding 16 youth patients missing any form of data, and potentially significant differences from included participants were not evaluated (Scheibe et al., 2013).

Finally, through using only retrospective review of clinical records to identify care-terminating outcomes, both studies face significant threats to the validity of measurements of mortality and, consequently, attrition from care. Previous studies in sub-Saharan Africa have indicated that mortality reporting within healthcare facilities is often incomplete, requiring follow-up tracing for greater accuracy (Holmes et al., 2018). Thus, the true rates of mortality in both cohorts were likely higher than those reported, based on facilities' vital registry data (Brinkhof et al., 2009). Additionally, in measuring retention in care, Chan et al. did not account for possible transfers to other facilities when patients were considered lost to follow-up (LTFU) (Chan et al., 2010). By contrast, Scheibe et al. corrected rates of attrition for documented instances of patient transfers to different facilities (Scheibe et al., 2013).

Both studies were judged to have serious risk of bias, particularly in two domains. Baseline confounding due to biased allocation into study arms, without sufficient controls for baseline differences, was a source of bias for both studies. Additionally, the Ugandan study had serious risk of selection bias for participation in the study, due to excluding potential participants who did not have patient files

(16.9% of the sample, across all ages) (Scheibe et al., 2013). The study in Malawi also faced serious risk of bias from delivering the integrated primary care co-intervention, the effects of which could not be separated from those of decentralising ART care (Chan et al., 2010). Alongside decentralising HIV care, Chan et al. were assessing the effects of integrating primary care into HIV care at lower-level facilities, with provision of physical resources and staff training to implement this integrated care model. Full details of authors' judgment for risk of bias for each domain are available in Supplementary Table 1C.

Table 5. Summary of included studies, listed in reverse chronological order

Study author(s) and year of publication	Study design	Study location and dates	Total participant population and sample size	Setting	Mode of decentralisation and visit frequency	Cadres of healthcare providers at decentralised sites	Criteria for decentralisation eligibility	Outcomes measured
Scheibe et al., 2013	Retrospective cohort study	Iganga District, Uganda, April 2004-September 2009	All patients who were diagnosed with HIV and registered on ART in the included facilities during study period, n=973 (decentralised n=271) Gender: 63.0% female, 37.0% male Age (median, IQR): 36 (30-43)	1 general hospital and 4 health centres (3 level IV, 1 level III)	ART management (from December 2005) and initiation (from February 2007) Visit frequency: monthly	Nurse, clinical officer, midwife	N/A	1. Attrition (not attending facility for >90 days before audit, excl. transfers) 2. Effective coverage (ratio of number of patients currently receiving ART: number of people living with HIV needing ART) 3. Probability of retention in care

Chan et al., 2010	Retrospective cohort study	Zomba District, Malawi, October 2004-December 2008	All patients who initiated ART in the included facilities during study period, n=8093 (decentralised n=3440) Gender: 63.0% female, 37.0% male Age (mean, SD): 33.2 (±13.6) in centralised, 35.0 (±16.7) in decentralised	1 tertiary hospital and 16 rural health centres	ART management (from March 2007) and initiation (from April 2008) Visit frequency: monthly for first 6 months after initiation, then as per provider assessment	Physician (visiting), clinical officer, nurse, medical assistant	National criteria: 1. Stable on first-line ART for >3 months 2. No active opportunistic infection or drug intolerance 3. ART provider confidence in patient adherence 4. Patient closer to health centre than hospital	1. All-cause mortality 2. Defaulting (not seen for >3 months after scheduled follow-up)

IQR: Interquartile range; N/A: Not available; SD: Standard deviation

Study Findings

Table 7 summarises the characteristics and main findings of included studies, restricted to adolescent- and youth-specific data. For comparison between decentralised and centralised arms, neither study reported youths' outcomes beyond attrition-related data. While Chan et al. presented retention and care and mortality outcomes separately, Scheibe et al. reported on overall attrition, which is comprised of both loss to follow-up and mortality (Chan et al., 2010; Scheibe et al., 2013). Below, we present findings from both studies on these outcomes for adolescents and youths aged 10-24 at baseline.

In Uganda, a total of 63 participants included in the study were aged 10-24 at baseline, among whom the median age was 19 years (IQR 13-22) (Scheibe et al., 2013). Decentralisation status was determined by the site of ART initiation, with 47 (74.6%) initiating at the hospital and 16 (25.4%) initiating at a health centre. Because ART was available at the hospital before the health centres, the median time on ART was longer for centralised adolescents and youths ($p<0.001$). Attrition from care was defined as not attending the facility at least once during the 90 days prior to the audit in September 2009 (including mortality), except for documented transfers to another facility. In the centralised arm, attrition from care was observed for 26/47 (55.3%) youths, of whom 13 (50%) had passed away and 8 (30.8%) had been officially classified as lost to follow-up. By contrast, in the decentralised arm, 6/16 (37.5%) demonstrated attrition from care according to the study definition. However, in a multivariate Cox regression, decentralised care did not significantly predict attrition from care (aHR 0.79 [95%CI 0.26-2.40], p=0.681), controlling for sex, most recent WHO stage, and time from HIV test to

ART start. Only 56 participants were included in this analysis, because complete-case analysis was applied, and 7 participants were missing at least one data point included in the regression.

In Malawi, among the 1062 participants aged 10-24 at baseline in the study, median age at initiation was 21 (IQR 14-23) (Chan et al., 2010). Decentralised patients were designated as those receiving ART management at a health centre rather than the central hospital (n=436, 41.1%). Study authors provided data on the total number of participants in each arm who reached the final outcomes of all-cause mortality and defaulting from care. Defaulting was defined as not attending the facility for >3 months since the last scheduled visit, censored to the end of data collection. Testing for uncontrolled between-group differences via Chi-square test, decentralised participants were significantly less likely than centralised participants to have passed away (OR 0.14 [95%CI 0.07-0.29], $p<0.001$) and less likely to have defaulted from care (OR 0.37 [95%CI 0.26-0.55], $p<0.001$). However, because individual-level data was not available for the 10-24 year old subsample, we were not able to calculate adjusted odds ratios for outcomes, accounting for other covariates such as gender, WHO stage at initiation, or duration on ART.

Table 6. Included studies' characteristics and main findings based on age-disaggregated data (10-24 years old)

Study author(s) and year of publication	Study design	Study location and dates	Adolescent and youth sample size	Adolescent and youth characteristics	Outcomes measured	Main results
Scheibe et al., 2013	Retrospective cohort study	Iganga District, Uganda, April 2004-September 2009	n=63 (decentralised n=16)	Gender: 71.4% female Age (median, IQR): 19 (13-22)	1. Attrition rate 2. Probability of retention on ART	1. In centralised arm, 55.3% (n=26) dropped out; in the decentralised arm, 37.5% dropped out (n=6) 2. Overall probability of retention on ART for youths 10-24 was 0.71 (95%CI 0.58-0.80) at 6 months, 0.62 (95%CI 0.48-0.73) at 12 months, and 0.45 (95%CI 0.31-0.58) at 18 and 24 months 3. Receiving centralised care was not significantly associated with attrition from care in multivariate Cox analysis (aHR 1.26 [95%CI 0.42-3.81], *p*=0.681)
Chan et al., 2010	Retrospective cohort study	Zomba District, Malawi, October 2004-December 2008	n=1062 (decentralised n=436)	Gender: 75.1% female Age at initiation (median, IQR): 21 (14-23) in centralised, 21 (14-23) in decentralised	1. WHO stage at ART initiation (n) 2. Mortality (n) 3. Defaulted (n)	1. Using crude ORs, there was no significant difference between study arms for WHO Stage I/II vs. Stage III/IV at initiation (OR 0.92 [95%CI 0.70-1.22], *p*=0.585) 2. Using crude ORs, decentralised care was significantly associated with a lower rate of mortality (OR

						0.14 [95%CI 0.07-0.29], $p<0.001$) 3. Using crude ORs, decentralised care was significantly associated with a lower rate of defaulting from care (OR 0.37 [95%CI 0.26-0.55], $p<0.001$)

aHR: Adjusted hazard ratio; CI: Confidence interval; IQR: Interquartile range; OR: Odds ratio; WHO: World Health Organisation

Discussion

Although decentralised ART has been rolled out across LMICs, we identified only two studies that reviewed its effectiveness for adolescent and youth health outcomes. Both were retrospective cohort studies from sub-Saharan Africa that analysed clinic-based records for all ART patients at those facilities, across all ages.

After disaggregating data for participants aged 10-24, findings in both studies were limited to attrition-related outcomes, such as retention in care and mortality. The heterogeneity in implementation of decentralisation and limited availability of age-specific data between the two studies did not allow for meta-analysis. Furthermore, the studies approximated attrition using non-interchangeable definitions. While the study in Uganda evaluated overall attrition (inclusive of all-cause mortality but adjusting for facility transfers), the study in Malawi defined defaulting from care separate from all-cause mortality (without adjusting for facility transfers). Because both studies relied solely on retrospective review of facilities' vital registries to determine mortality, both likely underestimate the amount of attrition due to mortality (Brinkhof et al., 2009). By accounting for transfers, Scheibe et al. provided a more conservative and realistic estimate of true attrition from care in Uganda, while Chan et al. likely overestimated attrition by not accounting for transfers in Malawi.

Nevertheless, results from these two studies indicated the potential for decentralised HIV care to result in at least equivalent attrition-related outcomes as routine, centralised care for adolescents and youth. Both studies reported low

rates of overall retention in HIV care for this population—consistent with findings from previous studies—but decentralising ART delivery seemed to provide a sustainable model for servicing a growing patient population in resource-limited settings (Enane et al., 2018). However, to maintain safe and efficacious delivery of care, the actual implementation of decentralisation is critical.

In achieving at least equivalent outcomes on decentralised care, Chan et al. particularly note the significance of differentiating care across primary versus tertiary sites based on patient stability and care needs (Chan et al., 2010). In theory, decentralisation should allow for patient mobility across care levels, such that patients presenting with complications at a primary clinic, including new opportunistic infections or treatment failure, should be able to return to tertiary care until reaching stability again (Kredo et al., 2013). Hence, these studies confirm the importance of proper selection of patients suitable for decentralised care at primary sites.

Furthermore, both studies highlight the need to consider service and supply factors within decentralised care, beyond the relocation of stable patients to primary care sites. In particular, both studies note that differences in performance between decentralised and centralised sites may be more dependent on clinical staff-related factors such as staff retention and turnover as well as supply-side factors like consistent availability of antiretroviral drugs and laboratory services (Chan et al., 2010; Scheibe et al., 2013).

However, the quality and sample sizes of data do not permit clear conclusions to be drawn for this population in LMICs, particularly as both studies did not sufficiently match the control groups or account for potential biases.

The study in Uganda reported that decentralised patients were significantly less likely to die or drop out of care. However, the application of complete case analysis excluded potential participants without patient files. Because hospital-based patients were found to be more likely to lack patient files, this mode of analysis introduces potential survivorship bias, likely towards null or favouring decentralised outcomes (Scheibe et al., 2013). Additionally, analyses did not sufficiently adjust for baseline differences between decentralised and centralised groups. The higher morbidity and longer duration in care within the centralised arm could also have biased results towards null. Similarly, Chan et al. noted that there was significant selection bias in allocation to study arms, whereby stable patients were more likely to receive decentralised care. This selection bias introduces bias towards positive outcomes for decentralised youths. Because of the limited data available for adolescents and young people specifically, between-group comparisons for rates of mortality and retention in care could not be adjusted for baseline clinical staging or other covariates, as was done in the full sample.

Indeed, most studies on the effectiveness of decentralised care in paediatric and adult cohorts are limited by similar challenges in between-group controls (Balcha and Jeppsson, 2010; Hagstromer et al., 2013; Fayorsey et al., 2013). Some studies controlled for differences in baseline health profiles of study arms by adjusting for CD4 values, but adjustments were limited by incomplete coverage of CD4 testing, often disproportionately in the decentralised arm (Assefa et al., 2012; Reidy et al., 2014; Massaquoi et al., 2009). However, one of the more rigorously designed cohort studies—which controlled for baseline body mass

index (BMI), history of ART use, CD4 count, and WHO stage—found higher mortality and attrition among centralised adults on ART in rural Malawi, compared to decentralised adults (McGuire et al., 2012).

Generalisability of findings from included studies is further limited by the narrow feasibility and applicability of the decentralisation model tested in Malawi, given the intensive, frequent NGO support (Scheibe et al., 2013). In the early years of decentralisation rollout, including the years of data collection, substantial NGO support was frequent in order to build capacity and test feasibility for this new model of care (Bemelmans et al., 2010; Fatti et al., 2011; Emdin et al., 2013). However, in recent years, such intensive NGO support has become increasingly uncommon in public facilities and varies across and within countries, making interventions run with substantial NGO support non-representative (Labhardt et al., 2013). Since 2010, although the number of patients receiving decentralised HIV care has increased, responsibility for delivering sustainable decentralised care has significantly shifted towards public facilities themselves (Binagwaho et al., 2016; Goosby et al., 2012).

Nevertheless, this review identifies an important gap in knowledge about the effects of this widespread public health approach for this particularly vulnerable population, which has already been rolled out in many LMICs. Several cohort studies trace the health outcomes of adolescents and young persons receiving decentralised care. However, this review found only two that allowed for the comparison of their health outcomes while in decentralised versus centralised care, which would inform how best to optimise care for this population (Evans et al., 2013; Lamb et al., 2014; Okoboi et al., 2016; Nglazi et al., 2012; Agwu and

Fairlie, 2013). The literature gap identified here has several key implications for future research and practice.

Although 11 potentially eligible studies included adolescents and youths within their cohorts, only 2 studies were able to disaggregate data for them. In part, the limited data available for this population is because the WHO and many other organisations have summarised adult and paediatric data as ≥15 years and <15 years categories, respectively (UNAIDS, 2015a). Consequently, national data specific to health outcomes for this population is frequently unavailable. Due to recognition of the importance of this vulnerable population in recent years, countries have been requested to disaggregate data for this population. However, most countries lack sufficient health system infrastructure to do so. This review contributes to the literature indicating the urgent need for strengthened health systems that allow for this more granular focus on adolescents and youths within routine health monitoring programming (Slogrove and Sohn, 2018; Mark et al., 2018).

Furthermore, this review highlights another key gap in the literature: the scarcity of studies evaluating the effects of decentralised HIV care within the past 5-8 years. More recent studies would reflect the current reality of decentralisation, rather than the landscape in its early years. In fact, of the 11 studies whose authors were contacted for age-disaggregated data, only 4 had any post-2011 data (McNairy et al., 2017; Long et al., 2016; Mutenda et al., 2016; Megerso and Garoma, 2016). Thus, this review indicates the urgent need for more up-to-date studies evaluating decentralised HIV care as it is currently being implemented, using recent—and therefore relevant—health outcome data.

Finally, across studies evaluated for this review, outcome data was most comprehensive for attrition-related measures, including mortality and loss to follow-up. Very few studies of decentralisation, across all ages, evaluated health outcomes beyond “end-of-care” events, such as virological, immunological, or morbidity outcomes. Only 3 of the 11 potentially eligible studies for this review included any outcomes beyond mortality, loss to follow-up, and transfers out of care (Long et al., 2016; Megerso and Garoma, 2016; McGuire et al., 2012). This review highlights the need for studies to rigorously evaluate the effects of decentralisation on these non-terminal outcomes, which provide a more comprehensive understanding of the lived experience of ART patients and their outcomes while within care.

This review provides a comprehensive assessment of the effect of decentralising HIV care for adolescents and youths living in LMICs. It is the first systematic review to focus on this model of care delivery for this population. Strengths of this review include its inclusive search strategy, including grey literature and multiple databases and allowing for the age disaggregation of data for studies including the target population. Additionally, this review provided rigorous critical appraisal of included studies’ quality and risk of bias. However, limitations include restriction of the search to English-language studies, which may have omitted evaluations published in other languages. An additional limitation is suboptimal reporting of outcome data for adolescents and youths in the included studies, which did not allow for meta-analysis of findings and subsequently for clear conclusions to be drawn.

Conclusions

As decentralised ART care continues to scale up globally, further primary research is urgently required to evaluate the effects of decentralising HIV care delivery for adolescents and young people in LMICs, particularly using recent data that reflects the current landscape of health systems' care burdens. Although decentralised ART delivery is already being implemented worldwide, further research is required to evaluate the efficacy of this approach for HIV-positive youth in order to identify opportunities for optimising care outcomes. Importantly, more rigorous study designs are required to truly examine the effect of decentralisation, as well as evaluations of outcomes beyond attrition that characterise health progression within care. Existing evidence is limited in both quantity and quality. The evidence base on decentralisation is largely limited to adult and paediatric populations, with very few studies able to provide adolescent- and youth-specific data that would allow for an understanding of how this mode of care delivery affects one of the most vulnerable populations living with HIV.

Narrative Review of Excluded Studies

This section provides a narrative review of 20 quantitative studies excluded from the systematic review, including the 9 potentially eligible studies that were unable to provide age-disaggregated data. Although these studies were excluded because they did not meet the age criterion, they provide useful parallel evidence in adult and paediatric populations on decentralising facility-based ART delivery in sub-Saharan Africa (Table 5). No major differences in trends were observed between studies of adult vs. paediatric cohorts, or between studies evaluating decentralisation of ART initiation only vs. initiation and management.

Across these 20 studies, data were most comprehensive on loss to follow-up in care (LTFU) and mortality. Overall, decentralised care groups demonstrated lower rates of LTFU but equivalent rates of mortality, compared to centralised care groups. Among the 12 studies that assessed LTFU, 9 reported lower rates for patients receiving decentralised care, and only 2 reported higher rates for this group. Out of the 11 studies that analysed mortality, 7 reported equivalent outcomes between decentralised and centralised patients, with 3 studies finding lower rates of mortality for the decentralised group.

Several studies noted that mortality and LTFU rates were at their highest for both decentralised and centralised groups within the early period after ART initiation (Kipp et al., 2012; Hagstromer et al., 2013; Morsheimer et al., 2014; Ocero et al., 2009). McGuire et al. (2012) noted that rates of mortality and LTFU in the first year post-ART initiation were higher in the first six months than the second half. Similarly, Massaquoi et al. (2009) found that 75% of reported deaths occurred within 3 months after ART initiation, and Morsheimer et al. (2014) reported that 57% of deaths within the first 3 months on ART occurred within 9 days post-initiation. These findings highlight the clinical instability that particularly characterises the first year on ART and the need for careful, continuous patient monitoring in the early months after ART initiation, regardless of mode of care delivery.

Table 7. Characteristics and findings of studies considered in the narrative review

First author, year	Study years	Country	Study design	Participants	Facilities	Type of non-physician	ART initiation and/or management	Outcomes	Results
Assefa, 2012	2007-2009	Ethiopia	Retrospective comparative cohort study (hospital vs. health centre)	38,135 patients initiated on ART (median age range from 30-33 years)	25 health centres and 30 hospitals	Nurse and health officer	Initiation and management	LTFU, mortality, CD4 count	Lower LTFU at primary health centres; no significant differences in mortality or CD4 count
Auld, 2016	2004-2010	Eswatini	Retrospective comparative cohort study (centralised "hub" vs. decentralised "spoke" facilities)	2008 children (<15 years old) initiated on ART in public healthcare facilities (median age 5 years)	4 hospitals, 4 health centres, and 4 primary care clinics	Nurse	Full (initiation and management) and partial (management only)	LTFU, mortality, attrition	Lower LTFU for down-referred children and those initiated in decentralised care; no significant differences in mortality
Balcha, 2010	2006-2009	Ethiopia	Retrospective comparative cohort study (hospital vs. health centre)	1709 patients on ART (median age 33 years old)	2 hospitals and 3 health centres	Nurse and health officer	Initiation and management	LTFU, mortality	Lower LTFU and mortality at primary health centres
Brennan, 2011	2008-2009	South Africa	Retrospective matched cohort study, with propensity score matching of ART-initiated adults at	2772 stable ART patients (≥18 years old) meeting down-referral criteria	1 down-referral primary health clinic and 1 governme nt HIV clinic	Nurse	Management	LTFU, mortality, viral rebound	Lower LTFU, mortality, and viral rebound for down-referred patients

			down-referral primary care clinic to government clinic(matched 1:3)						
Fayorsey, 2013	2008-2010	Kenya, Lesotho, Mozambique, Rwanda, and Tanzania	Retrospective comparative cohort study (primary health facilities vs. secondary and tertiary health facilities)	17,155 children (<15 years old) enrolled in HIV care from facilities receiving support from ICAP (median age <5 years old)	182 primary health facilities and 92 secondary and tertiary health facilities	Nurse	Initiation and management	LTFU, mortality	Lower LTFU and mortality at primary health centres
Hagströmer, 2013	2007-2012	Ethiopia	Retrospective comparative cohort study (public hospital vs. public health centres)	1960 children (<15 years old) either pre-ART or on ART (median age 5 years old)	5 public health centres and 1 hospital clinic	Nurse and health officer	Initiation and management	LTFU, mortality, retention in care, WAZ	No significant differences in LTFU, mortality, or overall retention in care
Long, 2016	2011-2014	South Africa	Retrospective matched cohort study evaluating costs and outcomes, with propensity score matching of ART-initiated adults at	800 adults (≥18 years old) initiated on ART	1 hospital and 1 primary care clinic in urban setting	Nurse	Initiation	LTFU, mortality, viral failure (≥1000 copies/mL); CD4 failure (decrease of >30% of highest value or drop below CD4 count at	No significant differences in retention, viral load, or CD4 results

			primary care clinic to hospital (matched 1:3)					ART initiation)	
Massaquoi, 2009	2006-2007	Malawi	Retrospective cohort study (hospital vs. primary health centre)	4074 patients initiating ART in rural public facilities during study period (median age 32 years)	1 hospital and 7 primary health centres	Nurse and medical assistant	Initiation	LTFU, mortality	Lower LTFU but higher mortality at primary health centres; no significant differences in overall attrition
McGuire, 2012	2001-2009	Malawi	Retrospective comparative cohort study (decentralised vs. centralised care)	15,412 patients ≥12 months after ART initiation in the Chiradzulu HIV programme in rural Malawi, supported by Médecins sans Frontières (median age >31 years at all study time points)	1 district hospital and 10 rural decentralised health centres	Nurse and medical assistant	Initiation	LTFU, mortality, attrition, virological suppression (<50 copies/mL) and immunological success (CD4 gain ≥100 cells/mm^3)	Lower mortality and overall attrition in decentralised sites; no difference in virological or immunological outcomes
McNairy, 2017	2012-2013	Côte d'Ivoire	Prospective cohort analysis of pilot program for HIV task-sharing with nurses	1224 patients enrolled in HIV care (94% ≥15 years old)	20 primary , 4 secondary, and 2 tertiary healthcare facilities	Nurse	Initiation and management	LTFU, mortality, transfer out of care	Lower LTFU in primary care facilities
Megerso, 2016	2010-2014	Ethiopia	Retrospective comparative cohort study	1895 adults (≥15 years old) newly initiated on ART	1 hospital and primary	Nurse and health officer	Initiation	LTFU, mortality, CD4 gain	No significant differences in LTFU or mortality;

			(hospital vs. primary health care centre)	(median age 24 years)	health care centre (unspecified number)				greater CD4 gain at primary centres
Morsheimer, 2014	2004-2009	South Africa	Retrospective comparative cohort study (ART initiation in clinic vs. down-referred to clinic after ART initiation in hospital)	613 children (<14 years old) newly initiated on ART or down-referred for ART management (median age 2.2 years)	7 paediatric ART clinics and tertiary hospitals	Nurse	Initiation	LTFU, mortality, viral failure,	Lower viral failure for patients initiated in primary clinics; higher LTFU in primary clinics; no significant differences in mortality
Mutenda, 2016	2012-2014	Namibia	Retrospective study of adult and paediatric indicators of drug-resistance at all public ART facilities	37,814 adults (≥15 years old) and 6,913 children	50 centralised and 143 decentralised sites	N/A	Initiation and management	Retention in care 12 months post-ART initiation	No significant differences in retention for adult or paediatric cohorts
Nuwagaba-Biribonwoha, 2013	2005-2011	Tanzania	Prospective cohort study	62,801 patients at public and private HIV care clinics, supported by ICAP (92.5% adults ≥15 years old, median adult age 35.2 years)	16 public primary care facilities, 13 public secondary care facilities,	N/A	Initiation	Characteristics at HIV care enrolment and ART initiation	Median CD4 count increased and WHO stage decreased at ART enrolment decreased over time for the total cohort

					15 private clinics				
Ocero, 2009	2009	Uganda	Retrospective cohort study	402 ART-initiated patients (mean age 35.9 years old)	1 regional referral hospital, 1 district hospital, and 1 health centre IV	Nurse and clinical officer	Initiation and management	LTFU	Higher LTFU in decentralised health centre
Reidy, 2014	2006-2011	Kenya	Retrospective comparative cohort study (primary vs. secondary healthcare facility)	26,690 adult patients (>15 years old) enrolled in HIV care in Ministry of Health facilities	22 primary and 15 secondary healthcare facilities	Nurse and clinical officer	Initiation and management	LTFU and mortality	Lower LTFU in primary facilities after 6 months; no difference in mortality
van Dijk, 2014	2007-2012	Zambia	Observational cohort study	111 paediatric ART patients (<16 years old) registered at hospital HIV clinic (median age 3.4 years old)	1 hospital-affiliated clinic and 3 rural outreach clinics	Nurse and clinical officer	Management	CD4%, viral suppression %, ART adherence, WAZ	No significant differences in CD4, weight, ART adherence, or viral suppression (tested at 24 months)

ART: Antiretroviral therapy; ICAP: International Centre for AIDS Care and Treatment Programs; LTFU: Loss to follow-up; WAZ: Weight-for-age *z*-scores; WHO: World Health Organization

However, confounding by differences in baseline health status between decentralised and centralised patient groups may have affected reported outcomes. Studies included in this narrative review demonstrated a wide range in the availability and inclusion of clinical covariates such as viral load or CD4 count at ART initiation when adjusting analyses of LTFU and mortality. Thus, the frequent reporting of lower rates of LTFU among decentralised patients may actually reflect the bias resulting from healthier patients being selected for decentralised care.

A randomised controlled trial (RCT) would be best positioned to identify the causal effect of decentralising HIV care. Randomisation into decentralised or centralised care would balance participants' health profiles between groups and allow for the more reliable attribution of any differences in care outcomes to decentralisation (Fraser et al., 2009). Yet, none of the excluded studies were RCTs, largely due to the programmatic infeasibility of running an RCT on decentralisation when national governments were already implementing it at the recommendation of the WHO.

Nevertheless, excluded studies that more rigorously controlled for baseline health differences identified equivalent outcomes between decentralised and centralised care for LTFU and mortality (Megerso and Garoma, 2016; Long et al., 2016; Hagstromer et al., 2013; van Dijk et al., 2014). Notably, Long et al. (2016) identified equivalent rates of LTFU and mortality through a quasi-experimental design using propensity-score matching of decentralised and centralised adult patients in South Africa. In an earlier study from the same research group, Brennan et al. (2011) applied the same study design but found lower rates of

LTFU and mortality for decentralised patients. However, this study only included clinically stable patients who would theoretically have been eligible for down-referral in South Africa in 2011. By contrast, Long et al. did not a apply clinical stability criterion for study inclusion. In an HIV care landscape where patients are initiated and managed on ART at primary care clinics—regardless of clinical stability at enrolment—findings from Brennan et al. (2011) have limited relevance, compared to those of Long et al. (2016). Hence, this narrative review highlights the importance of accounting for differences in baseline health between patient groups when assessing the effects of decentralising HIV care for any population, including adolescents.

The excluded studies from this systematic review provided insufficient evidence for reliable conclusions on other health-related outcomes, including immunological, virological, or adherence outcomes. Many studies were limited by the poor availability and quality of monitoring, recording, and tracing patients' outcomes, especially viral loads and CD4 counts. For the five studies with any available viral load or CD4 outcomes, three and four studies found equivalent virological and immunological outcomes, respectively, between decentralised and centralised care (Megerso and Garoma, 2016; McGuire et al., 2012; Long et al., 2016; Assefa et al., 2012; Morsheimer et al., 2014).

Given the lack of studies on the effectiveness of decentralisation for ALHIV, current practice for this population is largely based on cohort studies among adult or paediatric populations. Studies in adult and paediatric cohorts suggest that decentralising HIV care may result in equivalent or better LTFU and mortality outcomes, compared to traditional, centralised care delivery. However, the

applicability of these findings for adolescents may be limited, given the unique context of adolescence, as discussed in this chapter. Importantly, all 20 studies evaluated health outcomes recorded before 2015. Given the significant changes in ART initiation criteria since 2015—and the rapidly evolving landscape of HIV care in sub-Saharan Africa—these findings may not reflect the current reality of care in decentralised HIV care systems.

Implications of Systematic Review Findings for this DPhil

The systematic review presented in this chapter synthesised evidence on the effects of decentralising HIV care on health outcomes for adolescents and young adults in low- and middle-income countries. This section summarises implications of the systematic review for the body of empirical work presented in this dissertation (Chapters 6 and 7).

In brief, findings from the systematic review informed the methodology used for clinical data collection in the Mzantsi Wakho cohort study, upon which the empirical papers of this dissertation are based. Additionally, systematic review findings shaped the framework through which this dissertation evaluated the decentralisation of HIV care delivery.

First, this systematic review highlighted the limited scope of health outcomes previously used to evaluate the effects of decentralising adolescent HIV care. In the systematic review, only 3 of the 11 eligible studies included outcomes beyond attrition (i.e. mortality, loss to follow-up, and retention in care) (McGuire et al., 2012; Long et al., 2016; Megerso and Garoma, 2016). To understand the lived experiences of adolescents in a decentralised HIV care system, non-terminal

outcomes that reflect clinical status and stability must also be evaluated, such as viral load, CD4 count, or morbidity. Therefore, both Chapters 6 and 7 evaluate viral suppression as an outcome, alongside mortality and loss to follow-up. Additionally, the systematic review highlighted the paucity of evidence evaluating decentralisation of HIV care using recent health outcomes from adolescents and youth. Accordingly, Chapters 6 and 7 evaluate HIV care outcomes and experiences through the end of 2017 for adolescents in South Africa, which more accurately represents the current landscape of decentralised HIV care delivery.

Furthermore, outcomes evaluated in included studies of the systematic review were limited to those derived from clinical records and therefore are biased by missing or outdated information in facilities' records. As a result, mortality rates in both studies are likely underestimated (Brinkhof et al., 2009). Identifying this limitation from the systematic review guided the development of a more accurate mortality estimate in the empirical studies of this dissertation. For primary data analyses in Chapters 6 and 7, clinical records were corrected using data from community tracing methods to improve the accuracy of reported mortality.

Similarly, facility-reported rates of loss to follow-up can be overestimated through failing to account for unrecorded, patient-initiated "silent" transfers to other facilities (Geng et al., 2010a; Chammartin et al., 2018). By including all ART-providing facilities within the district, the included study in Uganda minimises risk of biased estimates from silent transfers (Scheibe et al., 2013). However, silent transfers were unaccounted for in the included study from Malawi, as well as several other studies of adolescent HIV care in sub-Saharan Africa—particularly in contexts without unique patient identifiers or centralised electronic medical

records (Chan et al., 2010; Davies et al., 2017). This systematic review finding guided the clinical data collection approach of the Mzantsi Wakho study, which traced individual adolescents' care seeking across all facilities, including unofficial transfers. In Chapters 6 and 7, manual linkage of adolescents' clinical records across all included healthcare facilities was used to identify silent transfers in care and to correct loss to follow-up estimates for adolescents within the decentralised care system.

Second, the heterogeneity in implementing decentralisation between the two included studies points to the large variations in decentralisation uptake and modes of delivery throughout sub-Saharan Africa. In the systematic review, heterogeneity arose from implementation of a co-intervention and intensive involvement from a non-governmental organisation (NGO). However, across different clinics and country contexts, decentralisation cannot easily be defined as one clear mode of care – in large part due to the wide-ranging effects of this structural intervention (Roy et al., 2019). In alignment with each country's national guidelines and available resources, decentralisation of HIV care may be implemented to varying degrees—such as decentralisation of ART management but not initiation or further decentralisation from healthcare facilities to community-based care models (World Health Organization, 2016c). Therefore, this systematic review highlighted the importance of first understanding the current landscape of decentralised HIV care systems in their specific country and patient contexts, before developing recommendations for optimising care.

The variations in decentralisation highlighted by this systematic review suggested that the empirical papers of this thesis should frame findings within the

wider context of a decentralised HIV care setting—rather than attempt to establish control and case groups based on “exposure” to decentralised care. This principle subsequently guided the design and analysis of primary data from the Mzantsi Wakho cohort (Chapters 6 and 7).

Chapter 6 evaluates adolescent progression along the extended HIV care cascade to viral suppression in South Africa’s decentralised healthcare system. In doing so, Chapter 6 contextualises adolescent attainment of health and operational outcomes within the lived reality of a decentralised system, which includes up- and down-referrals across multiple care facilities. Because the study cohort includes those who did and did not directly experience decentralised care, Chapter 6 also examines the association of experiencing decentralised HIV care with progression along the care cascade.

Similarly, Chapter 7 investigates the multiple HIV care pathways for adolescents that exist within South Africa’s decentralised healthcare system—and health outcomes associated with these pathways. In particular, Chapter 7 characterises pathways for transition out of paediatric HIV care, given that decentralisation already introduces mobility across healthcare facilities and care providers outside the context of transition to adult HIV care.

Supplementary Tables

Supplementary Table 1A: Example search strategy (PubMed 1996-2016, 2016-2019)

PubMed: 11 October 2016

Search	Query	Items found
#1	Search HIV[MeSH] OR HIV Infections[MeSH] OR HIV[tw] OR HIV-1[tw] OR HIV-2[tw] OR HIV1[tw] OR HIV2[tw] OR HIV infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR AIDS[MeSH] OR AIDS[tw] OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw]	402354
#2	Search Antiretroviral Therapy, Highly Active[MeSH] OR Anti-Retroviral Agents[MeSH] OR Antiviral Agents[MeSH] OR Anti-HIV Agents[MeSH] OR antiretroviral therapy[tw] OR antiretroviral*[tw] OR HIV treatment[tw] OR ART[tw] OR ARV[tw] OR HAART[tw]	212292
#3	Search Decentralization[tw] OR decentralisation[tw] OR decentraliz*[tw] OR decentralis*[tw] OR task shift*[tw] OR task-shift*[tw] OR down refer*[tw] OR down-refer*[tw] OR Referral and Consultation[MeSH] OR referr*[tw] OR facility based[tiab] OR facility-based[tiab] OR hospital based[tiab] OR hospital-based[tiab] OR clinic based[tiab] OR clinic-based[tiab] OR facility care[tiab] OR delivery of health care[mh:noexp] OR healthcare provider*[tw] OR health care provider*[tw] OR skill mix*[tw] OR (substit* n3 (doctor* OR physician* OR clinic* OR nurs* OR GP*))[tw] OR (nurs* n3 (run OR manag* OR led OR direct* OR initiat*))[tw] OR (doctor* n3 (run OR manag* OR led OR direct* OR initiat*))[tw] OR (physician* n3 (run OR manag* OR led OR direct* OR initiat*))[tw] OR NIMART[tw] OR (healthcare n6 (facility OR facilities OR centre* OR center*))[tiab] OR (health care n6 (facility OR facilities OR centre* OR center*))[tiab] OR hospital*[ti] OR clinic*[ti] OR home based[tiab] OR home-based[tiab] OR home care[tiab]	1043115
#4	Search #1 AND #2 AND #3	5866
#5	Search Adolesce*[tw] OR youth[tw] OR teen*[tw] OR child*[tw] OR pediatric*[tw] OR paediatric*[tw] OR pediatrics[MeSH] OR Adolescent[MeSH]	3081363
#6	Search #4 AND #5	1300
#7	Search #6 AND Limits: Publication Date from 1996/01/01 to 2016/10/10	1267

PubMed: 15 February 2019

Search	Query	Items found
#1	Search HIV[MeSH] OR HIV Infections[MeSH] OR HIV[tw] OR HIV-1[tw] OR HIV-2[tw] OR HIV1[tw] OR HIV2[tw] OR HIV infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR AIDS[MeSH] OR AIDS[tw] OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw]	441846
#2	Search Antiretroviral Therapy, Highly Active[MeSH] OR Anti-Retroviral Agents[MeSH] OR Antiviral Agents[MeSH] OR Anti-HIV Agents[MeSH] OR antiretroviral therapy[tw] OR antiretroviral*[tw] OR HIV treatment[tw] OR ART[tw] OR ARV[tw] OR HAART[tw]	247611
#3	Search Decentralization[tw] OR decentralisation[tw] OR decentraliz*[tw] OR decentralis*[tw] OR task shift*[tw] OR task-shift*[tw] OR down refer*[tw] OR down-refer*[tw] OR Referral and Consultation[MeSH] OR referr*[tw] OR facility based[tiab] OR facility-based[tiab] OR hospital based[tiab] OR hospital-based[tiab] OR clinic based[tiab] OR clinic-based[tiab] OR facility care[tiab] OR delivery of health care[mh:noexp] OR healthcare provider*[tw] OR health care provider*[tw] OR skill mix*[tw] OR (substit* n3 (doctor* OR physician* OR clinic* OR nurs* OR GP*))[tw] OR (nurs* n3 (run OR manag* OR led OR direct* OR initiat*))[tw] OR (doctor* n3 (run OR manag* OR led OR direct* OR initiat*))[tw] OR (physician* n3 (run OR manag* OR led OR direct* OR initiat*))[tw] OR NIMART[tw] OR (healthcare n6 (facility OR facilities OR centre* OR center*))[tiab] OR (health care n6 (facility OR facilities OR centre* OR center*))[tiab] OR hospital*[ti] OR clinic*[ti] OR home based[tiab] OR home-based[tiab] OR home care[tiab]	1175141
#4	Search #1 AND #2 AND #3	6871
#5	Search Adolesce*[tw] OR youth[tw] OR teen*[tw] OR child*[tw] OR pediatric*[tw] OR paediatric*[tw] OR pediatrics[MeSH] OR Adolescent[MeSH]	3370082
#6	Search #4 AND #5	1568
#7	Search #6 AND Limits: Publication Date from 2016/10/10 to 2018/02/15	212

Supplementary Table 1B: TIDieR checklists for included studies

Author: Chan, A.K., Mateyu G., Jahn, A., Schouten, E., Arora, P., Mlotha, W., Kambanji, M., van Lettow, M.
Title: Outcome assessment of decentralization of antiretroviral therapy provision in a rural district of Malawi using an integrated primary care model
Year: 2010

Template for Intervention Description and Replication (TIDieR) Checklist

Item	Description	
1. Brief name	Decentralisation of antiretroviral therapy (ART) provision using an integrated primary care model	
2. Why Describe any rationale, theory, or goal of the elements essential to the intervention	To make the widespread roll-out of public ART feasible and to improve equity in ART access for the rural poor of Malawi	
3. Materials Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers.	16 rural health centres outfitted with infrastructural (rooms and storage spaces) and human support to provide ART care (training)	
4. Procedures Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Decentralisation process: 1. Health centre site assessment and selection based on standardised MOH criteria (available medical assistants/nurses, available HIV testing and counselling), presence of adequate counselling and consulting rooms, capability for drug storage 2. Capacity building and training of HC staff using standardised national training course (41 clinicians and 98 nurses trained) 3. Integration of ART follow-up visits with primary outpatient care services at health centres 4. On-going mentorship and supervision by clinical officer or clinic coordinator (biweekly to monthly basis, depending on patient volume). Baylor Paediatric AIDS Consultant also provided 1-day intensive Paediatric ART Training Course, followed by monthly/bi-monthly paediatric HIV/ART mentorship at mobile clinics Patient experience of decentralisation: decentralised for ART follow-up from tertiary hospital if they met eligibility criteria (see #9). Complicated cases (new opportunistic infections or drug toxicities) were referred to be seen by clinic officer/coordinator during mobile clinic visits.	
5. Who provided For each category of intervention provider, describe their expertise, background, and any specific training given.	**Hospital**	**HCs**
	2 physicians for specialist consultations and clinical mentorship (daily)	2 physicians for specialist consultations and monthly mentorship (as needed)
	3 Clinical Officers for patient consultation, 5 COs specifically for HIV/ARV management (daily)	1 CO for problem cases (biweekly to monthly), 5 COs & 20 Medical Assistants for ARV provision → 3 COs at one HC, 2 others at 1 each, 1 MA per HC
	5 nurses	70 nurses (1-2 nurses per HC)
	1 ART clerk, 1 ART counsellor, 3 nutrition and adherence counsellors	16 ART clerks and 16 ART counsellors (across 16 sites)
	7 expert patients for ART clerk assistance and light nursing tasks	Monthly to quarterly health surveillance assistants for defaulter tracing
		Community-based organisation for health promotion and training peer support
6. How Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Individual, face-to-face care at healthcare facilities. Both ART initiation and management were decentralised beginning from April 2008, with decentralised ART management commencing in March 2007.	
7. Where Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	16 rural health centres, typically located closer to patients' homes. Outpatient services integrated with HIV-related services in health centres.	
8. When and How Much Describe the number of times the intervention as delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose.	Routine follow-up arranged once per month for first 6 months after initiation, and after these 6 months, follow-up intervals were longer depending on provider assessment (exact time not specified).	
9. Tailoring If the intervention was planned to be personalised, titrated, or adapted, then describe what, why, when, and how.	Eligibility criteria based on Malawi's criteria: 1. Adult or older children on first-line ART for >3 months and stable 2. No evidence of active opportunistic infection or drug intolerance 3. ART provider confidence in patient adherence 4. Patient lives in location closer to health centre than hospital	
10. Modifications If the intervention was modified during the course of the study, describe the changes (what, why, when and how)	From October 2004-Feb 2007: all HIV care was done within hospital; from March 2007-March: all ART initiated in hospital, and 16 health centres provided management of care; from April 2008-December 2008, 7 health centres also initiated ART.	
11. How well: planned If intervention adherence or fidelity was assessed, describe how and by whom, and, if any strategies were used to maintain or improve fidelity, describe them	Intervention adherence/fidelity not assessed	
12. How well: actual If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned	NA	

Author: Scheibe, F.J.B., Waiswa, P., Kadobera, D., Müller, O., Ekström, A.M., Sarker, M., Neuhann, H.W.F.
Title: Effective Coverage for Antiretroviral Therapy in a Ugandan District with a Decentralized Model of Care
Year: 2013

Template for Intervention Description and Replication (TIDieR) Checklist

Item	Description
1. Brief name	Decentralisation of antiretroviral therapy (ART) initiation and management
2. Why Describe any rationale, theory, or goal of the elements essential to the intervention	To make the expansion of ART coverage more accessible and effective (reduce drop-out and drug resistance rates) in rural Uganda
3. Materials Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers.	4 health centres (physical and human infrastructure included), outfitted to provide patients with 30-day ARV supplies. HCs provided HIV testing but no CD4 count available in the district. Each facility had one ART register and equipment for weighing patients. Drug supply at the HCs delivered by the National Medical Store under the Ugandan Ministry of Health.
4. Procedures Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Patients routinely weighed, and clinical symptoms (if present) seen by clinical officer before drug dispensing. Patients received 30-day ARV supply.
5. Who provided For each category of intervention provider, describe their expertise, background, and any specific training given.	At level IV health centres, care was provided by clinical officers, nurses, or midwives who had undergone standardised national training course for comprehensive HIV care and ART. At level III health centre, care was provided by trained clinical officer and nurse.
6. How Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Individual, face-to-face care at healthcare facilities. Both ART initiation and management were decentralised beginning from February 2007
7. Where Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	1 level III health centre (targets populations of 20,000 patients) provided inpatient and outpatient care. 3 level IV health centres (target population of 100,000 patients) provided same services as level III plus surgery.
8. When and How Much Describe the number of times the intervention as delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose.	ART clinics operated once or twice a week, with patients scheduled for monthly visits
9. Tailoring If the intervention was planned to be personalised, titrated, or adapted, then describe what, why, when, and how.	Ugandan national guidelines for ART eligibility for adults and adolescents (≥15 years old): CD4 <200 (until 2008) or 250 cells/mm^3, or WHO stage III/IV
10. Modifications If the intervention was modified during the course of the study, describe the changes (what, why, when and how)	ART provision began in hospital in April 2004; decentralised ART provision began in December 2005 at one level IV HC, followed by 3 more since April/May 2007
11. How well: planned If intervention adherence or fidelity was assessed, describe how and by whom, and, if any strategies were used to maintain or improve fidelity, describe them	Intervention adherence/fidelity not assessed
12. How well: actual If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned	NA

Supplementary Table 1C: ROBINS-I assessment tools for included studies

The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

Version 19 September 2016

ROBINS-I tool (Stage I): At protocol stage

Specify the review question

Participants	Youths (aged 10-24) receiving antiretroviral therapy (ART) care in LMICs
Experimental intervention	Decentralisation of ART care from hospitals to health centres and/or clinics
Comparator	Centralised ART care at hospital (or remaining within secondary health facility)
Outcomes	Health outcomes, incl. mortality, retention in care, LTFU, viral suppression, CD4 count, morbidity

List the confounding domains relevant to all or most studies

Baseline health status of patient (WHO stage, CD4, VL), age of patient, gender of patient, ART regimen of patients, inclusion of "silent transfers" in LTFU

List co-interventions that could be different between intervention groups and that could impact on outcomes

Integrated primary care programmes, intensive training programmes for healthcare providers, decentralising ART care to home-based care or adherence clubs or pick-up points

ROBINS-I tool (Stage II): For each study

Specify a target randomized trial specific to the study

Design	Individually randomized
Participants	HIV+ youth on ART aged 10-24 at baseline
Experimental intervention	ART initiation and management at health centre
Comparator	ART initiation and management at hospital

Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Attrition from ART care

Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Adjusted hazard ratio for attrition from ART program if receiving hospital-based care: aHR = 1.26 (95%CI 0.42-3.81), $p = 0.68$

Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.
"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

(i) Confounding domains listed in the review protocol				
Confounding domain	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator?
Baseline health status of patient (WHO stage, CD4, VL)	Most recent documented WHO stage	No	No (not a baseline measure but effectively an outcome since it's most recent documented)	No information

Age of patients	Age at ART initiation	No	Yes	No information
Gender of patients	Gender	No	Yes	No information
ART regimen of patients	Type of ART regimen	No	No (not measured at all)	No information
Inclusion of "silent" transfers in LTFU	Undocumented transfers out of care	No	Yes (not measured, but accounted for in study design/data collection)	No information

(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important				
Confounding domain	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator?
Time from HIV test to ART start	Months from date of HIV test to date of ART start	No	Yes	No information
Time on ART	Days from date of ART start to data collection	No	No information (unclear if this actually reflects duration *on* treatment or time since ART start, regardless of retention)	No information

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that "no statistically significant association" is not the same as "not predictive".

Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important. "Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

(i) Co-interventions listed in the review protocol		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator
Implementation of integrated primary care model in decentralised sites	Yes (not administered)	No information
Intensive mentorship and training of lower-tier healthcare workers	Yes (not administered)	No information
Decentralising ART care to home-based care or adherence clubs or pick-up points	Yes (not administered)	No information

(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Signalling questions	**Description**	**Response options**
Bias due to confounding		
1.1 Is there potential for confounding of the effect of intervention in this study?	Bias in allocation to study arms (pre-intervention) by health status: there was no adjustment for differences in baseline health status (i.e. if hospital vs. HCs had healthier patients from baseline).	Y

If N/PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	The only adjustment for health status was done using most recent documented WHO stage, which is not necessarily a baseline/pre-intervention measure and may represent an outcome. "The considerable differences in the distribution of WHO clinical stages between HCs and the hospital may reflect systematic differences in the staging process and its documentation rather than differences in the patient population according to our observation." Additionally, the extent to which time on ART was controlled for is not clear. The paper notes that the hospital has had an ART programme for longer, so patients were on treatment longer at the hospital than in HCs. Type of ART regimen was also not controlled for, which is likely to produce bias if unbalanced between study arms.	
If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.		N
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)		NA
Questions relating to baseline confounding only		
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Analytic methods were appropriate, including multivariate regression models controlling for covariates that were significant in univariate analyses	Y
1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Baseline health status measured neither validly nor reliably because only measured using WHO stage (not including CD4 or VL count), potentially measured post-intervention	N
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	WHO stage measurement used as a control was the most recent documented WHO stage, which could have been post-intervention	PY
Questions relating to baseline and time-varying confounding		
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?		NA
1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NA
Risk of bias judgement	Baseline health status not controlled for, with healthier patients likely being treated in the HCs compared to hospitals; post-intervention variable was controlled for instead. Type of ART regimen was not controlled for either.	Serious
Optional: What is the predicted direction of bias due to confounding?	See above	Favours experimental

Bias in selection of participants into the study		
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If N/PN to 2.1:** go to 2.4	Yes, people who were registered on the ART programme but did not have patient files present were not included in the study. For the total cohort, this was 16.9% of the eligible study sample, but it is not clear how many potential participants aged 10-24 were excluded due to missing patient files.	PY
2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Yes, on average, the percentage of patient files found at HCs (75.1%) was lower than at the hospital (83.8%), with significant variability across facilities within the HC level.	PY
2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	If patient files were not available for patients, they were not likely to be receiving care in the facility (either LTFU or passed away), and, if they do arrive for care, the lack of information available would likely result in inferior care quality, given that the care provider is not aware of the patient's health history.	PY
2.4. Do start of follow-up and start of intervention coincide for most participants?	Yes, follow-up/data collection begins from ART initiation at facilities	Y

2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No adjustment techniques used: "The retrospective analysis was deliberately chosen to assess a "real-life" care model outside of prospective research activities or external support, thus our analysis is restricted to the information available at the health facility and district level." "Although every effort was made to retrieve all files and treatment charts, we cannot exclude that some patients whose files were lost or who were labelled LFTU were actually still on treatment. We are however very confident that this number would be low since we were able to visit the facilities at several occasions and actually helped to retrieve files."	N
Risk of bias judgement	Patients whose files were lost or unavailable in the facility were not included for analysis. Given percentages for the total cohort, if this included patients aged 10-24, most of them were likely to be initiated at HCs.	Serious
Optional: What is the predicted direction of bias due to selection of participants into the study?	Since loss of a patient file is likely to be associated with worse health outcomes (or discontinued care), excluding these patients from the study minimises the influence of this (negative) outcome, biasing towards a more positive finding for the experimental HC arm.	Favour experimental

Bias in classification of interventions		
3.1 Were intervention groups clearly defined?	Groups were defined based on the level of care where ART was initiated	Y
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes, based on patient files and HIV registers at the included facilities	Y
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?		N
Risk of bias judgement		Low
Optional: What is the predicted direction of bias due to classification of interventions?		Unpredictable

Bias due to deviations from intended interventions		
If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2		
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?		N
4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?		NA
If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
4.3. Were important co-interventions balanced across intervention groups?		NI
4.4. Was the intervention implemented successfully for most participants?		PY
4.5. Did study participants adhere to the assigned intervention regimen?		PY
4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?		NA
Risk of bias judgement		Low
Optional: What is the predicted direction of bias due to deviations from the intended interventions?		Unpredictable

Bias due to missing data		
5.1 Were outcome data available for all, or nearly all, participants?	For the age-disaggregated data for youths (10-24 years only, n=63), outcome data was available for all	Y
5.2 Were participants excluded due to missing data on intervention status?		N
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	For age-disaggregated data for youths, 7/63 (11.1%) were excluded from analysis due to missing or incomplete documentation that could have included age, ART start date, date of last visit, sex, or WHO stage	Y
5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?	Distribution of missing data (and therefore excluded participants) was not indicated in the age-disaggregated data	NI
5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?	For the total cohort (since sensitivity analysis was not indicated for age-disaggregated cohort): "In a sensitivity analysis including only health facilities having at least 80% of patient files present (hospital, HC A and HC C) we found similar rates of retention in care…at 12 months and…at 36 months after ART initiation."	PY
Risk of bias judgement	Sensitivity analysis and relatively low rates of exclusion due to missing data suggest only moderate risk of bias	Moderate
Optional: What is the predicted direction of bias due to missing data?	Unclear, given that the distribution of missing data was not clarified	Unpredictable

Bias in measurement of outcomes		
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?		N
6.2 Were outcome assessors aware of the intervention received by study participants?	Blinding by outcome assessors was likely not possible because treatment was clearly in either hospital or decentralised sites. The study does not indicate whether analyses were done blinded to intervention arm.	PY
6.3 Were the methods of outcome assessment comparable across intervention groups?		Y

6.4 Were any systematic errors in measurement of the outcome related to intervention received?	LTFU from care was not accurately measured because loss to follow-up did not account for "silent" transfers, so this outcome may overestimate the true extent of defaulting from care. However, the study design accounts for this as the authors indicate: "Some patients may have transferred themselves to receive treatment from other sources without notification of the system ("silent transfer") mainly within the district as described before or might have registered twice at different facilities…Since we included all ART providing facilities in the district, this rate should be lower here… It seems therefore unlikely that our data underestimates or overestimates the retention in care to a large extent."	PN
Risk of bias judgement	Potentially inaccurate estimate of LTFU due to "silent" transfers, but this is unlikely given the study design; blinding of outcome assessors unclear	Moderate
Optional: What is the predicted direction of bias due to measurement of outcomes?		Unpredictable

Bias in selection of the reported result		
Is the reported effect estimate likely to be selected, on the basis of the results, from...		
7.1. ... multiple outcome *measurements* within the outcome domain?	Probability of retention in care and risk factors for attrition from care both reported	N
7.2 ... multiple *analyses* of the intervention-outcome relationship?		N
7.3 ... different *subgroups*?		N
Risk of bias judgement	Moderate selected instead of Low because no protocol or *a priori* statistical analysis plan available, beyond what was provided within the manuscript	Moderate
Optional: What is the predicted direction of bias due to selection of the reported result?	No bias created	Unpredictable

Overall bias		
Risk of bias judgement	Serious confounding due to lack of correction for differences in baseline health status and ART regimen type in the study arms (and for invalid controlling of a post-intervention variable). Serious selection bias by exclusion of those without patient files.	Serious
Optional: What is the overall predicted direction of bias for this outcome?	Both forms of bias favour experimental because healthier patients are likely to be initiated in HCs, and those without patient files were probably more likely to be from HCs (if there were any from youths)	Favours experimental

The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

Version 19 September 2016

ROBINS-I tool (Stage I): At protocol stage

Specify the review question

Participants	Youths (aged 10-24) receiving antiretroviral therapy (ART) care in LMICs
Experimental intervention	Decentralisation of ART care from hospitals to health centres and/or clinics
Comparator	Centralised ART care at hospital (or remaining within secondary health facility)
Outcomes	Health outcomes, incl. mortality, retention in care, LTFU, viral suppression, CD4 count, morbidity

List the confounding domains relevant to all or most studies

Baseline health status of patient (WHO stage, CD4, VL), age of patient, gender of patient, ART regimen of patients, inclusion of "silent transfers" in LTFU

List co-interventions that could be different between intervention groups and that could impact on outcomes

Integrated primary care programmes, intensive training programmes for healthcare providers, decentralising ART care to home-based care or adherence clubs or pick-up points

ROBINS-I tool (Stage II): For each study

Specify a target randomized trial specific to the study

Design	Individually randomized
Participants	HIV+ youth on ART aged 10-24 at baseline
Experimental intervention	ART initiation and/or management at healthcare centre
Comparator	ART initiation and/or management at hospital

Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Retention in care	Mortality

Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Retention in care: OR 0.37 [95%CI 0.26-0.55], p<0.0001	Mortality: OR 0.14 [95%CI 0.07-0.29], p<0.0001

Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important. "Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

(i) Confounding domains listed in the review protocol				
Confounding domain	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator?
Baseline health status of patient (WHO stage, CD4, VL)	WHO clinical stage at ART initiation (baseline)	No	No (low validity)	Favour experimental
Age of patients	Age at ART initiation	No	Yes	No information
Gender of patients	Gender	No	Yes	No information

ART regimen of patients	Type of ART regimen	No	No information (no further information provided on ART regimen type)	No information
Inclusion of "silent" transfers in LTFU	Defaulting in care to account for transfer to other facilities within study	No	No	No information

(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important				
Confounding domain	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator?
Duration of treatment	Length of time on treatment (months, censored to censoring event or end of data collection)	No	Yes	No information
Presence of ART side effects	Presence of ART side effects reported in health mastercards	No	No information (no further information provided on how side effects were differentiated from morbidity/symptoms)	No information
Reason for ART initiation	Reason for ART initiation according to national eligibility, of the following options: (1) WHO Stage III/IV (2) CD4 count <250 cells/mm^3	No	Yes	Favour experimental

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that "no statistically significant association" is not the same as "not predictive".

Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important. "Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

(i) Co-interventions listed in the review protocol		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator
Implementation of integrated primary care model in decentralised sites	No	Favour experimental
Intensive mentorship and training of lower-tier healthcare workers	No	Favour experimental
Decentralising ART care to home-based care or adherence clubs or pick-up points	Yes (not administered)	No information

(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Signalling questions	**Description**	**Response options**
Bias due to confounding		

1.1 Is there potential for confounding of the effect of intervention in this study? **If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	Bias in allocation to study arms (pre-intervention):"Importantly, there is a significant selection bias programmatically in that more stable patients are selected for DC and initiation of ART at decentralized sites, however, attempts were made to adjust for this by adjusting for reason for initiation as well as length of time on treatment." Further, the only data available to adjust for pre-intervention/baseline health status was WHO stage, where a more rigorous adjustment would have included CD4 count or VL measurement. Bias in outcome measurement: defaulting in care did not account for possible self-initiated transfers to other facilities.	Y
If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.		N
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)		NA

Questions relating to baseline confounding only		
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Analytic methods were appropriate, including multivariate regression models controlling for baseline confounders	Y
1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Baseline health status not measured validly because only measured using WHO stage. Duration on treatment may be biased by not accounting for treatment that has been continued in another facility (via "silent" transfer).	PN
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	None	N
Questions relating to baseline and time-varying confounding		
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?		NA
1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NA
Risk of bias judgement	Risk of bias sourced from baseline confounding that biases allocation into decentralised study arm (healthier patients in decentralised care)	Serious
Optional: What is the predicted direction of bias due to confounding?	See above	Favours experimental

Bias in selection of participants into the study		
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If N/PN to 2.1:** go to 2.4	Selection into study was anyone initiating care at these sites with available information in the health facility	PN
2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention?		NA
2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA
2.4. Do start of follow-up and start of intervention coincide for most participants?	Follow-up began from ART initiation at facilities, with data collection commencing in October 2004 (clinic inception)	Y
2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?		NA
Risk of bias judgement		Low
Optional: What is the predicted direction of bias due to selection of participants into the study?		Unpredictable

Bias in classification of interventions		
3.1 Were intervention groups clearly defined?	Groups were based on whether the individual had ART care managed at the tertiary hospital vs. decentralised sites. The study does not provide clear details on what "managed" entails, which could have been better clarified, but the report clarifies that complicated cases are referred for consultation with clinic coordinators in a mobile clinic, not at the tertiary hospital.	PY
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Classification likely determined by information from patient files and where they were obtained, although exact information about how to define "managed" was not indicated (e.g. if initiated at one site but mostly treated at another)	NI
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?		N
Risk of bias judgement	Some aspects of intervention assignment were likely determined retrospectively, such as in the case of someone initiating care at the tertiary hospital but primarily receiving care at a decentralised site. Because no precise information is provided on how "managed" was defined, the extent of this bias is hard to determine	Moderate
Optional: What is the predicted direction of bias due to classification of interventions?	See above	Unpredictable

Bias due to deviations from intended interventions		
If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2		
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No, decentralising care for some ART patients will likely affect care outcomes for hospital-based patients because it reduces patient burden in the hospital, but this is accounted for in the theory of change for this intervention and is anticipated as an effect	PN
4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?		NA
If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
4.3. Were important co-interventions balanced across intervention groups?	The co-interventions of integrated primary care and intensive training of lower cadre health workers (with NGO support) was provided only to the decentralised study arm. This was intended to improve quality of services in decentralised care to be comparable to that of hospital-based care.	N
4.4. Was the intervention implemented successfully for most participants?		PY
4.5. Did study participants adhere to the assigned intervention regimen?	This is likely accounted for in definition of "managed," used to determine allocation to study arms.	PY
4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?		NA
Risk of bias judgement	Important co-interventions were not balanced across study arms, and the analysis was not appropriate to account for this imbalance	Serious
Optional: What is the predicted direction of bias due to deviations from the intended interventions?	Provision of additional support and integration of primary care services likely helped improve health outcomes in the experimental arm.	Favours experimental

Bias due to missing data		
5.1 Were outcome data available for all, or nearly all, participants?	No information provided about the extent of data missingness	NI
5.2 Were participants excluded due to missing data on intervention status?	No information provided about whether any potential participants were excluded due to missing data (e.g. due to not having patient files available in the facilities)	NI
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Not indicated in the report, so this type of exclusion was likely not applied to analyses	PN
5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?		NA
5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?		NA
Risk of bias judgement	Not enough information available about the extent of missing data and how it was handled to determine risk of bias	NI
Optional: What is the predicted direction of bias due to missing data?		Unpredictable

Bias in measurement of outcomes		
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?		N
6.2 Were outcome assessors aware of the intervention received by study participants?	Blinding by outcome assessors was likely not possible because treatment was clearly in either hospital or decentralised sites. The study does not indicate whether analyses were done blinded to intervention arm.	PY
6.3 Were the methods of outcome assessment comparable across intervention groups?		Y
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Mortality was measured as all-cause mortality, not illness-related mortality, so this outcome may not actually reflect the impact of the type of care on health outcomes for patients. Mortality due to accidents, injuries, etc. may bias results in one direction or another. Defaulting was not accurately measured because loss to follow-up did not account for "silent" transfers, so likely overestimates the true extent of defaulting from care.	Y
Risk of bias judgement	Both outcomes face non-differential measurement error	Moderate
Optional: What is the predicted direction of bias due to measurement of outcomes?	Affects both study arms	Unpredictable

Bias in selection of the reported result		
Is the reported effect estimate likely to be selected, on the basis of the results, from...		
7.1. ... multiple outcome *measurements* within the outcome domain?	All measured outcomes (mortality, defaulting) reported	N
7.2 ... multiple *analyses* of the intervention-outcome relationship?		N
7.3 ... different *subgroups*?		N
Risk of bias judgement	Moderate selected because no protocol or *a priori* statistical analysis plan available, beyond what was provided within the manuscript	Moderate
Optional: What is the predicted direction of bias due to selection of the reported result?	No bias created	Unpredictable

Overall bias		
Risk of bias judgement	Serious risk of bias due to baseline confounding and co-interventions that were not accounted for in analyses	Serious
Optional: What is the overall predicted direction of bias for this outcome?	Lack of adjustment of baseline confounders (esp. better baseline health status in decentralised arm) and provision of co-intervention with additional support. Both bias results to be more favourable in decentralised study arm	Favours experimental

Supplementary Table 1D: PRISMA 2009 Checklist for systematic review

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	59
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	60-61
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	62-65
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	65-66
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	65
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	66
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	66-67
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Table 1A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	68
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	68
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	68
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	68
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	68-69
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	68-69

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	68
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	69-70
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	70-73, Table 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	73-74
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	77-78, Table 6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary Table 1C
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Descriptive synthesis pgs 77-78
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	81-83
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	87
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	87
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A (incl. in submission to journal)

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 . For more information, visit: **www.prisma-statement.org**.

4. Methodology

This chapter provides greater methodological detail for the longitudinal Mzantsi Wakho cohort study on which Chapters 6 and 7 are based (DPhil Papers 2-3). The specific statistical and analytic methods for Chapters 4, 6, and 7 (DPhil Papers 1-3) are provided in their respective chapters in this dissertation.

1. Introduction

Overview of doctoral research

This doctoral research is comprised of (1) a systematic review and (2) primary analyses of cross-sectional and longitudinal data from a prospective cohort study of ART-initiated adolescents living with HIV in South Africa. Given the lack of large studies evaluating adolescent HIV care within public healthcare settings of sub-Saharan Africa—beyond studies based in a single healthcare facility—this research is uniquely positioned to contribute to the development of better models of care for this population.

The primary data analyses for this doctorate are nested within the Mzantsi Wakho research project, a larger longitudinal, mixed-methods study in the Eastern Cape province of South Africa (2014-2018). Because this doctoral research employs mostly quantitative methods, this chapter largely focuses on the following components of the Mzantsi Wakho quantitative study arm: overall research aims and design, study sampling, data collection tools, measures, and ethical considerations.

Overall Mzantsi Wakho research aims

Mzantsi Wakho seeks to understand the health needs of adolescents living with HIV growing up in high-risk contexts. In particular, it investigates how individual-, family-, community-, and structural-level factors may interact to affect adolescent ART adherence, uptake of sexual and reproductive health services, and health outcomes on ART. Mzantsi Wakho is a multi-year, three-wave longitudinal study of adolescents aged 10-19 years in the Eastern Cape, South Africa (2014-2018).

As a mixed-methods project, Mzantsi Wakho used quantitative and qualitative approaches to carry out the following research components:

1. **Longitudinal (three-wave) quantitative surveys** of 1080 ART-initiated ALHIV to assess risk- and resilience-promoting factors for ART adherence, uptake of sexual and reproductive health care, and positive health outcomes on ART. This quantitative component was directly informed by simultaneous, on-going qualitative research in Mzantsi Wakho.
2. In-depth **qualitative** research with ALHIV, caregivers, and health and social workers to explore (1) How ALHIV use and resist HIV treatment and sexual and reproductive health services; and (2) How those caring for ALHIV perceive and experience barriers and facilitators to ART adherence and sexual and reproductive health uptake.
3. Participatory **qualitative** workshops to collaborate with adolescents to design youth-driven tools for (1) Supporting ART adherence and sexual and reproductive health service uptake, (2) Assisting youth in negotiating barriers to retention in care, and (3) Customising ART and

sexual and reproductive health interventions for improved adolescent health outcomes.

Quantitative data collection tools included the following:

1. Three waves of a **self-reported questionnaire** that collects information about participants' sociodemographics, health service access, and risk- and resilience-promoting factors for ART adherence and service uptake. Questionnaires explored adolescents' experiences in their homes, communities, and healthcare facilities. Questionnaires were administered using audio mobile-assisted self-interviewing, with language and structures suggested by a Teen Advisory Group and adolescents living with HIV. Due to potentially low levels of literacy among participants, questionnaires were completed in the supportive presence of a local research assistant. Questionnaire data from the first (2014-2015) and second waves (2015-2017) of the study are available, and the third wave of data (2017-2018) is currently being cleaned for upcoming analyses.
2. Two rounds (2014-2015, 2016-2017) of **clinical record data extraction** for each participant from all healthcare facilities included in the study. These clinical records include data on CD4 cell count, viral load, ARV regimen, loss to follow-up, and mortality.
3. **Clinic-level questionnaires** delivered to staff at each facility included in the study, in order to assess the characteristics and types of services available.

The aims and methods for this project were developed through collaborative planning with the following stakeholders: adolescents living with HIV; clinical, public health, and social science researchers; UNICEF; the South African Departments of Health, Social Development, Basic Education, and Women, Children, and Disabilities; NGO Paediatric AIDS Treatment for Africa (PATA); and community-based organisations (Raphael Centre, Small Projects Foundation, and Keiskamma Trust). Ultimately, this interdisciplinary research project aims to inform an inclusive approach to HIV policy and programming, which creates an opportunity to bring the experiences of adolescents into the policy arena.

2. Research setting

This study was conducted in urban and rural locations of the Buffalo City Municipality and Amathole Health District of the Eastern Cape (Figure 6). The Eastern Cape is South Africa's second largest province and houses 12.6% of South Africa's total population (Statistics South Africa, 2016). However, it is also South Africa's poorest province and has an antenatal HIV prevalence rate of 31% (National Department of Health, 2013).

Figure 6. Map of districts in the Eastern Cape, South Africa

Source: South Africa Yearbook 2011/12, published by the Government Communication and Information System; http://www.ecdc.co.za

According to the most recent report from the Eastern Cape Provincial AIDS Council, the HIV prevalence rate for adults 15-49 years old in the Eastern Cape is 19.9%, which is slightly higher than the national adult HIV prevalence rate (19.7%) (Eastern Cape Provincial AIDS Council, 2016). In recent years, the province has made significant gains in increasing the proportion of people living with HIV who are accessing ART. In the most recent provincial mid-term report from 2015, at least 70% of individuals enrolled on ART were retained on treatment for ≥60 months (Eastern Cape Provincial AIDS Council, 2016). However, the proportion of eligible people who actually receive ART each year was only 58%, well below the 90% national target (Eastern Cape Provincial AIDS Council, 2016).

Under the current healthcare system, paediatric patients from birth up to 15 years of age are recorded in the system in one of three age groups: birth to 1 year, 1-5 years, and 6-15 years old. The total number of adolescents (10-19 years old) in facilities are still not reported in official statistics or in the National Paediatric and Adolescent Working Group's clinic register, which only records those under 15 years of age. Recent efforts have drawn attention to the need to focus on adolescents and youth as a separate category in the context of HIV/AIDS. As a result, plans are underway for establishing a national register that includes individual-level data (Human Sciences Research Council, 2019).

Yet, progress on this register has experienced significant delays in the Eastern Cape due to setbacks such as low levels of reporting from clinics with severe infrastructural challenges. These infrastructural limitations include the lack of functional computerised clinic registers, computer theft and breakage, low reliability of electricity in rural clinics, and lack of clinic staff training (Kaposhi et al.,

2015). The most recent audit of ART programme monitoring in the Eastern Cape (2015) found that the number of clients on ART was over-reported by 36.6% in the District Health Information System (Kaposhi et al., 2015). Smaller public health clinics reported more accurate data than large hospital-based facilities, especially when compared to facilities with >250 patients.

The audit also revealed that, in 33 of the 34 facilities visited, nurses in charge of the ART programme had received no training on completing ART registers or monthly reporting protocols during nurse-initiated management of antiretroviral treatment (NIMART) training (Kaposhi et al., 2015). As a result, ART registers in facilities are frequently incomplete or filled incorrectly, affecting the quality of patient care. Also, biomarker data such as CD4 counts and viral load tests taken at baseline, 6, 12, and 24 months were found to be highly inaccurate and unreliable (Kaposhi et al., 2015). Yet, the Regional Training Centre that conducts NIMART trainings for public facilities declares that the NIMART curriculum provides mentoring on topics of registers and clinical records (Kaposhi et al., 2015). This discrepancy suggests that, even if training is technically provided by the curriculum, there is a low level of understanding of recording and reporting procedures, which requires improved knowledge translation for practical implementation.

3. Mzantsi Wakho research team

An overview of the structure of the Mzantsi Wakho research team is presented in Figure 8. From July 2015 to February 2018, participants' clinical records were extracted from all 52 included facilities by the clinic-based research assistants. Data collection protocols were applied to respect the confidentiality and anonymity

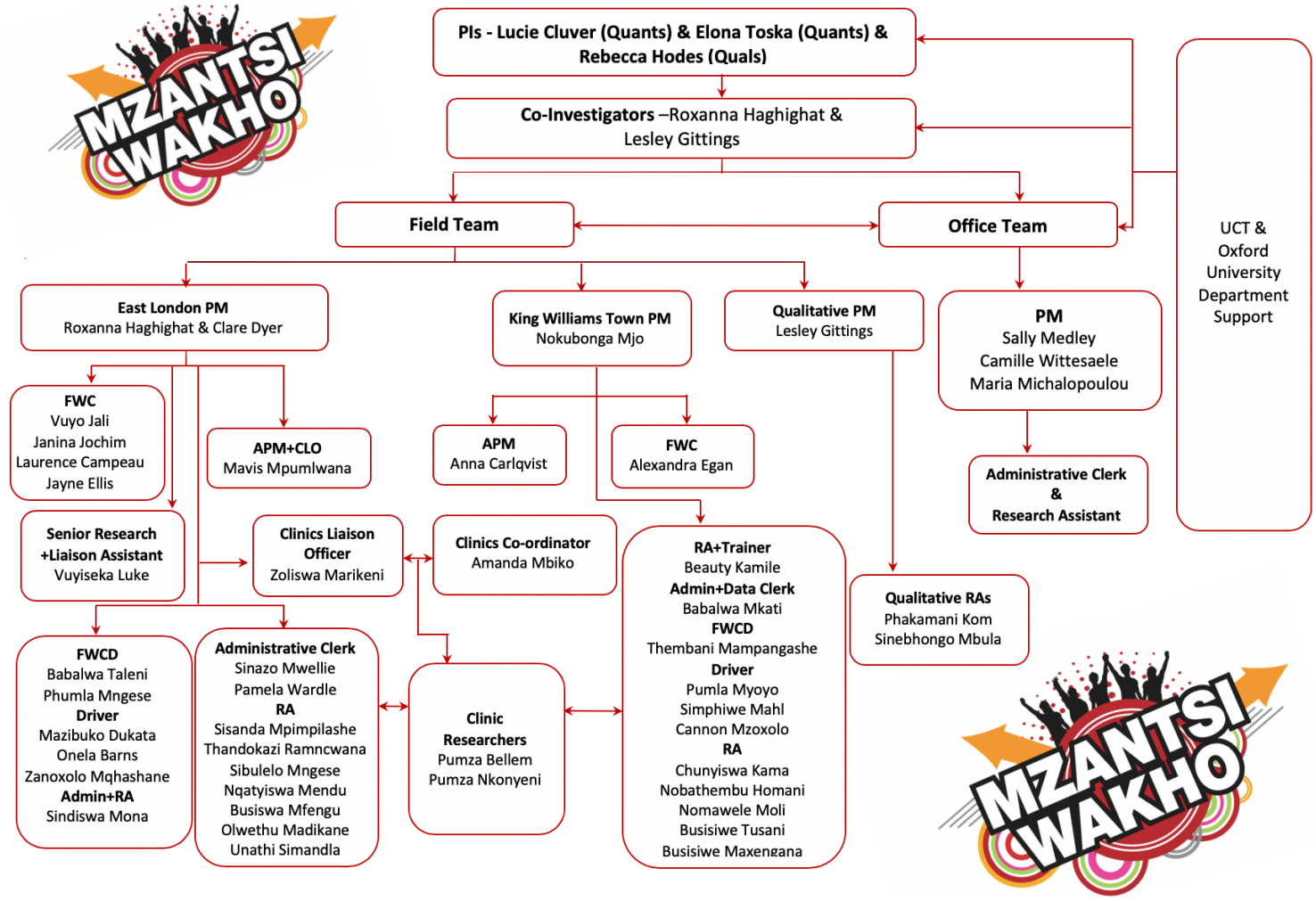
of adolescent participants. Hard copies of clinical record data extraction forms were entered into electronic tablets after data checking by the clinic team. From November 2015 to May 2017, clinic-level questionnaires were conducted by a former senior nurse with extensive experience working in the South African healthcare system, particularly in the Eastern Cape.

Figure 7. Full Mzantsi Wakho team during a team-building exercise

Source: Jense van der Wal

In parallel, participant-level questionnaires were conducted by a team of community-based research assistants, who interviewed adolescents in their homes or communities. The fieldwork team were locally recruited from the Eastern Cape. To ensure that the research tools were delivered in a rigorous and ethical manner, research assistants underwent a thorough training programme that focused on recruitment, potential ethical issues, and data collection techniques. Ethical protocols described in Section 7 of this chapter guided the work of the research team.

Figure 8. Organisation chart of the Mzantsi Wakho research team (accurate through end of candidate's fieldwork, Dec 2017)



PM, Project Manager; APM, Assistant Project Manager; CLO, Community Liaison Officer; FWC, Fieldwork Coordinator; FWCD, Fieldwork Coordinator/Driver; RA, Research Assistant

4. Mzantsi Wakho Sampling Strategy

This section outlines the sampling strategy used for the quantitative arm of Mzantsi Wakho and its rationale. Due to a lack of data on the population of ALHIV in South Africa and low disclosure rates, determining the composition of a representative sample remains difficult. As aforementioned, national-level data groups individuals by 0-14 years (paediatric) and 15-49 years (adult), thus precluding the accurate identification of all adolescents (Statistics South Africa, 2016).

For the quantitative arm of the study, Mzantsi Wakho adopted a sampling strategy as follows: (1a) Mapping of 81 ART-providing facilities using the Department of Health register; (1b) Health facilities sampling; (2a) Roster of eligible adolescent participants, based on participating health facilities; (2b) Community tracing of ART-initiated adolescents on health facilities' registers, including adolescents on treatment and adolescents who defaulted or were lost to follow-up. The first stage of the quantitative survey had aimed to interview 600 ALHIV but interviewed 1080 in total. Participants from the baseline year of the study were followed up annually for two more waves of interviews through May 2018.

Stage 1a: Selection of ART sites using the Department of Health register. Based on the Demographic Health Information System national database, the research team conducted an initial mapping of all 81 healthcare facilities providing ART in the Buffalo City Municipality. Using a standardised tool, information was collected on the type of facility, number of adolescent patients, and data availability at these

facilities. This information was used to select facilities for inclusion in the study.

Stage 1b: Health facilities sampling. Using information on clinic mapping from Stage 1a, 32 facilities were included based on the criteria of providing care for at least five adolescent patients living with HIV, having a register with records of patients lost to follow-up, and being government-run. These facilities were distributed across four size groups: 10 facilities with 5-9 adolescents on treatment, 10 facilities with 10-19 adolescents on treatment, and 10 facilities with 20-60 adolescents on treatment. The remaining two facilities (Cecilia Makiwane and Frere Hospitals) provide treatment for more than 300 adolescents each and, therefore, were included in a fourth group. At these 32 facilities, the research team found that many of the adolescents on facility lists were no longer receiving care at these facilities because they had been down-referred to other clinics. Through tracing these participants to their down-referred clinics, an additional 20 clinics (with at least five adolescent participants in care) were added to the Mzantsi Wakho study, bringing the total number of healthcare facilities to 52.

Stage 2a: Roster of eligible participants. Based on clinic records from the past three years, all adolescents (10-19 years old) who had ever initiated ART or been on treatment in these facilities were approached for voluntary participation in the study. Patients were eligible for inclusion in Mzantsi Wakho even if they had defaulted or were lost to follow-up. Inclusion of this group of adolescents living with HIV minimises potential bias towards adolescents more engaged in the HIV care system (Nachega et al., 2009; Lowenthal et al., 2012; Bakanda et al., 2011). Prior to Mzantsi Wakho, no known studies of adolescent ART adherence had

included this group.

Government approval from the Department of Health was given to access public clinics and hospitals, including clinical records from these facilities. Healthcare workers at the facilities were informed of the researchers' presence and purpose in the facilities, and they were encouraged to ask questions or make recommendations.

Participant recruitment for the quantitative study in clinics was conducted by research assistants. Adolescents who presented for treatment at the ARV, women's health, outpatient, and trauma clinics of healthcare facilities were approached with information about the study and a request to participate if interested. Section 7 of this chapter provides further clarification on the processes of obtaining assent and consent.

Stage 2b: Community tracing of community controls. Interviewing only adolescents living with HIV could potentially stigmatise adolescents in the community or cause unintended disclosure, given the high level of visibility in the included communities. To avoid these risks to participants, an additional 446 HIV-negative adolescents were recruited as a sub-sample that acted as "community controls." These adolescents were co-residing with participants or living in neighbouring homes. Because these adolescents were HIV-negative, they were given a version of the participant questionnaire that did not include items on HIV-related illnesses or ARVs. Given the high level of stigma towards HIV/AIDS-affected people in South Africa and low levels of disclosure among adolescents, recruitment did not use sampling approaches like respondent-driven sampling that could have led to unintentional disclosure or stigmatisation. Additionally, the study

was presented in the community as a general investigation into health and social service access for adolescents (Deacon and Stephney, 2007; Skinner and Mfecane, 2004; Petersen et al., 2010; Ferrand et al., 2009). Section 7 of this chapter provides further description of ethical considerations in the research design.

Inclusion and exclusion criteria for quantitative study

Participants were eligible for the quantitative arm of Mzantsi Wakho if

1. They were between the ages of 10-19 years at baseline;
2. They had ever been initiated on ART; and
3. If they were below 18 years old, they and their caregiver gave written, informed, and voluntary consent. If they were 18 years or older, they provided informed and voluntary consent.

Final sample for Mzantsi Wakho quantitative study

At baseline, the final sample comprised a total of 1526 adolescents (1080 adolescents living with HIV), who were receiving care across 52 government healthcare facilities. These healthcare facilities include 9 hospitals, 5 community health centres, and 38 primary care clinics. A total of 65% of the participants received care at peri-urban or urban facilities, while 35% received care at rural facilities.

The 1080 adolescents living with HIV who were interviewed at baseline comprised 90.1% of the eligible sample of ART-initiated adolescents. Among excluded but eligible adolescents, 4.1% refused (by caregiver or adolescent), 3.7% could not be traced, 0.9% were excluded due to severe cognitive impairment, and 1.2% were excluded for other reasons.

Further sociodemographic details about the sample of ALHIV are provided in Section 6 of this chapter. This candidate's doctoral research was based on analyses only among those living with HIV. After baseline, adolescents who had consented to be re-approached were interviewed for follow-up at a second study wave (94% retention). Retention between baseline and the third, final study wave was 93.5%. By the final wave of the study, 3.3% of the baseline cohort had passed away.

By February 2018, the clinic-based research staff completed follow-up patient file extraction from all included facilities. These clinical records over 3 years (2014-2017) provide information about the participants' viral loads, CD4 cell counts, ARV regimens, loss to follow-up in care, and mortality. Quality of clinical records ranged from poor to excellent, with significant variation across facilities and across patients.

Figure 9. Homes in a rural area near Keiskammahoek, Eastern Cape

Source: DPhil candidate

5. Mzantsi Wakho Quantitative Data Collection

The Mzantsi Wakho quantitative data collection process included (1) participant interviews, (2) clinical records of health outcomes from patient files, and (3) clinic-level questionnaires.

Participant-level questionnaire

The participant-level questionnaire explored information about individual-, family and community-, and structural-level factors in participants' lives. These factors ranged from personal mental health and beliefs to relationships with peers to social protection and economic factors. The participant-level questionnaire for Mzantsi Wakho was developed in extensive consultation with various stakeholders to ensure acceptability and validity of questions in the survey. These included AIDS-affected adolescents and 20 experts in the field of adolescent health. Where applicable, measures use tools validated in Southern Africa, and all measures were piloted prior to use (Boyes and Cluver, 2013; Boyes et al., 2012; Boyes et al., 2013). The final drafts of questionnaires and consent forms were translated and back-translated into Xhosa to ensure cultural equivalence of terms used. After finalisation of items, native speakers of each language (English and Xhosa) recorded audio tracks that accompanied each question to account for low literacy among participants (Dolezal et al., 2012; Jones, 2003).

Digital tablets were provided to participants for completing the questionnaire. Trained community-based research assistants sat with the adolescents to demonstrate how to use the tablet properly and guided the participant when necessary. Participants were then offered the opportunity to complete the questionnaire autonomously in the language of their choice. The

tablet-based questionnaire included youth-friendly graphics and interactive games to encourage greater acceptability and completion. The names and contact details of participants are not included in the questionnaire, as each individual is only identified through a unique study participant ID. Thus, during data collation, confidentiality of the participant was maintained—except when participants were facing significant risk of harm or requested assistance themselves. Further ethical considerations for these exceptional circumstances are provided in Section 7 of this chapter.

Multiple studies using mobile devices have reported that this method allows for more truthful answers and greater confidentiality, particularly in the context of stigmatised behaviours (Gorbach et al., 2013; Malotte et al., 2011; Jaspan et al., 2007). One study among students in South Africa reported that most students perceived electronic questionnaires to be a more confidential method of answering sex-related questions, compared to paper-based questionnaires (Mukoma et al., 2004).

The final version of the questionnaire for ALHIV who were aware of their status consisted of 427 questions. However, skip patterns that were written into the programming of the electronic questionnaire removed non-applicable questions automatically. The questionnaire was composed of 12 sections, each of which was based on a different theme relevant to adolescent lifestyles (Appendix 4C). Thus, the questionnaire captured information about health outcomes (including ART adherence and sexual and reproductive health) and individual-, family- and community-, and structural-level factors that may influence these outcomes.

Because not all participants living with HIV were aware of their status, a separate version of the questionnaire was provided to adolescents suspected of being unaware. For those adolescents unaware of their status, HIV/AIDS and ARVs were never specifically mentioned. Instead, in sections about medicines-taking, the items referred to general illness and non-specific medications. Using this version of the questionnaire for participants unaware of their HIV status was essential for respecting the confidentiality of the adolescents and their caregivers.

Clinical records

At all 52 healthcare facilities included in the study, the clinic research team recorded information for all participants for whom patient files were available at that facility. By looking for *all* participants at *all* facilities, this clinic-based data collection approach was able to evaluate participants' health, as recorded across multiple facilities. This data collection approach was selected because of the high degree of inter-facility mobility within this population and the lack of unique patient IDs in South Africa's public healthcare system. Patients' inter-facility mobility could reflect either simultaneous care from multiple facilities or linear transfers of care from one facility to another. This intensive data collection approach allowed for the linkage of individual patients across multiple facilities, including instances of unofficial, unrecorded ("silent") care transfers initiated by the patient. This approach also enabled the clinical dataset to include participants who may have seroconverted during the study period.

To identify available clinical records at each facility, the research staff searched individually for every Mzantsi Wakho participant on each facility's register of ART patients. Research assistants searched for common alternate

spellings of participants' names as well, under the supervision of the facility data capturer. When a participant was listed on that facility's patient register, the research staff searched for the adolescent's physical patient file. Research staff also searched for all Mzantsi Wakho participants on each facility's electronic record database (Tier.net). In South Africa's public healthcare facilities, Tier.net is an electronic database that includes information on patients' viral load and CD4 test results, among other laboratory tests. This database is not linked across facilities and is generally on a single computer in each facility, containing health records from that facility only. Searching on Tier.net allowed for the identification of any test results that were not yet in the participant's physical patient file and of any files that were physically missing but available electronically. In several healthcare facilities, Tier.net was unavailable due to the lack of a functional computer or inability to access the database.

Data were extracted using a standardised questionnaire, according to a protocol previously applied in other studies of ART-initiated adolescents and adapted to the patient file system in the included healthcare facilities (Nglazi et al., 2012). Data were extracted from patient files at baseline (for records through December 2015), and the second round of patient file extraction (for January 2016-December 2017 records) was completed by February 2018.

Figure 10. Clinic-based research assistants extracting clinical records from adolescents' patient files in Cecilia Makiwane Hospital

Source: DPhil candidate

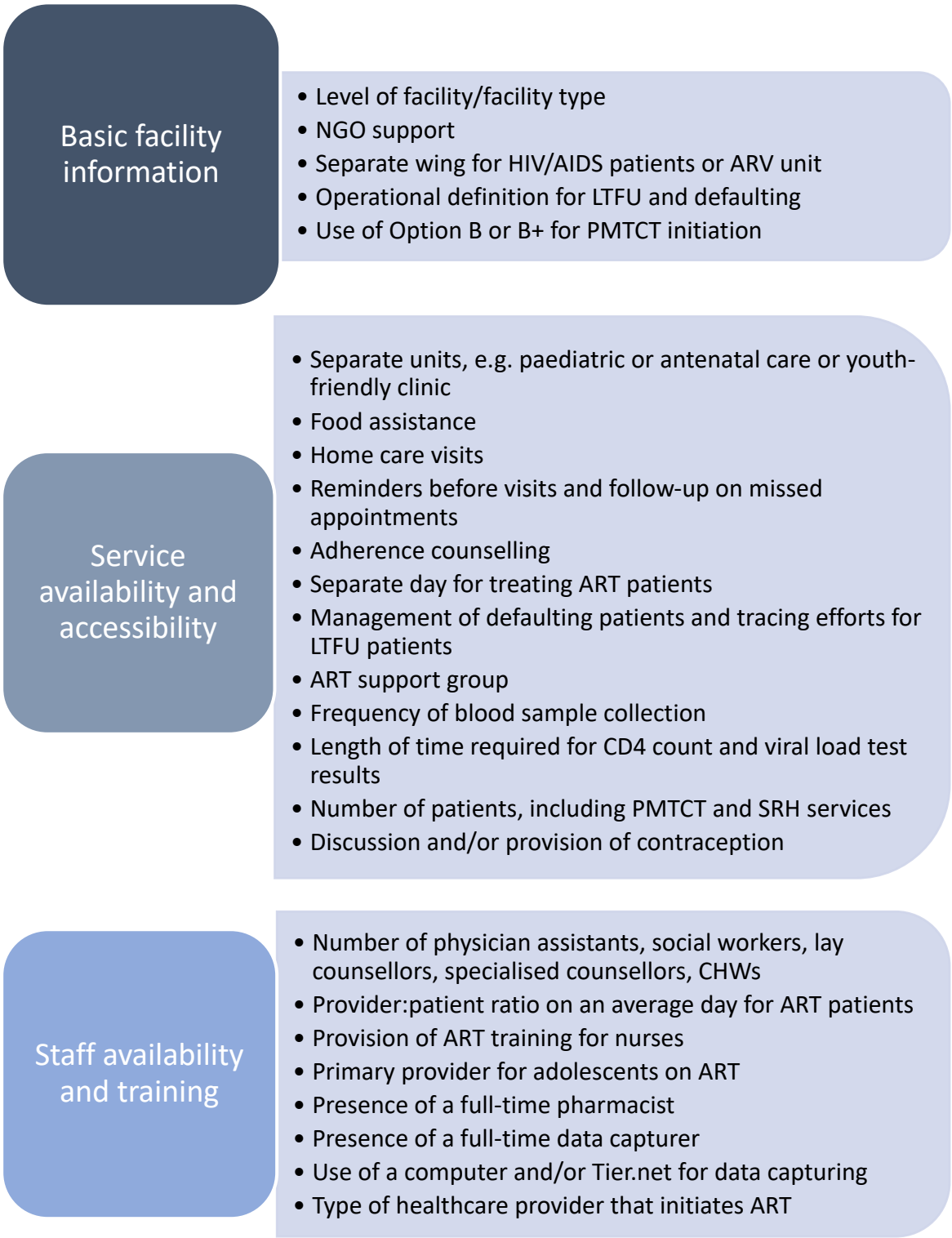
Clinic-level questionnaire

A systematic review on factors affecting ART adherence and access to HIV care among adolescents in low- and middle-income countries indicated that a series of clinic-level factors may affect both adherence and access to care (Hudelson and Cluver, 2015). Therefore, the Mzantsi Wakho research team, including this candidate, developed a semi-structured clinic-level questionnaire that was delivered by the Senior Clinic Researcher at every healthcare facility included in the study. The Senior Clinic Researcher completed the questionnaire with healthcare facility staff—including facility directors, heads of individual care units, physicians, nurses, and data capturers—in order to create a facility-level "profile" for each facility.

The semi-structured interview consisted of 87 questions across 8 sections, and an overview of the factors evaluated by the clinic-level questionnaire is provided in Figure 11. These factors were explored through a combination of

multiple-choice and open-ended questions. Interviewed staff were also given the opportunity to further clarify responses to multiple-choice questions, and these details were also recorded in the clinic-level questionnaires.

Figure 11. Service-level factors assessed in Mzantsi Wakho clinic-level questionnaires



ARV, Antiretroviral; ART, Antiretroviral therapy; CHW, Community health worker; LTFU, Loss to follow-up; NGO, Non-governmental organisation; PMTCT, Prevention of mother-to-child transmission; SRH, Sexual and reproductive health

6. Methods Specific to this Dissertation

Overview

This candidate's dissertation constitutes a sub-study within the larger Mzantsi Wakho project described in this chapter. The first research aim of this thesis is addressed through a systematic review. The second and third research aims are addressed through analyses of primary data from the Mzantsi Wakho cohort.

Study sample

Because this dissertation explores health outcomes and experiences for ART-initiated adolescents, analyses only included Mzantsi Wakho participants living with HIV (n=1080). At baseline, 57% of this cohort were 10-14 years old, and 43% were 15-19 years old. Participants in this sample lived in both urban/peri-urban (77%) and rural areas (23%). Female participants made up 55% of the sample, and almost all (96%) of the sample's first language was Xhosa. Only 68% of participants were aware of their HIV status at baseline. Additionally, at baseline, 38.2% of participants reported that they mostly received care at primary care clinics, 24.2% at community health centres, and 36.5% at hospitals.

Quantitative data measures

An overview of the three datasets comprising the quantitative arm of the Mzantsi Wakho study is provided in Figure 12. For each adolescent participant, three sources of quantitative data relevant to their health and health-seeking behaviours were obtained: (1) Participant-level questionnaires – Interviews with the adolescents; (2) Clinical records – Extraction of clinical records from paper-based and electronic records across 52 healthcare facilities; and (3) Clinic-level

questionnaires – Semi-structured interviews with healthcare facility staff at included healthcare facilities. The time periods covered by these three quantitative datasets are outlined in Figure 13.

The research undertaken by this candidate and presented in this dissertation draws from the adolescent participants' clinical records and clinic-level questionnaires conducted with healthcare staff at facilities attended by them. As discussed in Chapter 1.2, this candidate designed the data collection tools and implemented the data collection strategy for these two datasets in field in the Eastern Cape as well. For this dissertation, only key sociodemographic and HIV-related factors were obtained from the participant-level questionnaires as covariates in analyses (e.g. age, rural/urban residence, mode of infection).

Figure 12. Overview of Mzantsi Wakho quantitative datasets

Datasets analysed by this candidate for the present dissertation are colour-coded in red and highlighted within the red box.

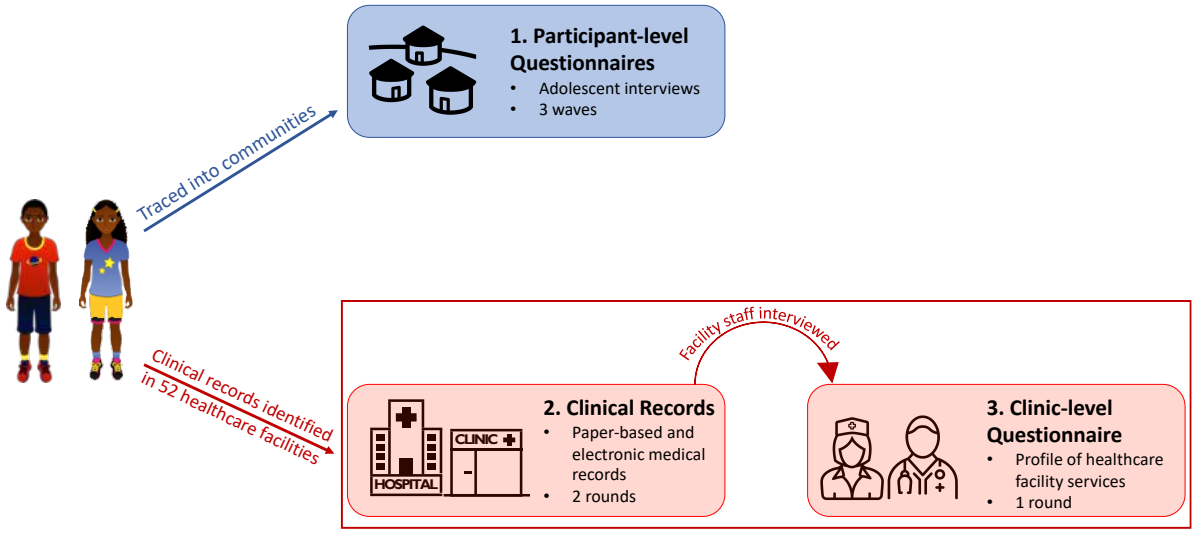
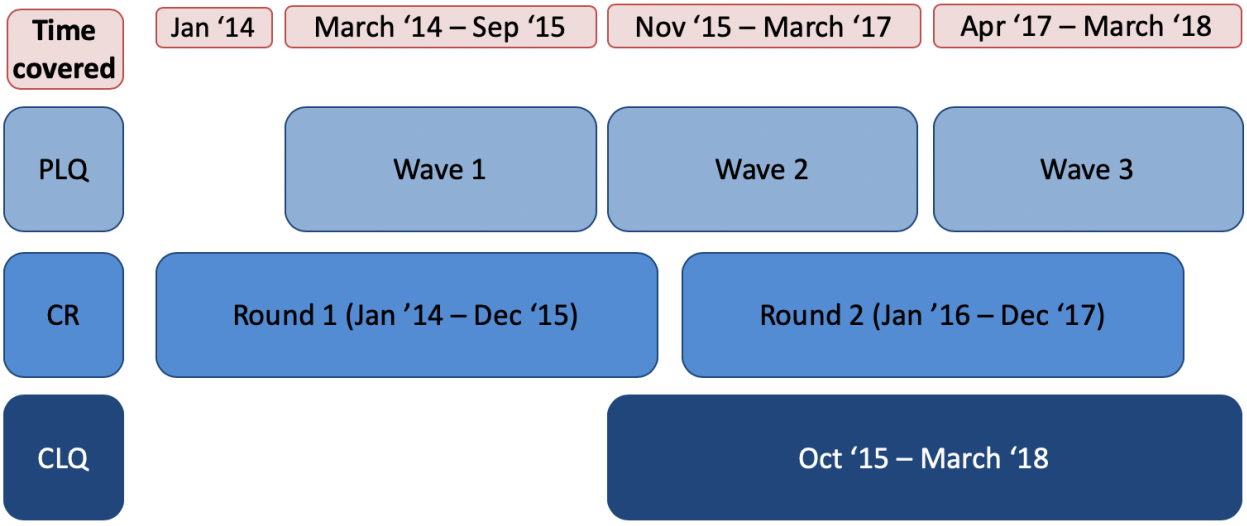


Figure 13. Time periods of data coverage for Mzantsi Wakho quantitative datasets



PLQ, Participant-level questionnaire; CR, Clinical records; CLQ, Clinic-level questionnaire

Sociodemographic characteristics

Sociodemographic characteristics including age, sex, and urban/rural residence were measured in the participant-level questionnaire by items adapted from the South African census (Statistics South Africa, 2012).

Health-related outcomes

Health-related outcomes were obtained from both clinical records and participant-level questionnaires (study Waves 1-3).

At each round of patient file extraction, extracted data included the following: date of opening patient file at the specific facility, date of first visit to the facility, ART start date at the facility, first CD4 count recorded at the facility, first viral load recorded at the facility, first WHO stage recorded at the facility, most recent CD4 count recorded at the facility (through time of data collection), most recent viral load recorded at the facility, most recent WHO stage recorded at the facility, current ART medication (at time of data collection), and, where relevant, reason for patient disengagement from care at the current facility at time of data collection (transfer to new facility, loss to follow-up, mortality, or lost file).

In Round 1 of clinical data collection, extracted data from clinical records included clinical records from participants' first visit at the facility and records from their most recent visit through December 2015. In Round 2 at the same facility, extracted data were the participants' most recent records through December 2017. If the participant had transferred to the facility after 2015, first visit records at that facility were extracted in Round 2 as well. Hence, for a given facility, participants could have a maximum of three visits' records (including viral load and CD4 count), assuming no missing data. However, if a participant attended multiple care facilities, the multiple corresponding clinical records could generate more than three visit records.

Mortality outcomes were also ascertained through community tracing for follow-up interviews through March 2018. For instance, research assistants returning for a follow-up interview in the third study wave may have learned from community members that the participant had passed away, even if this had not been reported in clinical records.

Mode of HIV infection was determined using an algorithm beginning with participants' age at ART initiation (≤10 years old), following existing sub-Saharan African paediatric cohorts, and then following a branching structure (He et al., 2018). This branching structure validated the initial assessment of mode of infection against social, health, and clinical factors associated with each mode, including self-reported sexual history and parental deaths. The items to determine mode of infection were drawn from the self-reported participant-level questionnaire.

Clinic-based experiences and services

Availability and uptake of healthcare services were assessed by the clinic-level questionnaires. Items in the clinic-level questionnaire gather information about the type of facility (i.e. primary clinic, community health centre, district hospital, or provincial hospital), type of care (i.e. paediatric, adult, or generalised), availability of NGO support and the roles that they fulfil, the types and numbers of non-clinicians providing support, number and frequency of staff trainings on nurse-initiated and -managed antiretroviral treatment (NIMART), and the types of care providers (e.g. doctor vs. nurse) who administer ART. Open-ended questions include further explanations of how the facility provides differentiated care for different patient groups (e.g. separate ARV or youth care units), protocols for transferring adolescent patients to and from other facilities, clarification of how they provide "youth-friendly" services (if indicated), and average provider-to-patient ratios during the week.

This information is also complemented by participants' self-reported experiences with clinical services, based on responses to the participant-level questionnaire. Items in the participant-level questionnaire explore accessibility, affordability, and acceptability of services. Interactions with healthcare providers are assessed in the participant-level questionnaire using 12 questions piloted with the Teen Advisory Group, based on items from the PREPARE trial and previous qualitative findings from adolescents living with HIV in sub-Saharan Africa (Busza, 2011; Obare et al., 2012). Although these items were not explored in depth for this dissertation, this candidate plans to evaluate the effect of these patient-level factors on health outcomes in future post-doctoral research, as further described in Chapter 8.6.

Data management and storage

Data quality was ensured through rigorous training of research staff and through pre-set codes in the tablet-based electronic questionnaire for data entry that did not allow for illogical responses. Spot-checking of data was done in parallel with data collection as data were validated regularly on a weekly basis before final submission to a server. Data cleaning was conducted at the end of each year of data collection. All collected data were automatically uploaded to a secure server through an open-source software platform—Open Data Kit (www.opendatakit.org)—which was anonymised prior to data analysis to ensure participant confidentiality. Regular backups of data ensured that the database was safe, and the server was accessible by a password known only by the project management team.

The longitudinal dataset for participant-level questionnaires (Waves 1-3) was created in STATA, and the clinic-level questionnaire dataset was created in SPSS. The clinical record database was built in R software, using the same unique identifiers as the STATA and SPSS databases. Participants' unique study IDs have been coded so that only researchers can access identifiable information, using a study master list available only to the study investigators and project managers. No potentially individual-identifying information is disclosed in reports, publications, or presentations.

Figure 14. Mzantsi Wakho's clinic-based research assistants at the project office in King William's Town

Source: DPhil candidate

7. Ethical considerations

Ethical and regulatory compliance

The ethical guidelines for this study were informed by a number of sources. These included on-going academic debates on informed consent and confidentiality, ethical requirements of the universities and research institutions involved in the research design, and ethical guidelines from psychological research bodies such as the British Psychological Society (Morrow and Richards, 1996; The British Psychological Society, 2009).

In planning the study design and ethical protocols, key research guidelines and legislation in South Africa were considered, including the Ethics in Health Research Guidelines (2004), Guidelines for Good Clinical Practice in South Africa

(2006), the Open Society Foundation for South Africa's "Best Practice Guide to HIV Disclosure" (2009), the AIDS Law Project's "HIV and the Law: A Resource Manual" (Barrett-Grant, 2003), "Selected ethical-legal norms in child and adolescent HIV prevention research: Consent, confidentiality and mandatory reporting" (Strode and Slack, 2012), the National Health Act 61 of 2003 (enforced starting 2012), the Children's Act 38 (2005), the Children's Amendment Act 41 (2007), and the Sexual Offences Act 32 (2007). These South Africa-specific documents were supplemented by international guidelines, such as the WHO's Guidelines on HIV Disclosure and Counselling for Children up to 12 Years of Age (2011) and the Helsinki Declaration (World Medical Association, 2001).

Process of obtaining informed assent and consent

Information sheets and consent forms were given to potential participants and their caregivers by members of the fieldwork team. These forms were read to participants in their preferred language to prevent poor literacy from limiting participants' understanding of the methods and purpose of the study. All participants were told that they had the right to decline to participate or exit the study at any time. They were also informed that all findings would remain confidential. Written informed consent was obtained from each participant in this study. Avoidance of study participation was understood as a lack or withdrawal of consent. Participants could consent to participate only after having the information sheet read to them and having been given an opportunity to ask questions in their preferred language.

Consent for adolescents to participate

In order to ensure fully informed voluntary consent for adolescent participants, if

participants were illiterate, they had to provide verbal consent and indicate this consent with a cross on the signature line. The adolescent was asked for consent to participate only after the purpose of the study and the format of the interview had been explained. Particular attention was given to issues surrounding statutory requirements to break confidentiality (i.e. if the adolescent or a member of their household is at significant risk).

All attempts were made to ensure that the research was a positive and participatory experience for all participants and that consent was both voluntary and informed. If the participants had sensory difficulties, the research team ensured they could access the questions. For example, a signer would sign the questions to deaf adolescents. The audio recording of questions in the audio computer-assisted self-interviewing (ACASI) tool ensured that blind adolescents could participate with the help of research assistants.

To ensure that children and adolescents did not feel obliged to participate in the research, emphasis was placed on their ability to refuse to participate at any point during the research. All research materials were provided in English and Xhosa.

Legal guardian consent for adolescent participation

The following process was applicable only to adolescents under the age of 18. Adolescents ≥18 years old were treated as adults with respect to issues of informed consent in compliance with previously cited regulations.

For adolescents <18 years old, caregivers were also required to provide consent for participation in the study, and they were provided with information describing the study in their preferred language. The National Technical Working

Group for Paediatric and Adolescent Health defines a caregiver as anyone who is primarily responsible for the care of a child and, according to the South Africa Child Health Act, may include:

- Grandmothers, aunts, and other relatives;
- A foster parent;
- A child (16 years and older) heading a household (child-headed household); or
- A Child and Youth Care Worker supporting a child without family care in the community.

Mzantsi Wakho team members consulted colleagues at the University of Cape Town Health Sciences Research Ethics Committee, the University of Witwatersrand, and social workers at Cape Town Child Welfare for guidance on ethical protocols. The team also consulted South African legislation, particularly the Ethics in Health Research Guidelines (2004). The ethics processes and procedures proposed in this research project were reviewed and approved by the following ethics committees and institutions:

1. I-DREC of the Social Sciences and Humanities Division, University of Oxford (Ref No: SSD/CUREC2/12-21) – Appendix 1A.
2. Centre for Social Science Research, University of Cape Town (CSSR2013/04) – Appendix 1B.
3. Eastern Cape Department of Health – Appendix 1C.
4. Eastern Cape Department of Basic Education– Appendix 1E.

In some exceptional circumstances related to HIV/AIDS vulnerability, the

adolescent may wish to participate, but the legal guardian may be unavailable (through death, living away and not contactable, or being too sick to give consent). In these cases, adolescents had the option to nominate another adult whom they trusted in the place of a guardian, such as a grandmother or social worker. These circumstances included adolescents in child-headed households and adolescents whose primary caregiver was experiencing severe AIDS-related dementia. Adolescents could also nominate an alternative adult to give consent in place of their primary caregiver if asking for legal caregiver consent would result in involuntary disclosure of their HIV status.

Where the adolescent stated that his or her caregiver would not consent to their participation in the study—due to fear that abuse of the adolescent would be revealed—researchers asked the adolescent to identify another trusted adult who would be able to consent to their participation. Researchers subsequently made social services referrals for all children and adolescents in abusive situations. In the total cohort, 94 referrals were made to the relevant health or social services (Cluver et al., 2018).

The research team understood to not take advantage of this concession in order to sidestep caregiver consent. This protocol for seeking consent was only used for this specific subset of children and adolescents. Any adolescent who declined to participate before or after the interviewer had explained the project was not interviewed, even if the legal guardian or nominated adult had consented or encouraged participation.

Ethical compliance for clinic-based research

Consent to extract clinical information from participants' clinical records was also

included in the consent agreement for participating in the Mzantsi Wakho study. Data from clinical records were linked to adolescents' interviews using anonymous unique study IDs, which protect participant confidentiality. As part of ethical approval from the Eastern Cape Department of Health, Mzantsi Wakho provided updates on project findings to the provincial department every three months. In addition to provincial approval, the clinic-based research team obtained approval of the clinic operational manager at each facility before beginning data extraction. The clinic-based research assistants received instruction and guidance on where to find physical patient files from clinic staff, usually nurses or data capturers. Additionally, the clinic-based research assistants accessed Tier.Net only under the supervision of the facility's data capturer, who entered the password to access electronic clinical records and then assisted the clinic-based team to ensure appropriate and safe use of clinical records, according to facility protocol.

Risks and benefits to participants

Because study participants were as young as 10 years old and the interviewers (research assistants) were adults, this study context presented a significant power inequality, which was sensitively and carefully considered. Building trust and rapport with participants during data collection, data analysis, and reporting of the study are all essential in generating high-quality data and research findings. When fieldworkers were employed and trained for the study, attention was focused on unequal power relations and how to reduce the impact on adolescents. However, it is also important to recognise that, in a positive and youth-centred research environment, adolescents may have benefitted from the opportunity to interact

with adult facilitators, even though data were collected primarily through digital tablets. In order to reduce any risk of participants becoming distressed during the interview, guidelines were developed for research assistants.

Participants had an opportunity to share their experiences and concerns with trusted adults and to access referrals where necessary. Where possible, the research project assisted adolescents in accessing health and social services. Given the network of partners and collaborators as well as the objectives of this research project, participants' responses will be used to inform health policy and programming for youth at local, national and regional levels. Health facilities and organisations participating in the study receive specific (though anonymous) feedback about the experiences of their young clients, with the aim of improving service provision.

Privacy and confidentiality

Participants chose the time, location, and nature of their engagement with the research team. The use of digital tablets increased the privacy and confidentiality of the answers given by participants by ensuring that fieldworkers did not see answers unless the participant chose to share them. The cell phone number made available in recruiting material was accessible only to the research team. If participants left a free "please call me" text message, only the research team contacted them. Should participants have shared their contact details with researchers, this information was kept confidential.

Reimbursement for participation

All participants were given snacks while participating in structured research

activities as well as participant packs containing useful items such as toothbrushes and socks for school uniforms. Additionally, all participants received a Certificate of Participation. Adolescents who refused to participate or who stopped the interview still received snacks and certificates. Participants chose the site of their interviews to avoid unnecessary transport or child-minding costs, but, if they chose to travel for the purpose of maintaining privacy, they were reimbursed for travel costs.

Financial rewards were not provided to participants for two primary reasons: (1) In some cases, financial incentives can lead to conflicts within the community or household, and (2) To prevent adolescents from agreeing to participate in the study in order to gain compensation, which would undermine the voluntary nature of consent.

Community engagement and fieldwork challenges

In practice, obtaining informed consent from adolescent participants and their caregivers was deeply intertwined with building and maintaining trust within their communities. Prior to interviewing adolescents at baseline, senior research assistants and project managers “opened” communities by introducing the study to gatekeepers such as ward councillors and community leaders and addressing any questions or concerns. Prior to re-entry into communities for both follow-up waves of adolescent interviews, community leaders were re-approached. These follow-up meetings also included presentation of preliminary findings (focusing on non-HIV-specific topics like general access to healthcare and experiences in schools and the community) and updates on dissemination and policy impact.

These meetings and regular feedback were crucial for establishing goodwill between the Mzantsi Wakho research project and the community.

For instance, during this candidate's fieldwork, a rumour began circulating in some townships that a European research project was harvesting blood from children in the community with unknown intentions. Although Mzantsi Wakho was not collecting any biological specimens and was known to the community by this point, the stigma and fear surrounding foreign research projects also affected perception of the study in these townships. To address this challenge, this candidate and assistant project managers met with ward councillors to reassure them of the project's intentions and to establish a plan for allaying community fears. Ward councillors reached out to their communities, and research assistants used less distinguishable vehicles for entering these townships. Within two weeks, these fears were dispelled. Individual participants and caregivers with concerns were also further reassured about the intent of Mzantsi Wakho and how the data would be anonymised. This ongoing process of maintaining community trust underscored the importance of having recruited study staff from the same communities as adolescent participants, as they both had greater familiarity with community structures and were not perceived as extractive foreign researchers.

An additional consequence of recruiting research staff from the study setting was the connection between research assistants and some study participants. Through the longitudinal study design of Mzantsi Wakho, adolescents were typically re-interviewed by the same research assistant when possible. Although research assistants were instructed to not offer counselling or social support—as they were not trained counsellors or social workers—some

adolescents experienced this longitudinal connection as a form of social support. A few adolescents remained in contact with research staff throughout the year, but these cases were the exception to the rule. However, a more likely systemic impact of this unique relationship with the community was the high rate of retention across all three waves of adolescent interviews.

As previously discussed, direct intervention by research staff was only done in cases where non-intervention would have been ethically negligent. If research assistants identified an urgent need for adolescents to access more extensive support, referrals were made by the project on a case-by-case basis with the participant's consent. These cases included situations such as the following: (1) sexual assault within the past few days that required immediate referral to healthcare facility to receive post-exposure prophylaxis for prevention of HIV infection; (2) adolescent disclosure of severe physical, emotional, or sexual abuse by a household member; (3) adolescent disclosure of recent suicide attempts or acute suicidal ideation; and (4) severe and acute illness requiring immediate medical attention. Across these situations, referrals were made to the appropriate mental health counsellors, social workers, or healthcare facility staff, with initial provision of transport to these services.

5. DPhil Paper 2: The extended HIV care cascade for adolescents initiated on antiretroviral therapy in a health district of South Africa: an observational cohort study

This is the first empirical paper of this dissertation, based on analysis of primary data. It evaluates adolescent progression along an extended HIV care cascade from ART initiation to viral suppression in the decentralised public HIV care system of South Africa. This paper is currently under review in BMC Infectious Diseases.

Objectives: (1) To evaluate progression through an extended HIV care cascade across public healthcare facilities in South Africa for a large cohort of ART-initiated adolescents and (2) to identify predictors of attaining cascade steps

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Statement of Authorship
I confirm that I completed the majority of the work in this study (>70%). I conceptualised and led the quantitative assessment of adolescents' clinical records in the Mzantsi Wakho study. I co-designed the study measures with Elona Toska and Lucie Cluver, and I led the quantitative data collection process, including data cleaning. I conducted all analyses reported in this manuscript and drafted the first version of this article. Nontuthuzelo Bungane contributed to the implementation of the data collection strategy. Elona Toska contributed to the development of the research question and interpretation of findings. Elona Toska and Lucie Cluver also suggested further analysis refinements. All co-authors further contributed to the finalisation of the manuscript.

Abstract

Background

Little evidence exists to comprehensively estimate adolescent viral suppression after initiation on antiretroviral therapy in sub-Saharan Africa. This study examines adolescent progression along an extended HIV care cascade to viral suppression for adolescents initiated on antiretroviral therapy in South Africa.

Methods

All adolescents ever initiated on antiretroviral therapy (n=1080) by 2015 in a health district of the Eastern Cape, South Africa, were interviewed in 2014-2015. Clinical records were extracted from 52 healthcare facilities through December 2017 (including records in multiple facilities). Mortality and loss to follow-up rates were corrected for care transfers. Predictors of progression through the extended care cascade were tested using sequential multivariable logistic regressions. Predicted probabilities for the effects of significant predictors were estimated by sex and mode of infection.

Results

Corrected mortality and loss to follow-up rates were 3.3% and 16.9%, respectively. Among adolescents with clinical records, 92.3% had ≥1 viral load, but only 51.1% of viral loads were from the past 12 months. Adolescents on ART for ≥2 years (AOR 3.42 [95%CI 2.14-5.47], $p<0.001$) and who experienced decentralised care (AOR 1.39 [95%CI 1.06-1.83], $p=0.018$) were more likely to have a recent viral load. The average effect of decentralised care on recent viral load was greater for female (AOR 2.39 [95%CI 1.29-4.43], $p=0.006$) and sexually infected adolescents (AOR 3.48 [95%CI 1.04-11.65], $p=0.043$). Of the total cohort,

47.5% were recorded as fully virally suppressed at most recent test. Only 23.2% were recorded as fully virally suppressed within the past 12 months. Younger adolescents (AOR 1.39 [95%CI 1.06-1.82], *p*=0.017) and those on ART for ≥2 years (AOR 1.70 [95%CI 1.12-2.58], *p*=0.013) were more likely to be fully viral suppressed.

Conclusions

Viral load recording and viral suppression rates remain low for ART-initiated adolescents in South Africa. Improved outcomes for this population require stronger engagement in care and viral load monitoring.

Background

The expansion of access to antiretroviral therapy (ART) has enabled more children vertically infected with HIV to survive into adolescence (UNAIDS, 2015a). In parallel, the high rate of new HIV infections through sexual transmission among youth has contributed to a growing population of adolescents living with HIV. Of the estimated 2.1 million adolescents living with HIV, 85% reside in sub-Saharan Africa (UNAIDS, 2017b; UNAIDS, 2017a; UNAIDS, 2015a). Concern about the growing population of adolescents requiring lifelong ART has drawn increasing global attention to the need to better monitor this key population and to tailor treatment services (Slogrove and Sohn, 2018; UNAIDS, 2015a).

Previous studies have demonstrated that, even on treatment, adolescents exhibit the worst health outcomes compared to all other age groups (UNAIDS, 2017b; Adejumo et al., 2015). In South Africa, which houses the world's largest ART programme, adolescents have repeatedly demonstrated the lowest rates of retention in care and viral suppression compared to other age groups (Zanoni et al., 2016). The HIV care cascade has been widely used among various patient populations to identify progress at critical stages along the continuum of care from HIV testing to ART initiation and viral suppression (MacCarthy et al., 2015). This tool allows for both the monitoring of health and identification of key gaps in care that can be targeted by interventions in alignment with the UNAIDS 90-90-90 treatment target for 2020 (UNAIDS, 2014a; Jose et al., 2018).

Although progress along the HIV care cascade has been well documented globally for adults and adult key populations, less evidence exists for adolescents living with HIV (Zanoni et al., 2016; Jose et al., 2018; MacCarthy et al., 2015). A

recent retrospective analysis of individually linked records from South Africa's National Health Laboratory Service database estimated that 66% of older adolescents (15-19 years old) had initiated ART by 2016 (Maskew et al., 2019). While the study provides a robust estimate for the second cascade step of ART initiation, it does not extend analyses to evaluate rates of viral suppression for the third target in the care cascade.

In South Africa, one systematic review of data from youth living with HIV estimated that only 10% were virally suppressed as of 2013, before implementation of universal test and treat in 2016 (Zanoni et al., 2016). However, the review estimated viral suppression using rates reported for patients aged 9-29, well beyond the window of adolescence (Southern African HIV Clinicians Society, 2017). Similarly, the 2017 South African National HIV Prevalence, Incidence, Behaviour, and Communication Survey estimated viral suppression for youths aged 15-24, with no discrete data for all adolescents aged 10-19 (Human Sciences Research Council, 2019). This lack of disaggregated data for adolescents limits the applicability of findings for this key population (Slogrove and Sohn, 2018). Furthermore, viral suppression in the survey was calculated by active collection and testing of blood samples, not evaluation of clinical records that would be available to healthcare providers. Research is urgently required to understand the *current* reality of adolescent HIV care progression to the final cascade step of viral suppression in South Africa, in contexts beyond well-resourced clinics or urban centres (Wong et al., 2017).

In this study, we evaluate the progression of ART-initiated adolescents to viral suppression along an extended HIV care cascade in South Africa, including

operational outcomes as well as mortality and retention in care, using data through 2017 from multiple healthcare facilities within South Africa's decentralised public healthcare system. In addition, we report associations between stages of the cascade and adolescents' sociodemographic and treatment-related characteristics.

Methods

Participants and Procedures

This study used a longitudinal prospective cohort design to analyse data from clinical records and interviews with ART-initiated adolescents in rural, peri-urban, and urban locations of a health district in the Eastern Cape, South Africa. The healthcare system of this region is characterised by high HIV and TB burden, limited infrastructure, and significant human resource challenges (Massyn et al., 2017). Study recruitment took place from March 2014 to September 2015, as described elsewhere (Cluver et al., 2018). All healthcare facilities within the sub-district that provided ART to at least five adolescents were included in the study (n=52, including 8 hospital wards, 5 community health centres, and 39 primary care clinics). At each healthcare facility, patient registers and clinical records were reviewed to identify all adolescents aged 10-19 years who had ever initiated ART, including those who had defaulted in care or been lost to follow up (LTFU). Adolescents identified through clinical records were traced to >180 communities and interviewed at home.

Data Collection

Clinical record review

At each healthcare facility, routine paper-based and electronic clinical records were searched for every study participant. This intensive data collection approach enables the extraction of participants' records from all included facilities where they may have received care, including undocumented silent transfers to a new facility. Data were extracted using a standardised form adapted to facilities' clinical record systems. Data were extracted in two rounds, covering records from 2014-2015 and 2016-2017 respectively, and included plasma viral load, CD4 cell count, and WHO staging.

Adolescent interviews

Participants completed tablet-based surveys in two study waves (0 and 18 months follow-up) with the support of research assistants trained in working with South African adolescents. Surveys included questions about adolescents' lifestyles, health, and health-seeking behaviours, and they were developed to be easily understandable and non-stigmatising through extensive stakeholder consultation (Cluver et al., 2018; Hodes et al., 2018). For the present analyses, self-reported data were only used to determine participants' sociodemographic and treatment-related characteristics. Further study information, including study protocol, is available at www.mzantsiwakho.org.za.

Measures

The HIV care cascade was extended by additional operational steps between ART initiation and viral suppression: availability of any clinical records, having at least one viral load recorded within clinical records, having a viral load recorded

within the past 12 months (backdated from the date of extraction), and viral suppression measured at two thresholds (HIV-1 RNA <1000 copies/mL and full viral suppression designated at HIV-1 RNA <50 copies/mL) (World Health Organization, 2016b). Viral suppression was determined using the most recent viral load available across records, including in multiple facilities. Mortality was ascertained from both clinical records and during community tracing for participant interviews through May 2018. LTFU was defined as recorded in participants' most recent clinical records, adjusted for mortality and silent transfers into care at new facilities. Silent transfers were identified when a patient re-entered care in a new facility without an official notification to the former facility of care. Participants without an available clinical record were assumed to be LTFU.

In total, seven covariates were included in analyses: (1) Age (younger adolescents aged 10-14 years vs. older adolescents aged 15-19 years); (2) sex; (3) residential location at baseline (urban vs. rural); (4) sexual vs. vertical mode of infection (determined following existing sub-Saharan African paediatric cohorts: age of ART initiation cut-off [≤10 years] (Slogrove et al., 2017), validated and updated with a detailed algorithm that considered other strong evidence (i.e. self-reported sexual history and parental death) (He et al., 2018); (5) time on ART (≥2 vs. <2 years, measured from ART initiation to date of viral load); (6) experiencing decentralised care (either exclusively at primary care clinics or experienced down-referral from a higher- to lower-level facility); and (7) mortality. For analyses of viral suppression, age at most recent viral load was binarised and used as the age covariate (10-14 vs. 15-19 years). For other outcomes, binarised age at study enrolment was used (10-14 vs. 15-19 years). Mortality was included as a

covariate only for analyses of operational outcomes (having a clinical record and having at least one viral load in clinical records).

Statistical Analysis

First, we summarised sociodemographic and treatment-related characteristics of the cohort using descriptive statistics. Second, we calculated the relevant proportion of participants who had reached each step of the extended HIV care cascade. The proportion of participants with clinical records was measured out of the total study cohort, and the proportion of participants with available viral loads was calculated relative to participants with available clinical records. The proportions of participants with viral loads recorded in the past 12 months and viral suppression were calculated relative to the number of participants with at least one recorded viral load.

Third, we tested associations between each step of the extended HIV care cascade and sociodemographic and treatment-related predictors, using a sequential multivariable logistic regression approach recommended by Hosmer and Lemeshow (Hosmer Jr et al., 2013). Variables were removed sequentially after simultaneous inclusion of all covariates in the first model: the second and third models retained only variables significant at $p<0.10$ and $p<0.05$, respectively. Final models for each extended cascade outcome were corrected for false discovery rate using the Benjamini-Hochberg step-up procedure (Hochberg, 1988). For all models, correlation matrices indicated no multicollinearity between variables. All possible two- and three-way interactive effects between covariates significant in the final model were also tested and corrected using the Benjamini-

Hochberg procedure, using the Wald test for significance. Fourth, predicted probabilities for covariates significant in the final model were estimated by sex and mode of infection (Buis, 2010). Multivariable logistic regressions and marginal probability models were performed using SPSS version 23 (IBM Corp, Armonk, NY) and STATA/SE 15.1 (StataCorp, College Station, TX), respectively.

Ethical Approval

Ethical approval was given by the University of Oxford (SSD/CUREC2/12-21) and the University of Cape Town (CSSR 2013/4), as well as the Eastern Cape Departments of Health and Basic Education and ethical review boards of participating healthcare facilities. Adolescent participants and their caregivers provided voluntary, informed, and written consent for participation, including interviews and access to clinical records. In cases of low literacy, all information and consent procedures were read aloud in the participant's preferred language. No incentives were provided, but all participants received a certificate of participation, snacks, and a small gift pack including basic items like pencils. Adolescents who refused to participate were still given snacks and certificates. To minimise risk of stigma, all publicly available materials referred to the study as one about general adolescent health in South Africa.

Results

A total 1080 ART-initiated adolescents were recruited into the study. Years of ART initiation ranged from 2000 to 2017, resulting in 6921 person-years of study follow-up. Median age at study enrolment was 13 years (IQR: 11-16 years), and

55.3% of participants were female (Table 8). Most participants were living in urban locations (76.7%) and vertically infected (74.8%). In the total cohort, mortality and corrected LTFU rates (including those without clinical records) were 3.3% (n=36) and 16.9% (n=183), respectively. Overall, 37.9% of all facility-designated LTFU patients (n=95) were found to be misclassified: 7.4% (n=7) due to unrecorded mortality, and 30.5% (n=29) from re-entry into care after silent transfer to a new facility. Clinical records only captured 33.3% (n=12) of the total deaths observed in the adolescent cohort.

Of the total adolescent cohort, 88.1% (n=951) had at least one clinical record available (Figure 15). Attending multiple care facilities was common, with 29.8% (n=283) of participants having files from at least two facilities. In total, 51.3% (n=488) experienced decentralised care.

Among those with clinical records, median age at ART initiation was 9 years (IQR: 6-12 years), and median follow-up time since ART initiation was 7.2 years (IQR: 4.7-9.8 years). At baseline on ART, the majority of adolescents were viraemic, with 72.1% reporting detectable viral loads (≥50 copies/mL) (Table 8). However, at baseline the majority were not severely immunocompromised (47.7% with CD4 ≥350 cells/mm^3) and were either asymptomatic or mildly symptomatic (41.7% at WHO Clinical Stage I/II).

Table 8. Baseline demographic and clinical characteristics of study cohort

	Number of participants, % (n=1080)
Sex	
Female	597 (55.3%)
Male	483 (44.7%)
Location	
Urban	828 (76.7%)
Rural	252 (23.3%)
Age	
Age at study enrolment (yrs, median (IQR))	13 (11-16)
Age at ART initiation (yrs, median (IQR))*	9 (6-12)
Mode of infection	
Vertically infected (n,%)	808 (74.8%)
Sexually infected (n,%)	272 (25.2%)
Year of ART initiation	
2000-2009	436 (40.4%)
2010-2013	373 (34.5%)
2014-2017	114 (10.6%)
Data not available	157 (14.5%)
Baseline viral load	
<50 copies/mL	99 (9.2%)
51-999 copies/mL	401 (37.1%)
≥1000 copies/mL	378 (35.0%)
Data not available	202 (18.7%)
Baseline CD4 count	
<200 cells/mm^3	205 (19.0%)
200-349 cells/mm^3	192 (17.8%)
≥350 cells/mm^3	515 (47.7%)
Data not available	169 (15.6%)
Baseline WHO Clinical Stage	
Stage I	283 (26.2%)
Stage II	167 (15.5%)
Stage III	212 (19.6%)
Stage IV	29 (2.7%)
Data not available	388 (35.9%)
Follow-up time	
Study follow-up time since ART initiation (yrs, median (IQR))*	7.2 (4.7-9.8)

ART: Antiretroviral therapy; IQR: Interquartile Range; LTFU: Lost to follow-up
* Median values calculated among participants with available clinical records

Among those with clinical records, a further 92.3% (n=878) had at least one viral load recorded within their files (Figure 15). Of those with any viral load data, 75.4% (n=662) and 51.1% (n=449) had their most recent viral load recorded in the

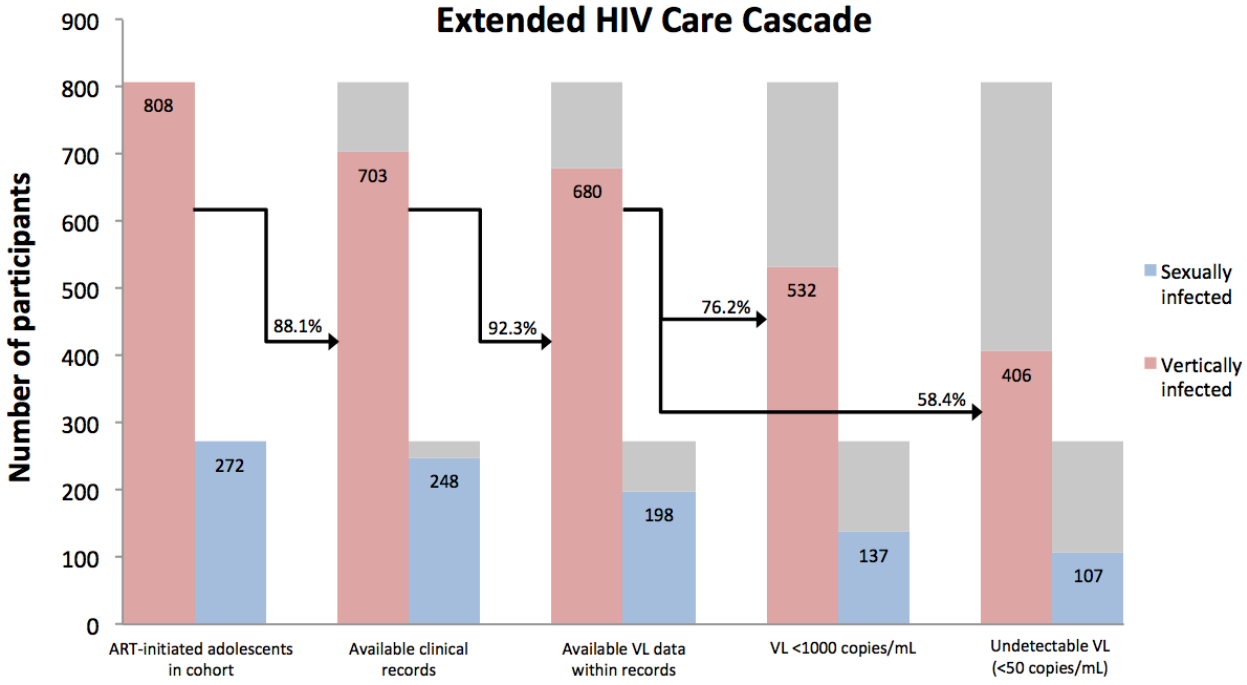
past 24 and 12 months, respectively. Median age at most recent viral load was 14 years (IQR: 12-17 years). Approximately equal proportions of adolescents had their most recent viral load recorded at a hospital (39.0%, n=342) and a primary care clinic (39.7%, n=349), with 21.3% (n=187) recorded at a community health centre. At most recent viral load, 74.1% (n=651) were on first-line ART with an NNRTI backbone, and 19.2% (n=169) were on second-line ART with a PI backbone. A further 6.6% (n=58) were on an NRTI-only or unspecified ARV regimen.

At most recent viral load, 76.2% (n=669) of those with viral load data were virally suppressed at <1000 copies/mL, and 58.4% (n=513) were fully virally suppressed at <50 copies/mL (Figure 15). This rate corresponds to 47.5% full viral suppression at most recent viral load for the total adolescent cohort. Only 23.2% (n=251) of the total cohort demonstrated full viral suppression within the past 12 months.

In the final multivariable model, male (AOR 1.55 [95%CI 1.05-2.28], p=0.026) and sexually infected adolescents (AOR 1.71 [95%CI 1.06-2.74], p=0.028) were more likely to have an available clinical record (Table 9). However, sexual infection (AOR 0.28 [95%CI 0.15-0.52], p<0.001) and older age at study enrolment (AOR 0.32 [95%CI 0.16-0.62], p=0.001) were associated with lower likelihood of having at least one recorded viral load. Male (AOR 2.36 [95%CI 1.28-4.37], p=0.006) and rural living adolescents (AOR 2.13 [95%CI 1.07-4.27], p=0.033) were more likely to have a viral load available in clinical records (Table 9).

Figure 15. Extended HIV care cascade by mode of infection

Numbers reflect ART-initiated adolescents in Mzantsi Wakho cohort who attained each outcome in the extended HIV care cascade. Percentages reflect proportions of adolescents achieving the subsequent cascade outcome, relative to those who attained the relevant prior cascade outcome. Among adolescents with available viral load data, the most recent viral load available was selected to evaluate suppression levels.



ART: Antiretroviral therapy; VL: Viral load

Longer time on ART (AOR 3.42 [95%CI 2.14-5.47], $p<0.001$) and experiencing decentralised care (AOR 1.39 [95%CI 1.06-1.83], $p=0.018$) were associated with having a viral load recorded in the past 12 months (Table 9). Longer time on ART was also associated with viral suppression at <1000 copies/mL (AOR 1.72 [95%CI 1.09-2.72], $p=0.020$). However, adolescents who were older at most recent viral load (AOR 0.54 [95%CI 0.39-0.75], $p<0.001$) and rural-residing (AOR 0.66 [95%CI 0.46-0.93], $p=0.019$) were less likely to be virally suppressed at this level. Similarly, adolescents on ART for longer were more likely to be fully virally suppressed at <50 copies/mL (AOR 1.70 [95%CI 1.12-2.58], $p=0.013$), but adolescents who were older at most recent viral load were less likely to be fully virally suppressed (AOR 0.72 [95%CI 0.55-0.94], $p=0.017$).

Full results for all model stages for each extended cascade outcome are provided in Supplementary Tables 2A and 2B. No significant three-way interactions were found between variables significant in the final models for any outcome. The average effect of decentralised care on likelihood of having a viral load in the past 12 months was greater for females than males (AOR 2.39 [95%CI 1.29-4.43], Wald χ^2=7.60, *p*=0.006), and greater for sexually infected adolescents than vertically infected counterparts (AOR 3.48 [95%CI 1.04-11.65], Wald χ^2=4.10, *p*=0.043) (Figure 16).

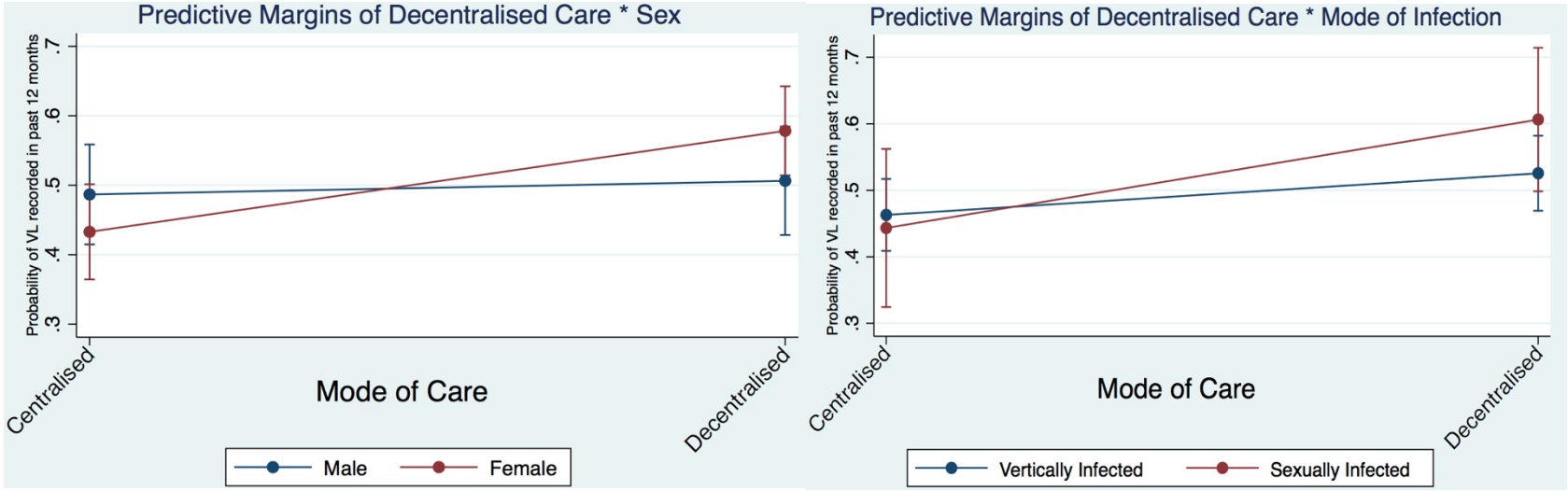
Table 9. Final models for associations between each extended HIV care cascade outcome and sociodemographic and treatment-related characteristics. Adjusted odds ratios only indicated for variables remaining in the final model for each outcome.

	Available clinical record (n=951) AOR (95% CI); *p* value	**Available VL data within records (n=878) AOR (95% CI); *p* value**	**VL recorded in past 12 months (n=449) AOR (95% CI); *p* value**	**Most recent VL <1000 copies/mL (n=669) AOR (95% CI); *p* value**	**Most recent VL <50 copies/mL (n=513) AOR (95% CI); *p* value**
Mortality	-	-			
Rural living	-	2.13 (1.07-4.27); 0.033	-	0.66 (0.46-0.93); 0.019	-
Sex (male)	1.55 (1.05-2.28); 0.026	2.36 (1.28-4.37); 0.006	-	-	-
Age at study enrolment (≥15 years)	-	0.32 (0.16-0.62); 0.001	0.82 (0.62-1.10); 0.181		
Sexually infected	1.71 (1.06-2.74); 0.028	0.28 (0.15-0.52); <0.0001	-	-	-
Decentralised care		-	1.39 (1.06-1.83); 0.018	-	-
Time on ART (≥2 years)			3.42 (2.14-5.47); <0.0001	1.72 (1.09-2.72); 0.020	1.70 (1.12-2.58); 0.013
Age at most recent VL (≥15 years)				0.54 (0.39-0.75); <0.0001	0.72 (0.55-0.94); 0.017

AOR: Adjusted odds ratio; ART: Antiretroviral therapy; CI: 95% Confidence interval; VL: Viral load

Note: Boxes shaded in grey indicate variables that were not applicable to analyses. Boxes filled with a dash indicate variables not included in the final model because they had failed to reach significance in prior models.

Figure 16. Predicted probabilities for effect of decentralised care by sex (left) and mode of infection (right) for having a viral load recorded in the past 12 months.



VL: Viral load

Discussion

This study provides a comprehensive estimate of the current reality of adolescent HIV care and progression to viral suppression through an extended HIV care cascade in South Africa's public healthcare system. These results highlight not only the low rate of past-year viral suppression among adolescents but also the importance of timely viral load monitoring. To our knowledge, this is the first study to evaluate both the timing and rate of viral suppression for a large cohort of adolescents across facilities in a sub-Saharan African public healthcare setting (Slogrove et al., 2018; Slogrove and Sohn, 2018).

By tracing participants in the community and across all 52 public facilities, this extended HIV care cascade adjusted for under-reported mortality and silent transfers in estimates of LTFU. At 16.9%, this study suggests that the true rate of LTFU is higher than previously reported for vertically infected adolescents in sub-Saharan Africa. This difference may result from this study's inclusion of adolescents sexually infected with HIV, a sub-population previously found to be at higher risk for LTFU (Adejumo et al., 2015; Slogrove et al., 2018).

This study found that roughly 38% of adolescents designated as LTFU by facilities were misclassified due to under-reported mortality and silent transfers. The discrepancy between community-traced and clinic-recorded rates of mortality suggests that mortality rates for adolescents living with HIV may be significantly underestimated. This further indicates the need to validate mortality estimates against a second approach, such as community tracing or vital registries. The importance of including silent transfers for accurately assessing patient outcomes

has been noted elsewhere, particularly in settings like South Africa without universal unique patient identifiers (Davies et al., 2017). The high rate of silent transfer may reflect adolescents' residential mobility; adolescents' actively self-specialising care services across multiple sites; or the effect of decentralising HIV care, through which patients' care is distributed across healthcare levels (Davies et al., 2017; South African National AIDS Council, 2017). Therefore, facility-based approaches to HIV care and treatment in South Africa must account for adolescents' mobility across sites.

Findings suggest that South African adolescent progression to the final "90" of viral suppression in the UNAIDS 90-90-90 treatment goal remains difficult, at 47.5% for ART-initiated adolescents aged 10-19 years. Therefore, this study extends evidence on the adolescent HIV care cascade in South Africa, beyond ART initiation rates previously reported by Maskew et al. (2019) to the next step of viral suppression, linked across healthcare facilities.

Further, this study investigated the critical implementation question of the frequency of viral load testing. This operational outcome reflects the extent to which adolescent HIV care in South Africa's decentralised health system actually adheres to national guidelines, which recommend at least annual viral load testing for all adolescents, even in the most decentralised community-based care models (Southern African HIV Clinicians Society, 2017). We found that only half of adolescents with available viral loads had their most recent viral load tested in the past 12 months. This rate of adolescents' viral load testing is far below the provincial estimate of 80% of all ART-initiated patients having a viral load within the past 12 months (World Bank, 2016). Although adolescents' viral load

availability may be high, these results suggest that adolescents' viral loads are often out-dated. Because viral load monitoring is the primary approach for South African healthcare providers to determine patients' clinical care needs, the lack of recent viral load data available in routine clinical records may significantly reduce their ability to make appropriate care decisions (Southern African HIV Clinicians Society, 2017).

Only 23.2% of all adolescents were documented to be virally suppressed in the past year. This low rate of past-year viral suppression potentially provides a more meaningful representation of the current state of adolescent HIV care in South Africa. As younger adolescents age and become sexually active and have children, routine viral load monitoring and suppression become even more crucial for prevention of onwards transmission to partners and children (UNAIDS, 2015a). While longer time on ART and receiving decentralised care were associated with having a viral load reported in the past 12 months, the protective effect of decentralised care was stronger for females and for sexually infected adolescents. These sub-populations may be more likely to engage with decentralised care through access to sexual and reproductive health services at primary level clinics.

This study has several limitations. Because study eligibility was limited to ART-initiated adolescents, findings are not generalisable to rates of viral suppression for adolescents living with HIV who have not been tested or initiated on ART, in the first two steps of the UNAIDS 90-90-90 target and care cascade. However, this study's inclusion of adolescents who were LTFU or disengaged from care minimised the risk of sample selection bias. Because this prospective cohort study analysed routine clinical records, it is only able to present estimates

based on data that would be available to healthcare providers in facilities. Rates of viral suppression presented in this study represent the proportion of adolescents known and documented to have achieved viral suppression. Although adolescents without any viral load records could potentially be virally suppressed, this information was not available, and these adolescents are likely disengaged from care and at higher risk of viral failure (Nachega et al., 2010; Long et al., 2016).

Additionally, this study is unable to identify precise reasons for out-dated or missing viral loads. On the provider side, healthcare staff could have missed scheduled blood tests due to inconsistent record-keeping systems, tests may have generated invalid results, or test results could have been lost (Euvrard et al., 2019; Granich et al., 2017). From the patient side, adolescents may be truly disengaged from care, picking up medications but unable to queue for blood tests, having a proxy pick up medications and report on their health, or unwilling to take blood tests. Potential transfers to facilities beyond the health district or into private care were not captured.

However, this study has several methodological strengths. Notably, participant tracing in the community allowed for correction of facilities' mortality records. Tracing individual patients across 52 healthcare facilities enabled a more accurate evaluation of adolescents' health by including unrecorded patient-initiated silent transfers to new facilities (Davies et al., 2017; Slogrove et al., 2018). This improved estimates for not only LTFU but also most recent viral loads. Analysis of clinical records through December 2017 also allowed for evaluation of adolescent viral load monitoring and HIV care outcomes in the era of universal

test and treat. These outcomes reflect the current reality of how ART-initiated adolescents are receiving follow-up care and responding to treatment within a healthcare system responsible for a patient population larger than even before. Additionally, through linking adolescents' self-reported information to clinical records, this cohort study was able to evaluate the effects of individual-level predictors of progression along the HIV care cascade, such as mode of infection and residential location, which has not been possible in previous analyses of records from national databases (Maskew et al., 2019; Slogrove et al., 2018).

Further longitudinal analysis of outcomes is required to investigate the cyclical nature of engagement with HIV care, in order to identify when and which adolescents disengage from the extended HIV care cascade (UNAIDS, 2016). Future research within this adolescent cohort should also examine self-reported clinical care experiences as predictors of HIV care outcomes. Identifying reasons for gaps in operational outcomes from this extended HIV care cascade and strategies to improve timely viral load monitoring for adolescents is critical for effective programmatic and policy changes.

Conclusions

This study documents progression of ART-initiated adolescents across an extended HIV care cascade to viral suppression in a sub-Saharan African decentralised public healthcare setting, accounting for mortality and silent transfers. Adolescents living with HIV in South Africa demonstrate low rates of viral suppression, and viral load monitoring practices fall well below national guidelines. The effectiveness of UNAIDS 90-90-90 goals for achieving HIV

treatment success requires not only viral suppression but also routine, up-to-date viral load monitoring and recording.

Implications of the Present Study for this DPhil

The systematic review (Chapter 4) highlighted the lack of recent and rigorous evidence on the effects of decentralising ART delivery for ALHIV in sub-Saharan Africa. Chapter 6 addresses that gap in evidence by providing recent estimates of care outcomes for ART-initiated adolescents across a large number of centralised and decentralised public facilities in South Africa. Informed by the findings of the systematic review, Chapter 6 evaluated the health outcomes for ALHIV within the context of a decentralised HIV care system. Through this approach, Chapter 6 indicated the high level of inter-facility mobility that ALHIV experience within the decentralised HIV care system, often as a result of up- and down-referrals across clinical sites.

Accordingly, the data collection and analysis used in Chapter 6 accounted for this high level of mobility by individually linking adolescents' clinical records across the 52 healthcare facilities and accounting for "silent" care transfers and unrecorded mortality. This approach allowed for a more accurate mapping of the real-world complexity of care-seeking behaviours for ALHIV in South Africa. In turn, this linkage and correction of clinical records provided more robust estimates of LTFU and mortality for ALHIV in South Africa's decentralised HIV care system, where Chapter 4 found that existing attrition estimates often did not account for care transfers.

Additionally, the systematic review reported that evidence for ALHIV was largely limited to findings on LTFU and mortality. Chapter 6 extends the evidence by measuring not only the level of viral suppression for ART-initiated ALHIV but also the availability of viral load data for these patients. Chapter 6 also separately examines the effect of receiving decentralised HIV care as a predictor for attainment of operational and health outcomes along the extended HIV care cascade, accounting for adolescents' baseline health status. Indeed, this chapter identified the potential interaction of decentralisation with adolescent's sex and mode of infection on regular engagement with HIV care, as reflected by the availability of a recent viral load.

In the context of this DPhil, findings from Chapter 6 also raised these questions: in a decentralised care context, if ALHIV already experience high levels of clinical mobility—regardless of their age—and can initiate and maintain ART within generalised primary care clinics, what does transition out of paediatric HIV care actually look like? Within and beyond HIV care, transition out of paediatric clinical settings is often a pivotal clinical experience for adolescents that introduces inter-facility mobility with movement from paediatric to non-paediatric care. In the real-world context, how does the structural change of decentralising HIV care interact with the experience of transition? These questions are addressed in Chapter 7 of this DPhil.

Additionally, given the lack of recent viral loads in adolescents' clinical records, Chapter 6 raises the question of how healthcare providers actually carry out clinical decision-making for adolescents' key events, such as when to

transition out of paediatric HIV care. This research question is also addressed in Chapter 7, through semi-structured interviews with healthcare providers.

Supplementary Tables

Supplementary Table 2A: Full results from sequential multivariable logistic regression analysis, testing associations between baseline sociodemographic and treatment-related variables and operational outcomes in the extended HIV care cascade. Goodness of model fit was assessed via Hosmer and Lemeshow test.

	Available clinical record (n=951/1080)			**Available VL data within clinical record (n=878/951)**		
	AOR	**Lower CI**	**Upper CI**	**AOR**	**Lower CI**	**Upper CI**
Step 1						
Mortality	0.84	0.32	2.23	0.60	0.18	1.99
Rural living	0.97	0.63	1.50	2.30*	1.14	4.63
Sex (male)	1.55*	1.05	2.28	2.31**	1.24	4.29
Age at study enrolment (≥15 years)	0.96	0.62	1.50	0.35**	0.18	0.70
Sexually infected	1.74*	1.02	2.98	0.29**	0.15	0.53
Decentralised care	-	-	-	0.59†	0.34	1.03
Step 2						
Mortality	-	-	-	-	-	-
Rural living	-	-	-	2.32*	1.15	4.67
Sex (male)	1.55*	1.05	2.28	2.30**	1.24	4.27
Age at study enrolment (≥15 years)	-	-	-	0.34**	0.17	0.67
Sexually infected	1.71*	1.06	2.74	0.29**	0.16	0.54
Decentralised care	-	-	-	0.59†	0.34	1.02
Step 3						
Mortality	-	-	-	-	-	-
Rural living	-	-	-	2.13*	1.07	4.27
Sex (male)	-	-	-	2.36**	1.28	4.37
Age at study enrolment (≥15 years)	-	-	-	0.32**	0.16	0.62
Sexually infected	-	-	-	0.28**	0.15	0.52
Decentralised care	-	-	-	-	-	-
Final model fit (X^2(df), p)	X^2 (2) = 0.48, p = 0.789			X^2 (6) =6.55, p = 0.365		

AOR: Adjusted odds ratio; ART: Antiretroviral therapy; CI: 95% Confidence interval; VL: Viral load
†p<0.1; * p<0.05 ; ** p<0.01

Supplementary Table 2B: Full results from sequential multivariable logistic regression analysis, testing associations between baseline sociodemographic and treatment-related variables and viral load outcomes in the extended HIV care cascade. Goodness of model fit was assessed via Hosmer and Lemeshow test.

	VL recorded in past 12 months (n=449/878)			Most recent VL <1000 copies/mL (n=669/878)			Most recent VL <50 copies/mL (n=513/878)		
	AOR	**Lower CI**	**Upper CI**	**AOR**	**Lower CI**	**Upper CI**	**AOR**	**Lower CI**	**Upper CI**
Step 1									
Mortality	-	-	-	-	-	-	-	-	-
Rural living	0.93	0.67	1.29	0.65*	0.45	0.94	0.77	0.56	1.06
Sex (male)	1.02	0.77	1.35	0.84	0.61	1.17	0.90	0.68	1.18
Age at study enrolment (≥15 years)	0.72[†]	0.52	1.00	-	-	-	-	-	-
Sexually infected	1.39[†]	0.95	2.03	0.83	0.56	1.24	1.00	0.70	1.43
Decentralised care	1.40*	1.06	1.85	0.99	0.72	1.38	0.80	0.60	1.05
Time on ART (≥2 years)	3.63**	2.25	5.85	1.68*	1.05	2.69	1.75*	1.14	2.68
Age at most recent VL (≥15 years)	-	-	-	0.56**	0.40	0.79	0.71*	0.53	0.96
Step 2									
Mortality	-	-	-	-	-	-	-	-	-
Rural living	-	-	-	0.66*	0.46	0.93	-	-	-
Sex (male)	-	-	-	-	-	-	-	-	-
Age at study enrolment (≥15 years)	0.72*	0.52	1.00	-	-	-	-	-	-
Sexually infected	1.39[†]	0.95	2.02	-	-	-	-	-	-
Decentralised care	1.38*	1.05	1.81	-	-	-	-	-	-
Time on ART (≥2 years)	3.61**	2.24	5.81	1.72*	1.09	2.72	1.70*	1.12	2.58
Age at most recent VL (≥15 years)	-	-	-	0.54**	0.39	0.75	0.72*	0.55	0.94
Step 3									
Mortality	-	-	-	-	-	-	-	-	-
Rural living	-	-	-	-	-	-	-	-	-

Sex (male)	-	-	-	-	-	-	-	-	-
Age at study enrolment (≥15 years)	0.82	0.62	1.10	-	-	-	-	-	-
Sexually infected	-	-	-	-	-	-	-	-	-
Decentralised care	1.39*	1.06	1.83	-	-	-	-	-	-
Time on ART (≥2 years)	3.42**	2.14	5.48						
Age at most recent VL (≥15 years)	-	-	-	-	-	-	-	-	-
Final model fit (X^2(df), p)	X^2 (3) = 0.45, p = 0.929			X^2 (5) = 4.04, p = 0.543			X^2 (1) = 0.06, p = 0.815		

AOR: Adjusted odds ratio; ART: Antiretroviral therapy; CI: 95% Confidence interval; VL: Viral load
†p<0.1; * p<0.05 ; ** p<0.01

7. DPhil Paper 3: Transition pathways out of paediatric care and associated HIV outcomes for adolescents living with HIV in South Africa

This paper is the second empirical analysis and paper based on primary data from the Mzantsi Wakho cohort. This paper characterises pathways for transition out of paediatric HIV care and health outcomes associated with these pathways for adolescents in South Africa's decentralised HIV care system. This paper was published in the Journal of Acquired Immune Deficiency Syndromes in October 2019.

Objectives: (1) To characterise pathways of transition out of paediatric HIV care for ART-initiated adolescents in South Africa's decentralised public care setting and (2) to identify associations between transition pathways and HIV outcomes

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Statement of Authorship

I confirm that I completed the majority of the work in this study (>70%). I conceptualised and led the quantitative assessment of adolescents' clinical records in the Mzantsi Wakho study. I developed the research question presented in this manuscript and its methodological approach, with contributions from Elona Toska, Lucie Cluver, and Laurie Gulaid. I co-designed the study measures with Elona Toska and Lucie Cluver. I led the quantitative data collection process, including data cleaning. I conducted all analyses reported in this manuscript, with

refinements suggested by Elona Toska. I drafted the first version of this article, with contributions to the write-up from Elona Toska and Daniella Mark. All co-authors further contributed to the interpretation of findings and final review of the manuscript.

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Abstract

Background

Research on adolescent transitions out of paediatric HIV care has focused on high-income countries, with limited understanding of transitions in sub-Saharan Africa's public health sector.

Methods

Patient file data was extracted through December 2017 for all 10- to 19-year-olds ever initiated on ART in a health district of the Eastern Cape, South Africa (n=951). Pathways in HIV care were identified by tracing movements across facility care types and levels. Associations between pathways and viral failure, mortality, loss to follow-up, and viral load change were tested in sequential multivariable regressions. Analyses controlled for sociodemographic and treatment-related variables. Thematic analyses of semi-structured healthcare provider interviews identified transition support at included facilities.

Results

Only 57.8% of adolescents had initiated ART in paediatric care, and 20.4% of the total cohort had transitioned out of paediatric HIV care. Among the 42.2% who had initiated in non-paediatric care, 93.8% remained exclusively in non-paediatric care. Median age at first transition was 14 years. Two main pathways were identified: *classical transition* to adult HIV care (43.3%) and *down-referral transition* to primary healthcare clinics (56.7%). Across pathways, 27.3%

experienced *cyclical transition*, or repeated movement between paediatric and non-paediatric care. Independent of covariates, adolescents with *down-referral transition* were less likely to demonstrate viral failure (AOR 0.21 [95%CI 0.10-0.42], $p<0.001$). Mortality and loss to follow-up were not associated with either pathway. Median post-transition viral load change was not clinically significant (0.00 [IQR: 0.00-0.35]) or associated with transition pathways. Healthcare providers described informal “protocols” for mitigating risk of negative post-transition HIV outcomes.

Conclusions

This study proposes a contextually relevant model for transitions out of paediatric HIV care in South Africa. Feasible, scalable “protocols” may mitigate risk of worsening post-transition HIV outcomes.

Background

Adolescents living with HIV demonstrate the poorest health outcomes in care, compared to all other age groups (UNAIDS, 2017b; Adejumo et al., 2015). In resource-limited settings such as sub-Saharan Africa, where the majority reside, adolescents remain largely underserved and their specific needs in HIV care poorly understood—including how those needs change as they become older (Mark et al., 2017; Shaw and Amico, 2016; Dahourou et al., 2017). As the growing cohort of adolescents on antiretroviral therapy (ART) ages into adulthood, facilitating smooth transition out of paediatric HIV care is essential to ensuring positive treatment outcomes, long-term well-being, and wider public health concerns (Mugavero et al., 2013; Lee and Hazra, 2015; Sohn et al., 2017; Hussen et al., 2014). Sustained retention in care and ART adherence into early adulthood is crucial for reducing risk of onwards transmission, particularly as adolescents become sexually active and enter child-bearing age (UNAIDS, 2014a).

Most published findings on adolescent transition are from high-income countries in North America and Europe, where the dominant transition pathway is from specialised paediatric to specialised adult care (Judd and Davies, 2018; Lam et al., 2017; Kakkar et al., 2016; Agwu et al., 2015; Fish et al., 2014; Philbin et al., 2017; Tanner et al., 2016). Applicability of this model of care to public healthcare systems in sub-Saharan Africa is not well documented, but the few studies from the region suggest far greater fluidity in transition process pathways and wide variation in implementation standards (Dahourou et al., 2017; Rakhmanina et al., 2016; Mark et al., 2017; Davies et al., 2017; Grewal, 2017). Without a clear understanding of actual transition experiences in sub-Saharan Africa, application

of guidelines from high-income countries may overlook the reality and needs of many adolescents in this setting.

Most transition support guidelines are highly individualised and resourced, including transition readiness assessments or dedicated transition case managers (Judd and Davies, 2018; Gillespie et al., 2016). However, these guidelines may not be relevant or feasible in resource-limited healthcare systems with high HIV burdens, where greatest efficiency at scale and limited operational demand are necessary. In countries like South Africa, these priorities have necessitated strategies for rapidly scaling up sustainable ART delivery, such as the decentralisation of HIV care to primary healthcare (PHC) clinics (Kredo et al., 2013). Since 2010, South Africa has been at the forefront of rapidly decentralising HIV care, including for children and adolescents living with HIV, which has increased not only care availability but also care-seeking mobility across facilities throughout childhood and adolescence (Copelyn et al., 2018; Davies et al., 2017; South African National AIDS Council, 2017). Although South African national guidelines on ART management include protocols for shifting from paediatric to adult ART regimens, there are no formalised guidelines for transitioning adolescents' ART care to the adult setting (National Department of Health, 2015; National Department of Health, 2019).

In practice, how do such transfers between healthcare facilities intersect with transition out of specialised paediatric health services? This understanding is critical to ensuring the provision of scalable, sustainable tools and resources that promote successful transition for adolescents living with HIV in high burden countries.

In this service delivery landscape, we investigate pathways of transition and their associations with HIV outcomes in a longitudinal cohort of adolescents living with HIV in South Africa, using both clinic-based and community-tracing methods to capture the true complexity of pathways in HIV care.

Methods

Participants

The study used a longitudinal prospective cohort design with adolescents living with HIV in rural, peri-urban, and urban locations of a district in the Eastern Cape province, South Africa. The healthcare system of this region is characterised by high HIV and TB burdens, limited infrastructure, and significant human resource challenges (Massyn et al., 2017). Recruitment took place from March 2014 to September 2015 (Cluver et al., 2018). Using a list of facilities from the National Department of Health, all healthcare facilities that provided ART to five or more adolescents were identified and included in the study (n=52, comprising eight hospital wards, five community health centres, and 39 PHC clinics). Each facility's patient register and clinic files were reviewed to identify all adolescents aged 10-19 years who had ever initiated ART, regardless of whether the adolescent was currently engaged in care or had been lost to follow-up (LTFU). Identified adolescents were then traced to over 180 communities and interviewed at a location of their choice. Overall, 90.1% of eligible adolescents were included in the study. Among those not included, 4.1% of adolescents or their caregivers refused participation, 3.7% were not traceable, 1.2% relocated outside the study area, and 0.9% were unable to participate due to severe cognitive delays (Cluver et al.,

2018). At 18 months post-baseline, adolescents who provided consent (or assent, when <18 years old) were re-interviewed in a second study wave, with 94% retention.

Data Collection

Clinical patient file review

At all healthcare facilities, paper-based and electronic patient files were searched for every study participant. When participants' files were found, data were extracted using a standardised form adapted to the clinical record system in each facility. Data were extracted in two rounds, the first covering records from 2014-2015 and the second 2016-2017, and included plasma viral load (VL), CD4 cell count, and WHO staging.

Adolescent interviews

Participants completed tablet-based surveys in two study waves with the support of research assistants trained in working with South African adolescents. Surveys included questions about adolescents' lifestyles, health, and health-seeking behaviours as well as experiences at home, in the community, and in healthcare facilities. The surveys were developed to be non-stigmatizing and easily understandable through extensive consultation with stakeholders (Cluver et al., 2018; Hodes et al., 2018). Surveys were available in both English and Xhosa. These surveys are available at www.mzantsiwakho.org.za.

Healthcare provider interviews

Semi-structured interviews were conducted with relevant healthcare staff at all healthcare facilities. Interviews characterised facilities' service availability and accessibility, human resource capacity, and operational processes.

Measures

In these analyses, adolescents' patient files were used to identify both clinical care outcomes and mobility across facilities, including transitions out of paediatric care. Adolescent interview data were only used for participants' sociodemographic information.

Paediatric care was designated by a dedicated space, day, or time at a facility wherein only children and adolescents received HIV healthcare services. *Non-paediatric care* was defined as a facility providing generalised care for all ages or one with a dedicated space, day, or time wherein only adults were seen. *Transition out of paediatric care* was identified by having a patient file opened in non-paediatric care, across all facilities, after ART initiation in paediatric care. Among those who transitioned, date of first transition was the date a patient file was first opened in non-paediatric care.

HIV outcomes included viral failure at most recent VL (HIV-1 RNA ≥1000 copies/mL at most recent VL measurement available across all files), mortality, LTFU, and post-transition VL change (World Health Organization, 2016b). *Mortality* was ascertained from both clinical records and during community tracing for participant interviews through May 2018. *LTFU* was defined as LTFU recorded in participants' patient files, adjusted for silent transfers found in data collection.

Most included healthcare facilities classified patients as LTFU if they had missed appointments for the past 3 months and were untraceable, when patient tracing was performed by the facility. *"Silent" transfers* were identified when a patient re-entered care in a new facility without an official transfer or notification to the former facility of care, where the patient had been deemed LTFU.

Post-transition VL change was calculated as the difference between log-transformed post-transition VL and log-transformed pre-transition VL. *Pre-transition VL* was the last VL available before the first transition out of paediatric care. *Post-transition VL* was the first VL available after the first transition out of paediatric care. Post-transition VL change was dichotomised as log VL change ≤0 and >0, with successful transition considered to be stable or reduced VL post-transition (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2015).

Statistical Analysis

Participants were eligible for inclusion in analyses if they had available patient files. For adolescents without patient files, data on clinical experiences and outcomes were unavailable, and these adolescents were therefore excluded from analyses. Study participants without patient files had been listed on an ART register in at least one healthcare facility, but actual patient files were missing or unavailable (across paper and electronic forms). An overview of quantitative analyses and their corresponding study sample populations is provided in Supplementary Table 3A.

First, we compared included and excluded adolescents on sociodemographic characteristics and outcomes (age, sex, urban/rural location, mode of infection, and mortality) using chi-square and Wilcoxon rank-sum tests for categorical and continuous variables, respectively. Second, using patient file, we characterised adolescent pathways in HIV care by tracing movements across facilities and care types (paediatric/non-paediatric care) over time. Pathways began with the facility care type (paediatric/non-paediatric) and level (hospital/community health centre/clinic) at ART initiation. Adolescents who had initiated ART in paediatric care but subsequently received HIV care in non-paediatric settings were considered to have experienced transition out of paediatric care. Third, for the identified transition pathways out of paediatric care, we compared sociodemographic, treatment-related, and outcome variables and tested for group-wise differences using Fisher's exact, chi-square, Kruskal-Wallis, and Wilcoxon rank-sum tests as appropriate.

Fourth, in a cross-sectional analysis, we tested associations between transitioning out of paediatric care and HIV outcomes among included participants using a sequential multivariable regression approach recommended by Hosmer and Lemeshow (Hosmer Jr et al., 2013). Variables were removed sequentially: only those significant at $p<0.1$ were retained in stage 2, with variables significant at $p<0.05$ retained in stage 3. Final models for each outcome were corrected for false discovery rate using the Benjamini-Hochberg step-up procedure (Hochberg, 1988). Analyses controlled for ten covariates: (1) Age at most recent VL (younger adolescents aged 10-14 years versus older adolescents aged 15-19); (2) sex; (3) residential location at baseline (urban versus rural); (4) horizontal versus vertical

mode of infection (Sherr et al., 2018); (5) year of ART initiation (2000-2009, 2010-2013, and 2013-2017); (6) time on ART (≥2 versus <2 years, measured from ART initiation to date of VL outcome); (7) baseline (first recorded) VL ≥1000 copies/mL; (8) immunologic instability (ever had recorded CD4 cell count ≤250 cells/mm^3) (Gilks et al., 2013); (9) "origin" healthcare facility level (hospital, community health centre, or clinic, defined as most recent facility level before transition out of paediatric care when applicable and ART initiation facility level when no transition was experienced) and (10) any experience of down-referral (patient file opened at a lower-level facility after having received care at a higher-level facility). Mortality and LTFU were analysed for all participants with available patient files, and viral failure at most recent VL only for participants with at least one recorded VL.

Fifth, we tested associations between post-transition VL change and sociodemographic and treatment-related covariates among adolescents who had transitioned, using the sequential multivariable logistic regression approach. Age at first transition out of paediatric care (dichotomised as younger versus older adolescents) was also included as a covariate in this analysis. Only adolescents who had at least one VL before and one VL after first transition out of paediatric care were included in analyses of post-transition VL change.

Risk of collinearity in regression analyses was assessed using correlation matrices with final models indicating no risk. Finally, thematic analyses of healthcare provider interviews identified transition support utilised at included facilities. All statistical analyses were performed using SPSS version 23 (IBM Corp, Armonk, NY).

Ethical Procedures

Ethical approval was provided by the University of Oxford (SSD/CUREC2/12-21) and University of Cape Town (CSSR 2013/4; 2017/3), the Eastern Cape Departments of Health and Basic Education, district health management, and management of participating healthcare facilities. All adolescents ≥18 years old provided voluntary, informed, and written consent for participation in the study, including both participant interviews and access to adolescents' full clinical records across all healthcare facilities included in the study. All included adolescents <18 years old provided assent, and their primary caregivers provided consent for participation. In cases of low literacy, all information and consent procedures were read aloud in the participant's preferred language. No incentives were provided, but all participants received a certificate of participation, snacks, and a small gift pack including basic items like pencils. Adolescents who chose not to participate were still given snacks and certificates. To minimise risk of involuntary disclosure and/or stigma, all publicly available study materials were focused on the general health of adolescents in South Africa. To improve reporting and minimise desirability bias, healthcare provider interviews were conducted by a nurse with over two decades of HIV care experience in the study setting.

Results

Cohort Characteristics

Of the 1080 adolescents living with HIV recruited into the study at baseline, patient files were found for 951 (89.8%) as of February 2018. There were no significant differences between included and excluded participants by

sociodemographic characteristics or mortality (Table 10). Of the 951 included participants, 54.3% were female, 26.1% horizontally infected, and the median age at study enrolment was 13 years (IQR: 11-16 years). Median follow-up time since ART initiation was 7.2 years (IQR: 4.7-9.8 years). At least one VL measurement was available for 92.3% of participants (n=878).

Table 10. Baseline demographic, clinical characteristics, and care outcomes of included and excluded participants. Treatment-related and care outcome data were derived from clinical records covering ART initiation through December 2017. Sociodemographic data were derived from interviews with adolescent participants.

	Included Participants (n=951)	**Excluded Participants (n=129)**	***P***
Outcomes			
Mortality (n,%)	31 (3.3%)	5 (3.9%)	0.714
LTFU (n,%)	84 (8.8%)	-	-
Viral failure (≥1000 copies/mL) (n,%)	282 (29.7%)	-	-
Sociodemographic			
Sex (n,%)	516 (54.3%)	81 (62.8%)	0.067
Age at study enrolment (yrs, median (IQR))	13 (11-16)	14 (11-16)	0.736
Horizontally infected (n,%)	248 (26.1%)	24 (18.6%)	0.067
Rural residence (n,%)	221 (23.2%)	31 (24%)	0.842
Treatment related			
Year of ART initiation (n,%) -2000-2009 -2010-2013 -2014-2017	 436 (45.8%) 372 (39.1%) 113 (11.9%)	-	-
Healthcare facility level (origin) (n,%) -Clinic -CHC -Hospital	 256 (26.9%) 184 (19.3%) 511 (53.7%)	-	-
Age at ART initiation (yrs, median (IQR))	9 (6-12)	-	-

ART: Antiretroviral therapy; CHC: Community health centre; IQR: Interquartile range; LTFU: Lost to follow-up; VL: Viral load

Among included participants, the median age at ART initiation was 9 years (IQR: 6-12 years), with 57.8% (n=550) having initiated ART in paediatric care at hospitals and CHCs (Figure 17). Conversely, 42.2% (n=401) initiated ART in non-paediatric care, a further 93.8% (n=376) of whom remained exclusively in non-

paediatric care. Among those who had initiated ART in paediatric care, 64.7% (n=356) remained within paediatric hospitals or CHCs and did not transition out of paediatric care. Only 35.3% (n=194) of adolescents initiated in paediatric care eventually transitioned out of paediatric care, representing 20.4% of the total cohort. Urban living, being on ART for ≥2 years, and a history of immunologic instability were associated with transition (Supplementary Table 3B).

Of those who had transitioned, 44.8% were female, 16.5% were horizontally infected, and 16.5% resided in rural locations (Table 11). Median age at first transition out of paediatric care was 14 years (IQR: 11-15 years), and median time on ART before first transition was 5.4 years (IQR: 3.3-8.4 years).

Transition Pathways

We identified two main typologies of transition out of paediatric HIV care: *classical transition to adult HIV care* and *down-referral transition to PHC* (Figure 17).

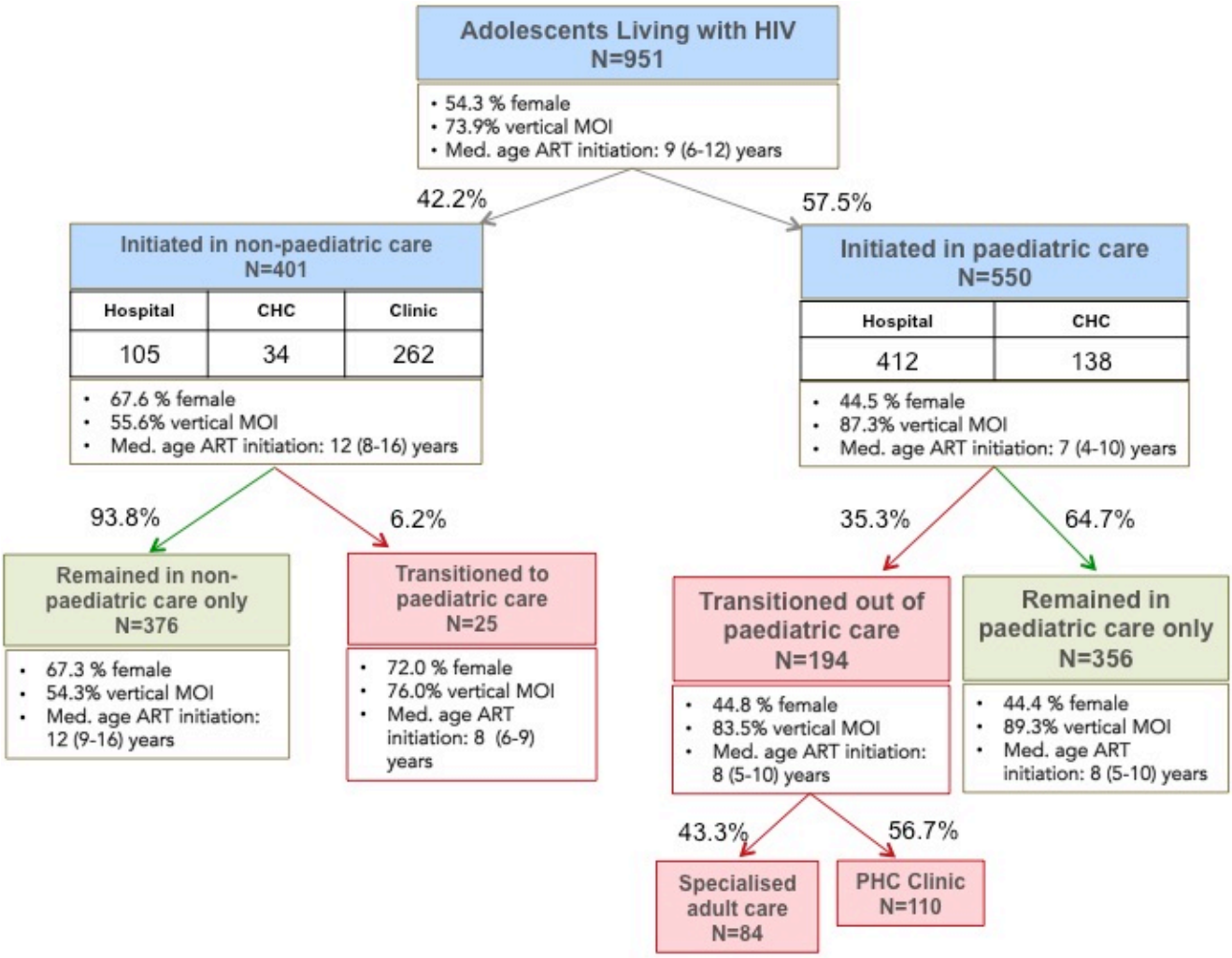
In the *classical transition* pathway, adolescents transitioned out of paediatric care into specialised adult HIV care in a hospital or CHC, remaining within secondary/tertiary care. In the *down-referral transition* pathway, adolescents experienced transition out of paediatric care simultaneously with—and as a result of—down-referral to a PHC clinic where they received generalised, non-paediatric HIV care (South African National AIDS Council, 2017). Among adolescents who transitioned out of paediatric care, 43.3% (n=84) experienced *classical transition*, and 56.7% (n=110) *down-referral transition.*

Compared with *classical transition,* adolescents who experienced *down-referral transition* were younger at study enrolment, ART initiation, and first

transition out of paediatric care (Table 11). Adolescents with *down-referral transition* were also on ART for longer before first transition and more likely to have transitioned out of paediatric hospital than community health centre. Adolescents who experienced *down-referral transition* also demonstrated lower rates of viral failure.

Of adolescents who transitioned through either pathway, 27.3% (n=53) experienced *cyclical transition*. *Cyclical transition* was defined as at least one repeated movement between paediatric and non-paediatric care, in which transition out of paediatric care was not a once-off initiating or concluding event. Adolescents who experienced *down-referral transition* demonstrated higher rates of *cyclical transition*.

Figure 17. Overview of adolescent pathways in HIV care, by type of care (paediatric/non-paediatric) and health facility (hospital/CHC/PHC clinic). Descriptive characteristics by sex, mode of infection, and median age at ART initiation are provided for each pathway.



ART: Antiretroviral therapy; CHC: Community health centre; MOI: Mode of infection; PHC: Primary healthcare

Table 11. Characteristics of adolescent participants by transition pathway out of paediatric care

	Classical Transition (n=84/194)	Down-Referral Transition (n=110/194)	All Transition (n=194)	*P*
Outcomes				
Mortality (n,%)	6 (7.1%)	1 (0.9%)	7 (3.6%)	**0.044**
LTFU (n,%)	5 (6.0%)	5 (4.5%)	10 (5.2%)	0.661
Viral failure (VL ≥1000 copies/mL) (n,%)	29 (34.5%)	9 (8.2%)	38 (19.6%)	**<0.001**
Post-transition VL change (median, IQR)	0.00 (-0.09-0.96)	0.00 (0.00-0.00)	0.00 (0.00-0.35)	0.067
Sociodemographic				
Sex (n,%)	41 (48.8%)	46 (41.8%)	87 (44.8%)	0.332
Age at study enrolment (yrs, median (IQR))	14.50 (13-16)	13 (11-15)	14 (11-16)	**<0.001**
Horizontally infected (n,%)	19 (22.6%)	13 (11.8%)	32 (16.5%)	0.045
Rural residence (n,%)	12 (14.3%)	20 (18.2%)	32 (16.5%)	0.469
Treatment related				
Year of ART initiation (n,%) -2000-2009 -2010-2013 -2014-2017	 53 (63.1%) 26 (31.0%) 5 (6.0%)	 81 (73.6%) 29 (26.4%) 0 (0.0%)	 134 (69.1%) 55 (28.4%) 5 (2.6%)	**0.022**
Age at ART initiation (yrs, median (IQR))	10 (7-11)	6 (4-9)	8 (5-10)	**<0.001**
Healthcare facility level (origin) -CHC -Hospital	 52 (61.9%) 32 (38.1%)	 9 (8.2%) 101 (91.8%)	 61 (31.4%) 133 (68.6%)	**<0.001**
Age at first transition (yrs, median (IQR))	14 (11-15)	13 (11-14)	14 (11-15)	**<0.001**
Time on ART before first transition (years, median (IQR))	4 (2.0-7.0)	6.5 (4.0-9.0)	5.4 (3.3-8.4)	**0.004**
Cyclical transition (n,%)	14 (16.7%)	39 (35.5%)	53 (27.3%)	**0.004**

ART: Antiretroviral therapy; CHC: Community healthcare centre IQR: Interquartile range; LTFU: Lost to follow-up; VL: Viral load

Associations between Transition out of Paediatric Care and HIV Outcomes

Overall mortality and LTFU rates in the sample were 3.3% and 8.8% respectively, while 29.7% of participants demonstrated viral failure at most recent VL.

Transitioning out of paediatric care through either pathway was not significantly associated with mortality or LTFU (Supplementary Table 3C). Transition out of paediatric care was also not associated with availability of VL data within patient

files (Supplementary Table 3D). VL data was unavailable for only 2.4% (n=2) of adolescents who experienced *classical transition* and for no adolescents with *down-referral transition*.

However, in the final multivariable model, adolescents who experienced *down-referral transition* were less likely to demonstrate viral failure at most recent VL (AOR: 0.25, 95%CI: 0.12-0.53, $p<0.001$), as well as those who transitioned out of a paediatric hospital (AOR 0.49, 95%CI: 0.33-0.73, $p=0.001$) (Table 12). Older age (AOR 1.76, 95%CI: 1.25-2.48, $p=0.001$), baseline VL ≥1000 copies/mL (AOR 3.64, 95%CI: 2.55-5.20, $p<0.001$), and immunologic instability (AOR: 1.64, 95%CI: 1.16-2.33, $p=0.005$) were significantly associated with viral failure at most recent VL.

Of the adolescents who transitioned out of paediatric care, 73.7% (n=143) had a VL available both before and after the first transition event, with a median log VL change of 0.00 (IQR: 0.00-0.35), indicating no significant change in VL post-transition. Median time from first transition to post-transition VL was 2 months (IQR: 0-9 months). There were no significant differences in post-transition VL change between *classical* and *down-referral transition* pathways (Supplementary Table 3E). None of the remaining variables were significantly associated with post-transition VL change.

Table 12. Sequential multivariable logistic regression analysis, testing associations between transition out of paediatric care and viral failure. Step 3 presents the final model results for viral failure at most recent measurement, retaining only variables that were significant at p < 0.05 in Step 2.

	AOR	Lower CI	Upper CI
Step 1			
Sex (female)	0.70†	0.49	1.00
Age at VL measurement (≥15 years)	1.84**	1.25	2.72
Horizontally infected	1.20	0.76	1.90
Rural living	1.47†	0.98	2.19
Baseline VL ≥1000 copies/mL	3.50**	2.43	5.05
Year of ART initiation - 2000-2009 - 2010-2013 - 2014-2017	- 1.04 0.59	- 0.70 0.28	- 1.55 1.26
Time on ART (≥2 years)	0.66	0.36	1.19
Immunologic instability (ever CD4 count ≤250 cells/mm^3)	1.64**	1.15	2.35
Healthcare facility level (origin) -Clinic -CHC -Hospital	- 0.61 0.46**	- 0.34 0.28	- 1.10 0.74
Ever down-referred in care	1.03	0.60	1.78
Classical transition	1.34	0.71	2.53
Down-referral transition	0.26**	0.11	0.63
Step 2			
Sex (female)	0.70†	0.49	1.00
Age at VL measurement (≥15 years)	1.89**	1.33	2.69
Rural living	1.43†	0.97	2.12
Baseline VL ≥1000 copies/mL	3.72**	2.60	5.32
Immunologic instability (ever CD4 count ≤250 cells/mm^3)	1.68**	1.18	2.38
Healthcare facility level (origin) -Clinic -CHC -Hospital	- 0.73 0.48**	- 0.44 0.31	- 1.22 0.73
Down-referral transition	0.25**	0.12	0.52
Step 3 (final model)			
Age at VL measurement (≥15 years)	1.76**	1.25	2.48
Baseline VL ≥1000 copies/mL	3.64**	2.55	5.20
Immunologic instability (ever CD4 count ≤250 cells/mm^3)	1.64**	1.16	2.33
Healthcare facility level (origin) -Clinic -CHC -Hospital	- 0.72 0.49**	- 0.44 0.33	- 1.18 0.73
Down-referral transition	0.25**	0.12	0.53

AOR: Adjusted odds ratio; ART: Antiretroviral therapy; CHC: Community healthcare centre; CI: 95% Confidence interval; VL: Viral load

† $p<0.1$; ** $p<0.01$

Healthcare Provider Perspectives and Practices of Adolescent Transition

In semi-structured interviews at the 13 hospitals and CHCs, healthcare providers were asked to identify criteria used to determine which adolescents to down-refer to PHC clinics. Of these facilities, 10 specified decision-making criteria based on patient health, using five major criteria: (1) viral suppression, (2) clinical "stability," (3) good ART adherence, (4) no treatment complications, and (5) patient willingness to down-refer. Viral suppression was the most commonly applied criterion, reported by eight of the 10 facilities. Clinical "stability" was reported by five facilities and described as subjectively determined by the attending healthcare provider. The remaining three criteria were reported by three facilities each.

Healthcare providers at paediatric hospitals described several approaches to mitigate risk of disengagement from care at the PHC clinic post-transition. These included the provision of continuous counselling and education before transition, with a clear explanation for down-referral; offering adolescents a range of clinics closer to home from which they could select their preferred down-referral site; contacting PHC clinics for them to anticipate new patients; and obtaining additional contact details from adolescents to check on progress in care after transition.

Discussion

Using data from routine patient files across 52 public healthcare facilities in a South African health district, this study characterised the complex reality of adolescent pathways in HIV care across facility care types and levels. Previous studies in sub-Saharan Africa have evaluated adolescent transfers from private care into the public sector or outcomes within specific youth-friendly models of

care after transition (Ramirez-Avila et al., 2017; Gillespie et al., 2016; Dahourou et al., 2017). However, this study is one of the first to quantitatively characterise and evaluate adolescent transitions out of paediatric HIV care within public healthcare in sub-Saharan Africa (Dahourou et al., 2017; Gillespie et al., 2016).

This study suggests that a shift in our current conceptualization of adolescent HIV transition is urgently needed to reflect realities in the sub-Saharan African context, beyond the model of a linear, once-off movement from specialised paediatric care to adult care observed in Europe and North America (Ryscavage et al., 2016; Agwu et al., 2015; Kakkar et al., 2016). Using patient files, this study identified two distinct typologies of adolescents' transitions out of paediatric HIV care: *classical transition* to adult care and *down-referral transition* to PHC. Within a decentralised HIV care model—demanded by high-burden, limited-resource contexts—the majority of adolescents first experienced transition out of paediatric care through *down-referral transition*. However, to our knowledge, no previous studies have documented this care trajectory as a transition pathway out of paediatric care. One study in the Western Cape, South Africa, also noted this pattern of care, although it was evaluated in combination with other care transfers, beyond transition out of paediatric care (Davies et al., 2017).

As sub-Saharan African countries continue scaling up HIV care, adolescent healthcare experiences must be considered in the context of structural changes, including decentralised and differentiated care (Fayorsey et al., 2013). For instance, only one-fifth of adolescents in this study had transitioned out of paediatric HIV care, with roughly 40% of adolescents never receiving specialised

paediatric care. With South Africa's rollout of nurse-initiated and managed antiretroviral therapy in PHC for patients of all ages, a growing number of children and adolescents have been initiated on ART in non-paediatric PHC clinics, even at young ages (Zuber et al., 2014). By initiating and continuing to receive care within non-paediatric PHC clinics, these adolescents may never enter paediatric HIV care to transition out of it. As decentralised care is rolled out in similar settings across the region, these findings have important implications for adolescent HIV care provision.

Conversely, 37% of adolescents remained exclusively within paediatric care, which may reflect three scenarios. First, younger adolescent participants may not have aged into eligibility for adult HIV care by the end of data collection. Second, through their informal "protocols," healthcare providers at included facilities may have delayed transition for specific patients deemed physically or psychosocially unprepared for adult HIV care. This scenario could include patients who were too clinically unstable to down-refer out of specialised paediatric care to generalised primary care in clinics. Third, older adolescents may have been instructed to transition out of paediatric care but refused to transfer facilities or care providers.

Applying this expanded and contextually relevant transition model, this study revealed that first transition begins at an earlier age than the reported standard practice of 15 years and older (Dahourou et al., 2017; Gillespie et al., 2016). This finding suggests that programs for facilitating transition must also include younger adolescents. Within South Africa's decentralised care model, there is no age cut-off for down-referral eligibility to PHC clinics (South African

National AIDS Council, 2017; Fayorsey et al., 2013). Hence, through *down-referral transitions,* many adolescents experience transitions out of paediatric care at young ages. In the *classical* model, transitions may be occurring at earlier ages due to patient-initiated transfers to adult care, reflective of patient maturity or preference for care separate from younger paediatric patients (Valenzuela et al., 2009).

Furthermore, this study highlights that transition is often not experienced as a once-off event, but rather a *cyclical* movement between paediatric and non-paediatric care after the first transition. In the *classical* model, this cyclical movement may suggest an adolescent patient acclimatizing to care in the non-paediatric setting over time through repeated visits. In the *down-referral* model, the cyclical movement may represent up- and down-referrals as required by fluctuations in the patient's stability or treatment outcomes, such as changing treatment regimens. Interventions and evaluations of transition must account for these potentially diverse treatment trajectories, combining different types and sequences of transitions in HIV care. Such evaluations should consider not only the immediate effects of transitions out of paediatric care, but also long-term effects that may emerge years later in late adolescence, when adolescents are particularly at risk for poor HIV care outcomes (Slogrove and Sohn, 2018).

In comparison to all other care trajectories, including remaining within paediatric care, experiencing *down-referral transition* was associated with lower probability of viral failure. *Classical transition* was not significantly associated with any HIV outcomes. These findings reflect expected treatment outcomes as a result of decentralisation, as only stable patients should be down-referred to PHC

clinics (Kredo et al., 2013). However, adolescents who experienced *down-referral transition* remained less likely to demonstrate viral failure, even after adjusting for any experience of down-referral (without transition), baseline VL, and immunologic instability. Moreover, median post-transition VL change was not clinically significant. These findings suggest that, in the overall adolescent population, regardless of ART initiation site, transition itself did not put adolescents at risk for worse or worsening HIV outcomes.

Our results may be due to the informal "protocols" for determining which adolescents to transition out of paediatric care, reported by healthcare providers in the included facilities. Healthcare providers indicated that adolescents were only transitioned out of paediatric care when the providers were confident in patient stability. Additionally, healthcare providers described measures taken to facilitate transition, including quality counselling and education for patients and communication with destination facilities. Hence, this study effectively tests the reality of how healthcare providers have interpreted and implemented clinical guidelines on transition in South Africa's public health sector. Healthcare providers have been mitigating the risk of negative health outcomes using basic triaging guidelines and transition planning with both patients and destination facilities, which are easily scalable and adoptable in other resource-limited settings.

Study limitations include incomplete patient file and viral load availability, with 7.7% of included adolescents lacking any recorded VLs. This study was not able to distinguish specific reasons for missing or infrequent VL recording, which may have resulted from either provider- or patient-side challenges. On the

provider end, healthcare staff may have missed scheduled appointments for blood tests due to inconsistent record-keeping systems; tests may have been ordered but carried out incorrectly, providing invalid results; or test results may have been lost or misfiled (Euvrard et al., 2019; Granich et al., 2017). On the patient end, adolescents could be truly LTFU or disengaged from care; regularly picking up medication but unable to wait in long queues for blood tests; or unwilling to take blood tests.

Consequently, VL outcomes could not be estimated for the total sample, and the ability to evaluate long-term outcomes of transition in care was limited. Also, despite intensive data collection within the study area, transfers to healthcare facilities beyond the health district were not captured. Exclusion of participants without patient files from analyses may have introduced potential bias in reported HIV outcomes. However, with the exception of transfers outside the health district, adolescents without patient files are likely LTFU, and their outcomes would not reflect outcomes in care. Excluding patients without VL data from analyses of the association of transition with viral failure and post-transition VL change may also have introduced bias, but the availability of VL data was not associated with transition out of paediatric care.

However, this study has several key methodological strengths, given the lack of unique national or provincial patient identifiers in the study area. Although most studies of adolescents living with HIV in South Africa have focused on a small number of facilities (Savage et al., 2017). this study looked for clinical records for all participants in all participating facilities. This intensive data collection approach enables the evaluation of adolescents' health as recorded

across multiple healthcare facilities, including unrecorded patient-initiated “silent” transfers to new facilities (Davies et al., 2017).

Further analysis is needed to investigate predictors of care outcomes, such as service availability and quality in destination facilities. Additionally, longitudinal analyses of adolescent transitions in care—with greater VL coverage—could better characterise the long-term effects of transition, including for those who transitioned as young adolescents. Finally, future analyses should further investigate and compare the health outcomes of adolescents in non-transitioning pathways, such as adolescents who were kept exclusively within paediatric care or who never received paediatric care. In particular, further work is required to understand why older adolescents may not be transitioning out of paediatric care and how to provide support for these adolescents as they enter young adulthood.

Conclusions

As the HIV/AIDS epidemic and its management has evolved in sub-Saharan Africa, research must consider increasingly complex initiation and transition experiences of adolescents, beyond models of care evaluated in high-income countries. This study is unique in documenting—with high rigor—the realities of HIV care trajectories of a large cohort of adolescents living with HIV in a resource-limited setting. With the continued decentralisation of HIV care to primary healthcare clinics in sub-Saharan Africa, the findings of this study will bear increasing relevance for the experiences of adolescents in other countries in the region.

Implications of the Present Study for this DPhil

Among the cohort of ART-initiated ALHIV in South Africa, Chapter 6 found a high rate of attending decentralised primary care clinics. Based on this finding, Chapter 7 used adolescents' individually linked clinical records to identify pathways of HIV care within South Africa's decentralised public HIV care system. This mapping of care pathways revealed multiple pathways that are generated by the decentralised HIV care system, including and beyond transition out of paediatric HIV care. Furthermore, Chapter 7 found that many ALHIV never experience transition out of paediatric HIV care because they initiate ART and remain exclusively within decentralised clinics that provide generalised primary care.

Among those who do transition, Chapter 7 indicated that decentralising HIV care has generated a new pathway for ALHIV: down-referral transition out of paediatric care into generalised primary care clinics. Indeed, Chapter 7 found that this transition pathway, which is unique to decentralised care systems, was the most commonly experienced mode of transition for ALHIV. Previous studies on adolescent transitions out of paediatric HIV care in sub-Saharan Africa had not explicitly identified this pathway and often presumed the classical model of transition from paediatric to adult HIV care, which is found in high-income settings.

Additionally, Chapter 7 evaluated the HIV care outcomes for ALHIV in these pathways. Down-referral transition was protective against viral failure. Given the lack of formal guidelines on how to clinically transition ALHIV, this finding suggested that care providers at the included healthcare facilities had developed their own protocols for mitigating risk of adverse outcomes post-transition. These informal protocols were identified through semi-structured interviews with

healthcare providers. Because of their feasibility in resource-limited settings, these protocols can potentially offer programmatic lessons for best practice in similar settings across sub-Saharan Africa, as further discussed in Chapter 8.

Together, findings from Chapters 6 and 7 indicate that official guidelines, when they exist, do not necessarily reflect the reality of HIV care. For instance, although patients ≥15 years are technically considered adults in South Africa's healthcare system, Chapter 7 reported transition out of paediatric HIV care beginning at younger ages. Similarly, although official guidelines require annual viral load testing, Chapter 6 found very low rates of recent viral load availability in adolescents' clinical records. As discussed in Chapter 8, findings from these chapters highlight the importance of first characterising the actual landscape of HIV care in order to identify critical implementation gaps, the consequences of these gaps, and subsequently ways to optimise adolescents' care outcomes.

In sum, findings from Chapter 6 and Chapter 7 demonstrate how decentralising HIV care affects both the health outcomes and care experiences for ALHIV in South Africa. However, both chapters also indicate the urgent need for further longitudinal analyses of adolescents' health outcomes to better identify predictors of longitudinal patient stability. Chapter 8 explores future research questions and efforts that will be undertaken by this candidate to address this limitation of the dissertation.

In the wider context of this DPhil, Chapter 7 was co-conceived with the UNICEF Eastern and Southern Africa Regional Office HIV/AIDS Programme and constitutes the closest direct engagement with policy partners undertaken by this candidate. Findings from Chapter 7, informed by Chapters 4 and 6, were also

fundamental for this candidate's collaboration with the Elizabeth Glaser Paediatric AIDS Foundation in developing a transition toolkit for healthcare providers, as discussed in Chapter 8.

Supplementary Tables

Supplementary Table 3A: Overview of study analyses and corresponding samples

Figure/Table	Analysis	Sample Description	Sample size
Table 1	Differences between included and excluded participants, based on patient file availability	All adolescent study participants	n=1080
Figure 1	Identification of pathways in HIV care, across facility care types and levels	Adolescent study participants with available patient files	n=951
Table, Supplemental Digital Content 2	Associations with transition out of paediatric care	Adolescent study participants with available patient files	n=951
Table 2	Comparison between adolescents who experienced down-referral vs. classical transition out of paediatric care	Adolescent study participants who transitioned out of paediatric care	n=194
Table, Supplemental Digital Content 3	Association between transition and mortality	Adolescent study participants with available patient files	n=951
Table, Supplemental Digital Content 3	Association between transition and LTFU	Adolescent study participants with available patient files	n=951
Table, Supplemental Digital Content 4	Association between transition and availability of VL data	Adolescent study participants with available patient files	n=951
Table 3	Association between transition and viral failure (VL ≥1000 copies/mL) at most recent VL	Adolescent study participants with VL data available in patient files	n=878
Table, Supplemental Digital Content 3	Association between transition and VL ≥200 copies/mL or VL ≥50 copies/mL at most recent VL	Adolescent study participants with VL data available in patient files	n=878
Table, Supplemental Digital Content 5	Associations with post-transition VL change	Adolescent study participants who had transitioned out of paediatric care AND who had ≥1 VL available *before* transition and ≥1 VL available *after* transition	n=143

LTFU: Lost to follow-up; VL: Viral load

Supplementary Table 3B: Sequential multivariable logistic regression analysis, testing associations between baseline sociodemographic and treatment-related variables and transition out of paediatric care. Step 3 presents the final model results for probability of transition out of paediatric care.

	AOR	Lower CI	Upper CI
Step 1			
Sex (female)	0.71*	0.51	0.99
Age at study enrolment (≥15 years)	1.48*	1.01	2.17
Horizontally infected	0.59*	0.36	0.95
Rural living	0.55**	0.36	0.84
Baseline VL ≥1000 copies/mL	1.32	0.94	1.85
Time on ART (≥2 years)	5.68**	2.25	14.33
Immunologic instability (ever CD4 count ≤250 cells/mm^3)	1.46*	1.03	2.07
Step 2			
Sex (female)	0.71	0.51	1.00
Age at study enrolment (≥15 years)	1.47	1.00	2.14
Horizontally infected	0.57*	0.35	0.93
Rural living	0.54**	0.35	0.83
Time on ART (≥2 years)	5.67**	2.25	14.30
Immunologic instability (ever CD4 count ≤250 cells/mm^3)	1.55*	1.10	2.18
Step 3 (final model)			
Horizontally infected	0.65	0.42	1.01
Rural living	0.54**	0.35	0.82
Time on ART (≥2 years)	5.53**	2.20	13.92
Immunologic instability (ever CD4 count ≤250 cells/mm^3)	1.53*	1.09	2.16

AOR: Adjusted odds ratio; ART: Antiretroviral therapy; CI: 95% Confidence interval; VL: Viral load
†p<0.1; * p<0.05 ; ** p<0.01

Supplementary Table 3C: Sequential multivariable logistic regression analysis, testing associations between transition out of paediatric care and clinical care outcomes

	Mortality (n=31/951)			LTFU (n=84/951)			VL ≥200 copies/mL (n=283/878)			VL ≥50 copies/mL (n=364/878)		
	AOR	Lower CI	Upper CI	AOR	Lower CI	Upper CI	AOR	Lower CI	Upper CI	AOR	Lower CI	Upper CI
Step 1												
Sex (female)	0.43†	0.18	1.05	0.96	0.54	1.70	0.74†	0.54	1.02	0.77†	0.57	1.04
Age at VL measurement (≥15 years)	3.28*	1.20	8.93	0.74	0.38	1.42	1.80**	1.27	2.55	1.45*	1.04	2.01
Horizontally infected	0.22*	0.05	0.91	2.60**	1.32	5.09	0.93	0.61	1.43	0.99	0.66	1.48
Rural living	0.75	0.26	2.23	0.59	0.28	1.20	1.50*	1.04	2.17	1.27	0.89	1.81
Baseline VL ≥1000 copies/mL	1.24	0.52	2.94	0.94	0.52	1.70	3.41**	2.45	4.74	3.11**	2.28	4.24
Year of ART initiation												
- 2001-2009	-	-	-	-	-	-	-	-	-	-	-	-
- 2010-2013	0.71	0.27	1.90	1.08	0.56	2.09	0.97	0.68	1.39	1.11	0.80	1.55
- 2014-2017	0.27	0.04	1.90	0.38	0.12	1.22	0.62	0.30	1.25	0.73	0.37	1.42
Time on ART (≥2 years)	0.11**	0.03	0.37	0.69	0.29	1.60	0.62	0.35	1.10	0.60†	0.34	1.03
Immunologic instability (ever CD4 count ≤250 cells/mm^3)	5.65**	2.22	14.35	1.14	0.63	2.06	1.57**	1.13	2.18	1.44*	<0.01	1.99
Healthcare facility level (origin)												
- Clinic	-	-	-	-	-	-	-	-	-	-	-	-
- CHC	0.64	0.15	2.83	0.81	0.38	1.71	0.70	0.41	1.20	0.75	0.46	1.24
- Hospital	0.67	0.20	2.23	0.18**	0.08	0.41	0.46**	0.29	0.74	0.48**	0.31	0.74
Ever down-referred in care	0.75	0.20	2.80	1.23	0.43	3.54	1.58	0.97	2.57	1.66*	1.04	2.65
Classical transition	2.55	0.66	9.85	0.68	0.22	2.10	1.03	0.57	1.85	1.12	0.64	1.96
Down-referral transition	0.33	0.03	3.57	0.96	0.25	3.72	0.34**	0.18	0.67	0.48*	0.27	0.88
Step 2												
Sex (female)	0.45†	0.19	1.06	-	-	-	0.72*	0.53	1.00	0.75†	0.56	1.02
Age at VL measurement (≥15 years)	3.49**	1.37	8.88	-	-	-	1.70**	1.23	2.33	1.39*	1.04	1.88
Horizontally infected	0.20*	0.05	0.76	2.08*	1.20	3.63	-	-	-	-	-	-
Rural living	-	-	-	-	-	-	1.57*	1.10	2.25	-	-	-
Baseline VL ≥1000 copies/mL	-	-	-	-	-	-	3.43**	2.49	4.74	3.21**	2.36	4.35
Year of ART initiation - 2001-2009 - 2010-2013 - 2014-2017	-	-	-	-	-	-	-	-	-	-	-	-
Time on ART (≥2 years)	0.17**	0.06	0.48	-	-	-	-	-	-	0.73	0.46	1.17
Immunologic instability (ever CD4 count ≤250 cells/mm^3)	5.58**	2.28	13.64	-	-	-	1.62**	1.18	2.24	1.46*	1.07	1.98
Healthcare facility level (origin) - Clinic - CHC - Hospital	-	-	-	- 1.10 0.27**	- 0.59 0.14	- 2.05 0.54	- 0.81 0.57**	- 0.50 0.38	- 1.31 0.85	- 0.80 0.48**	- 0.51 0.32	- 1.25 0.71
Ever down-referred in care	-	-	-	-	-	-	-	-	-	1.78*	1.14	2.75
Classical transition	-	-	-	-	-	-	-	-	-	-	-	-

Down-referral transition	-	-	-	-	-	-	0.48**	0.28	0.82	0.44**	0.25	0.78
Step 3												
Sex (female)	-	-	-	-	-	-	0.72*	0.53	1.00	-	-	-
Age at VL measurement (≥15 years)	2.94*	1.20	7.21	-	-	-	1.70**	1.23	2.33	1.32†	0.99	1.77
Horizontally infected	0.18*	0.05	0.69	-	-	-	-	-	-	-	-	-
Rural living	-	-	-	-	-	-	1.57*	1.10	2.25	-	-	-
Baseline VL ≥1000 copies/mL	-	-	-	-	-	-	3.43**	2.49	4.74	3.17**	2.34	4.29
Year of ART initiation - 2001-2009 - 2010-2013 - 2014-2017	-	-	-	-	-	-	-	-	-	-	-	-
Time on ART (≥2 years)	0.19**	0.07	0.52	-	-	-	-	-	-	-	-	-
Immunologic instability (ever CD4 count ≤250 cells/mm^3)	5.30**	2.17	12.91	-	-	-	1.62**	1.18	2.24	1.45*	1.06	1.99
Healthcare facility level (origin) - Clinic - CHC - Hospital	-	-	-	-	-	-	- 0.81 0.57**	- 0.50 0.38	- 1.31 0.85	- 0.83 0.50**	- 0.54 0.34	- 1.30 0.73
Ever down-referred in care	-	-	-	-	-	-	-	-	-	1.73*	1.12	2.68
Classical transition	-	-	-	-	-	-	-	-	-	-	-	-
Down-referral transition	-	-	-	-	-	-	0.48**	0.28	0.82	0.45**	0.25	0.79

AOR: Adjusted odds ratio; ART: Antiretroviral therapy; CHC: Community healthcare centre; CI: 95% Confidence interval; LTFU: Lost to follow-up; VL: Viral load
†$p<0.1$; * $p<0.05$; ** $p<0.01$

Supplementary Table 3D: Sequential multivariable logistic regression analysis, testing association between transition out of paediatric care and availability of VL data

	≥1 VL recorded in patient file (n=878/951)		
	AOR	**Lower CI**	**Upper CI**
Step 1			
Sex (female)	0.34*	0.13	0.90
Age at study enrolment (≥15 years)	0.49	0.17	1.40
Horizontally infected	0.28*	0.10	0.78
Rural living	2.18†	0.89	5.34
Year of ART initiation			
- 2001-2009	-	-	-
- 2010-2013	0.26	0.05	1.33
- 2014-2017	0.06**	0.01	0.32
Immunologic instability (ever CD4 count ≤250 cells/mm^3)	0.32**	0.15	0.66
Healthcare facility level (origin)			
- Clinic	-	-	-
- CHC	1.31	0.50	3.46
- Hospital	1.70	0.52	5.50
Ever down-referred in care	0.93	0.21	4.12
Transition out of paediatric care (classical or down-referral)	1.85	0.34	9.98
Step 2			
Sex (female)	0.29*	0.11	0.75
Age at study enrolment (≥15 years)	-	-	-
Horizontally infected	0.18**	0.07	0.43
Rural living	1.94	0.80	4.71
Year of ART initiation			
- 2001-2009	-	-	-
- 2010-2013	0.22†	0.05	1.01
- 2014-2017	0.04**	0.01	0.16
Immunologic instability (ever CD4 count ≤250 cells/mm^3)	0.33**	0.16	0.67
Healthcare facility level (origin)			
- Clinic	-	-	-
- CHC			
- Hospital			
Ever down-referred in care	-	-	-
Transition out of paediatric care (classical or down-referral)	-	-	-
Step 3			
Sex (female)	0.30*	0.12	0.77
Age at study enrolment (≥15 years)	-	-	-
Horizontally infected	0.17**	0.07	0.42
Rural living	-	-	-
Year of ART initiation			
- 2001-2009	-	-	-
- 2010-2013	0.21	0.05	0.99
- 2014-2017	0.04**	0.01	0.17
Immunologic instability (ever CD4 count ≤250 cells/mm^3)	0.34**	0.17	0.68
Healthcare facility level (origin)			
- Clinic	-	-	-
- CHC			
- Hospital			
Ever down-referred in care	-	-	-
Transition out of paediatric care (classical or down-referral)	-	-	-

AOR: Adjusted odds ratio; ART: Antiretroviral therapy; CHC: Community healthcare centre; CI: 95% Confidence interval; LTFU: Lost to follow-up; VL: Viral load

†p<0.1; * p<0.05 ; ** p<0.01

Supplementary Table 3E: Sequential multivariable logistic regression analysis, testing associations between baseline sociodemographic and treatment-related variables and post-transition VL change (log VL change ≤0)

	AOR	Lower CI	Upper CI	*P*
Sex (female)	1.81	0.81	4.04	0.148
Age at post-transition VL measurement (≥15 years)	0.40	0.06	2.63	0.340
Horizontally infected	2.33	0.64	9.49	0.200
Rural living	1.21	0.42	3.5	0.730
Year of ART initiation - 2001-2009 - 2010-2013 - 2014-2017	 - 1.79 0.98	 - 0.70 0.10	 - 4.61 9.40	 - 0.225 0.987
Time on ART (≥2 years)	0.87	0.18	4.17	0.860
Age at first transition (≥15 years)	0.68	0.09	5.29	0.710
Origin healthcare facility (hospital)	0.81	0.25	2.63	0.73
Cyclical transition	0.73	0.28	1.93	0.520
Down-referral transition	1.50	0.56	4.05	0.420

AOR: Adjusted odds ratio; ART: Antiretroviral therapy; CI: 95% Confidence interval; VL: Viral load

8. Discussion

1. Chapter Overview

The overall aim of this DPhil thesis is to evaluate the effects of decentralising HIV care delivery on the health outcomes and experiences of adolescents initiated on ART in South Africa's public healthcare system. These research aims were addressed through three specific sets of objectives, each resulting in a stand-alone manuscript:

1. To synthesise and critically assess the evidence base for the effects of decentralising ART delivery on health outcomes for adolescents and young adults living in low- and middle-income countries (DPhil Paper 1, published in *Global Health Action*)
2. (1) To evaluate progression through an extended HIV care cascade across public healthcare facilities in South Africa for a large cohort of ART-initiated adolescents and (2) to identify predictors of attaining cascade steps (DPhil Paper 2, under review in *BMC Infectious Diseases)*
3. (1) To characterise pathways of transition out of paediatric HIV care for ART-initiated adolescents in South Africa's decentralised public care setting and (2) to identify associations between transition pathways and HIV outcomes (DPhil Paper 3, published in *Journal of Acquired Immune Deficiency Syndromes*)

This chapter first summarises the key findings across the three included manuscripts, contextualised within the broader aims of this dissertation. Second is a discussion of the strengths and limitations of this research. The third section highlights key implications for policy and programming in South Africa and

beyond. This section is followed by a summary of local through international dissemination efforts and capacity building resulting from this dissertation, an exploration of future directions for research, and finally a conclusive summary of this dissertation.

2. Summary of DPhil Findings

In this DPhil thesis, I first demonstrate in a systematic review that very limited adolescent-specific and recent evidence exists on the effects of decentralisation in resource-limited settings (Paper 1). Looking to fill this research gap, I subsequently identify that adolescents in South Africa's decentralised healthcare system demonstrate low rates of viral suppression, with low rates of recent viral load testing (Paper 2). Critically, adolescents exhibit high rates of mobility across healthcare facilities, with clinical records underestimating both transfers out of care and mortality rates. Lastly, I explore how decentralising HIV care has transformed the experience of transition out of paediatric HIV care (Paper 3). With many adolescents initiating ART in generalised primary care clinics, most adolescents never transitioned out of paediatric HIV care. The most common mode of transition was through down-referral to a primary care clinic, following informal protocols developed by healthcare providers to mitigate risk of adverse post-transition outcomes.

This dissertation highlights the wide-ranging impacts that decentralising HIV care has generated for not only adolescent health but also clinical data management systems. Empirical findings from this thesis suggests that, although decentralising HIV care may have increased accessibility of care among adolescents in South Africa, it has also increased the complexity of care.

Decentralisation increases patient mobility across healthcare facilities and facility levels, which is compounded by the residential mobility of ALHIV and their transitions out of paediatric care facilities (Schuyler et al., 2017). Together, these factors generate a complex network of healthcare facilities for each adolescent patient.

In this section, I discuss the overarching findings from this dissertation, categorised into three themes: (1) Gaps in age-specific and recent evidence on decentralisation of adolescent HIV care; (2) Increased complexity of pathways of adolescent HIV care in a decentralised healthcare system; and (3) Accurately capturing adolescent HIV outcomes within a decentralised healthcare system.

Gaps in age-specific and recent evidence on decentralisation of adolescent HIV care

The systematic review (Chapter 4) found that only 2 of 11 eligible studies were able to provide age-disaggregated data for people aged 10-24 years. The limited availability of age-disaggregated data reflects the wider challenge of accessing data on adolescents beyond the WHO's paediatric age cut-off of 15 years (UNAIDS, 2015a). In sub-Saharan Africa, many national Departments of Health continue to categorise all ≥15-year-olds as adult patients, despite growing demands for adolescent-specific data on HIV care (Slogrove and Sohn, 2018; Idele et al., 2014).

In South Africa, a growing body of evidence is emerging for youth living with HIV, particularly for 15-24 year olds (Zanoni et al., 2016; Human Sciences Research Council, 2019). Through recent research efforts, such as those led by the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER),

more granular evidence on adolescents' HIV outcomes across the globe is emerging (Slogrove et al., 2018). This systematic review both contributes to the call for greater evidence on adolescent HIV care and informed the urgency of subsequent chapters of this thesis.

Second, this systematic review revealed the concerning lack of *recent* evidence on decentralising HIV care for adolescents. The two included studies analysed data collected from 2004-2009, and only 4 of the 11 eligible studies reported on any post-2011 data (Megerso and Garoma, 2016; Long et al., 2016; McNairy et al., 2017; Mutenda et al., 2016). Since 2011, both decentralised service delivery and ART eligibility have substantially changed, generating a shift in both healthcare provision and patients.

In 2010, the South African National Department of Health prioritised nurse-initiated and -managed antiretroviral treatment (NIMART) through which nurses can also initiate patients on ART at decentralised primary care clinics, including adolescents (Colvin et al., 2010). Beyond South Africa, NIMART adopted widely in sub-Saharan Africa along efforts to scale up care (Zuber et al., 2014). In 2013 and 2016, WHO guidelines for ART eligibility iteratively expanded, both enabling patients with more stable clinical profiles to initiate care and expanding the patient population (World Health Organization, 2016b). Research evaluating the effects of decentralisation must reflect this expanded patient population, as baseline health profiles at ART initiation have been associated with different patterns of care engagement and outcomes (Apondi et al., 2018; Maskew et al., 2019). Through use of data through 2017, Chapters 6 and 7 of this dissertation characterise this new context, including decentralised ART initiation through management.

Third, while numerous cohort studies have evaluated HIV outcomes for adolescents and youth *within* primary care clinics, this review highlighted that very little comparative evidence exists to frame the effects of decentralisation within care (Nglazi et al., 2012; Evans et al., 2013; Lamb et al., 2014; Okoboi et al., 2016; Agwu and Fairlie, 2013). Restricting cohort studies to adolescents within one care pathway (i.e. a cohort study in primary care clinics) limits the ability to evaluate how decentralised care differs from or affects other pathways, including pathways involving down-referrals from tertiary hospitals. Consequently, this review also highlighted the importance of analysing data from a large cohort of adolescents across multiple care pathways, across facilities and facility levels.

In 2020, the questions are not the feasibility of decentralising HIV care or whether decentralisation should be implemented in limited-resource settings. Rather, the pertinent questions are how decentralising HIV care—in its current implementation—is affecting adolescents' health and how it can be optimised. Chapters 6 and 7 of this thesis aim to address this first question and generate evidence towards answering the latter.

Increased complexity of adolescent pathways of HIV care in a decentralised healthcare system

Chapter 6 (DPhil Paper 2) identified high rates of inter-facility mobility within the adolescent cohort in South Africa, with one-third of adolescents attending at least two facilities. This finding underscores the importance of effective care linkage and record keeping across facilities (Sohn and Hazra, 2013). Beyond decentralisation, potential reasons for adolescents to attend multiple facilities include residential mobility and transition out of paediatric care (Schuyler et al.,

2017; McHenry et al., 2017; Davies et al., 2017; Southern African HIV Clinicians Society, 2017). However, decentralisation increases both the number of adolescents moving between facilities and the frequency of mobility through provider-initiated down-referral to lower-level healthcare facilities (Southern African HIV Clinicians Society, 2017). A further level of mobility is introduced by provider-initiated up-referral of patients back to specialised care in the event of complications (National AIDS & STI Control Program, 2009).

Additionally, through the combined rollout of decentralisation, NIMART, and task-shifting, a greater number of facilities are able to provide adolescent HIV care. This offers adolescents a greater range of facility options for self-specialising care by selecting specific clinics for specific needs, which further increases patient mobility between clinics (McHenry et al., 2017). Chapter 6 found that decentralised care was associated with having a recent viral load available, with a stronger effect for female and sexually infected adolescents. This finding may reflect a form of self-specialising care, whereby adolescents seeking sexual and reproductive health services at local primary care clinics are also engaged for routine viral load monitoring (Suthar et al., 2014). Indeed, ALHIV reported travelling to more distant healthcare facilities specifically for HIV-related services to avoid recognition by healthcare staff or other patients, which could result in suspicion or unintended disclosure of HIV status (McHenry et al., 2017).

Furthermore, the rollout of decentralisation has diversified the types of HIV care pathways for adolescents from ART initiation to management: to remain within centralised care facilities, within decentralised primary care clinics, or to move between centralised and decentralised facilities. Findings from Chapter 7

(DPhil Paper 3) indicated that over 40% of adolescents had initiated ART in non-paediatric care, the majority of whom had initiated in primary care clinics. Almost all adolescents who had initiated in non-paediatric care remained exclusively in non-paediatric care, across clinics and adult specialised care. Accordingly, Chapter 7 found that only 20.4% of the cohort had transitioned out of paediatric HIV care. This high rate of initiating and managing ART in decentralised care attests to the success of decentralising HIV care in South Africa. With the continued rollout of decentralisation across sub-Saharan Africa, experiencing HIV care exclusively in generalised, non-paediatric care is likely to becoming increasingly common for adolescents (Judd and Davies, 2018).

Finally, through down-referral to generalised primary care clinics, decentralisation has also generated a new pathway for adolescent transition out of paediatric HIV care in South Africa. To this candidate's knowledge, Chapter 7 is the first published work to document and quantitatively evaluate down-referral from paediatric HIV care to decentralised, generalised primary clinics as a form of adolescent care transition (Davies et al., 2017; Teasdale et al., 2017; Ramirez-Avila et al., 2017). Chapter 7 reported that the majority of adolescents who transitioned actually did so through down-referral transition, rather than the classical transition model from specialised paediatric to adult HIV care, as found in high-income contexts (Agwu et al., 2015; Kakkar et al., 2016).

Semi-structured interviews with healthcare providers identified informal protocols used both to determine which adolescents to down-refer and to facilitate an easier transition process for adolescents. Notably, a strict age cut-off was not applied, as also reported in a qualitative study of five public facilities in the

Western Cape (Kung et al., 2016). Hence, this dissertation underscores the importance of understanding adolescents' HIV care experiences in sub-Saharan Africa in their own lived contexts, rather than applying models documented in Western countries. Also, given this complexity of care, appropriate support from healthcare providers is crucial for ensuring successful linkage and outcomes in non-paediatric HIV care (Dahourou et al., 2017).

Accurately capturing adolescent HIV outcomes within a decentralised healthcare system

After adjusting for silent transfers in care and unreported mortality, Chapter 6 identified a loss to follow-up rate of 16.9%. This rate is higher than the estimate previously reported for vertically infected ALHIV in sub-Saharan Africa (13.2%) and underscores the continuing challenge of retention in care for ALHIV (Slogrove et al., 2018). Chapter 6 identified that one third of the ALHIV marked as lost to follow-up in clinical records had been misclassified due to silent transfer to new facilities. Similarly, a review of Tier.Net in Mpumalanga province, South Africa, found that 21.8% of adult patients living with HIV had been misclassified as lost to follow-up due to transfer to new clinics (Etoori et al., 2020). As further discussed in Chapter 8.4, these findings indicate the importance of patient-centred HIV care that links patients across healthcare facilities to ensure accurate clinical records, particularly in decentralised healthcare systems with high mobility.

By updating clinical records with community-tracing methods, Chapter 6 determined that the mortality rate was 3.3% during the period of cohort follow-up. Clinical records significantly underestimated mortality for the cohort and identified only 33.3% of these deaths. Under-identification of adolescent deaths in clinical records highlights the importance of adjusting loss to follow-up rates for mortality

as well, as reported in previous reviews of clinical records in South Africa (Fox et al., 2018; Van Cutsem et al., 2011).

Furthermore, Chapter 6 reveals that, while overall viral load coverage was high, many viral load results were out-dated. South African national guidelines require at least annual viral load monitoring, even in the most decentralised, community-based models of ART delivery (Southern African HIV Clinicians Society, 2017; National Department of Health, 2019). However, in this study, only half of adolescents with clinical records had a viral load from the past 12 months, far below the officially reported 2015 provincial estimate of 80% for patients of all ages (World Bank, 2016). This low rate of recent viral load coverage indicates poor engagement with HIV care. Moreover, it suggests that healthcare providers in South Africa's public facilities are often obligated to make critical care decisions for adolescents using only partial—or outdated—clinical records (Southern African HIV Clinicians Society, 2017).

At most recent viral load, Chapter 6 found that the viral suppression rate for the total ART-initiated cohort was 47.5%. This rate of viral suppression is lower than the 85.2% officially reported in national estimates from 2017 (Human Sciences Research Council, 2019). This national estimate was based on a survey that actively collected and tested blood samples, with significant risk of non-response bias, and did not reflect rates of viral suppression known through routine monitoring practices. While achieving the final "90" of the UNAIDS target by 2020 may be unattainable, this low rate of viral suppression indicates that rapid, substantial progress must be made for adolescents to reach the UNAIDS 95-95-95 targets for 2030 (UNAIDS, 2014b). Chapter 6 found that the rate of viral

suppression was even lower (23.2%) if only considering data from the past 12 months as per national guidelines. This finding indicates that programmatic evaluation of viral suppression must also consider the *timing* of viral loads and provide specificity beyond "most recent," as is commonly reported in other studies (Slogrove et al., 2018; Brittain et al., 2018).

Finally, Chapter 7 reported that adolescents who had experienced down-referral transition out of paediatric HIV care were more likely to be virally suppressed at most recent viral load. Healthcare providers reported informal protocols used to follow up with adolescents after transition, including communication with destination facilities and patient education. Most commonly reported criteria used to determine which adolescents to down-refer included viral suppression and subjective assessment of patient "stability." These informal protocols may partially account for the facilities' apparent success in transitioning adolescents into primary care clinics. Section 4 of this chapter discusses key scalable lessons from these informal protocols for adolescent HIV care provision in other sub-Saharan African contexts.

3. Limitations and Strengths

This DPhil thesis presents findings from the first known study to analyse clinical outcomes from routine clinical records collected for ART-initiated adolescents traced into their communities and across a large network of public healthcare facilities in sub-Saharan Africa.

Strengths and limitations of the systematic review (DPhil Paper 1, Chapter 4)

A systematic review is intended to collect and critically appraise evidence across a large body of research and to synthesise the findings into a comprehensible and succinct summary (Gough et al., 2012). A crucial step in the design of a systematic review is determining the breadth of this body of research. A preliminary search of evidence for ALHIV (10-19 years old) in sub-Saharan Africa yielded very few studies, including in grey literature. Therefore, the breadth of this systematic review was expanded to include youth up to the age of 24 across all LMICs. Thus, the remaining question of scope primarily pertained to the mode of decentralisation being evaluated. Namely, a critical decision in designing this systematic review was whether to limit the review's scope to facility-based decentralisation, or to include studies evaluating decentralisation of HIV care from healthcare facilities into the community or home-based care. As a wide-ranging structural intervention, decentralisation of HIV care has taken many forms and evolved over time, including decentralisation beyond the healthcare facility (International AIDS Society, 2017). However, in most sub-Saharan African countries, decentralisation of healthcare begins iteratively with decentralisation from specialised, tertiary care facilities to lower level health facilities, before any further decentralisation into communities (World Health Organization, 2017a).

Although a broader review can increase the generalisability of the systematic review, a narrower scope results in a more feasible review and one that may ultimately have greater applicability to a specific population or intervention, assuming sufficient homogeneity across included studies (Thomas et al., 2019). As a result, broader reviews are well-positioned to examine the differential effects of multiple implementation approaches of an intervention, such

as a review considering all forms of decentralisation (Deeks et al., 2019). However, the aim of this systematic review was not to compare the effects of decentralising HIV care on youth's health outcomes across different modes of implementation in resource-limited settings. Rather, this review specifically aimed to evaluate evidence on the first stage of decentralising ART delivery—from higher- to lower-level healthcare facilities—for adolescents and youth living with HIV in LMICs. For this reason, the systematic review in Chapter 4 focuses on evidence from studies of facility-based decentralisation, excluding studies evaluating decentralisation to purely community- or home-based care.

While this narrower scope of intervention allows for more precise interpretation of evidence on facility-based decentralisation, reviewing studies of all forms of decentralisation could arguably have produced a review with a more expansive conceptualisation of decentralisation. A wider scope may have also resulted in a greater number of included studies in the review, despite greater heterogeneity and risk of "mix[ing] apples and oranges" in any potential meta-analysis (Moayyedi, 2004). For maximal policy impact, this candidate focused on facility-based decentralisation, including evidence from grey literature, which remains an initial step towards widespread scale-up across sub-Saharan Africa (World Health Organization, 2017a).

Strengths of the empirical papers (DPhil Papers 2 and 3, Chapters 6 and 7)

Several of the unique contributions made by this DPhil thesis—and thus the critical strengths of these studies—stem directly from the study design and intensive data collection approach used in the Mzantsi Wakho study. Because

study eligibility was ever having been initiated on ART, including those not currently retained in care, this thesis was able to include and track outcomes for adolescents who were completely disengaged from care and those without available clinical records. Through collection of these adolescents' routine clinical records across 52 public healthcare facilities, findings from this thesis reflect the health status of adolescents as available to their healthcare providers. Outcomes reported in this thesis indicate what information their healthcare providers would actually have in order to make care and treatment decisions, thereby also highlighting critical gaps in information available to practitioners. Furthermore, by including clinical records across these 52 public facilities, findings from this thesis potentially represent the care experiences and outcomes for adolescents in similar settings across sub-Saharan Africa—beyond findings from highly resourced and externally supported clinics. Indeed, the Mzantsi Wakho study setting was specifically selected by study partners to reflect poverty and healthcare contexts most similar to other low-income Southern African contexts (Cluver et al., 2016).

By searching for paper and electronic clinical records for every adolescent participant at each of the 52 facilities, this study allowed for both the correction of reported loss to follow-up (by identifying "silent" transfers) and identification of the most recent viral load available across all facilities of the adolescent's care. Additionally, through community tracing of adolescents for interviews, this study identified instances of participant mortality that had not been recorded in clinical records, thus providing more accurate estimates of mortality and loss to follow-up. Collection of adolescents' clinical records extended through records from

December 2017, providing a much more recent estimate of adolescents' health outcomes than previously reported (Zanoni et al., 2016). This time period also enables evaluation of adolescents' health after South Africa's implementation of universal test and treat in September 2016. Hence, this thesis's findings demonstrate both how ART-initiated adolescents experience HIV care and their health outcomes within a decentralised HIV care system facing a patient burden larger than ever before.

In addition, through the adolescents' self-reported questionnaires, individual-level data were available for evaluation in the study as predictors of care experiences and outcomes. For this thesis, the primary variables evaluated from participant-level questionnaires were mode of infection and urban/rural residence. However, as discussed in Section 6 of this chapter, future analyses are planned to harness the larger potential of these linked datasets by further investigating the relationship between clinical outcomes and self-reported experiences at home, in the community, and in clinics. Finally, this thesis was able to draw upon findings from the qualitative arm of Mzantsi Wakho to apply a mixed-methods approach in Chapter 7. By reflecting upon transition processes described by healthcare providers in semi-structured interviews, this paper highlighted potential reasons for the apparent success of adolescent HIV care transitions in this context. However, several key limitations for the studies presented in this thesis must be taken in consideration when drawing inferences for policy and programming impact.

Limitations of the empirical papers (DPhil Papers 2 and 3, Chapters 6 and 7)

Cohort Characteristics

As described in Chapter 5, the Mzantsi Wakho observational cohort comprised adolescents who had already been initiated on ART at any point. This study aims to describe the health experiences and care-seeking behaviours of adolescents already linked to HIV care. As a result, this thesis is not positioned to describe health outcomes or experiences for adolescents living with HIV who have not been initiated on ART—including those who have not yet been tested for HIV or linked to care. Hence, findings from this thesis do not necessarily speak to the reality of care for *all* adolescents living with HIV. The inclusion criterion of ART initiation introduces two potential sources of selection bias.

First, adolescents already initiated on ART by 2015 (the end of study recruitment) arguably represents a population with greater access and linkage to care. Thus, the study cohort could be biased towards adolescents with fewer barriers to care—including lack of social support and resources, financial and temporal barriers to clinic travel, and individual-level barriers such as internalised stigma (Govindasamy et al., 2014). Effectively, by restricting the sample to ART-initiated adolescents, this study could potentially be excluding the most vulnerable ALHIV, who have not been able to or chosen not to access HIV testing or ART (Maskew et al., 2019). However, the Mzantsi Wakho study sample still remains characterised by multiple vulnerabilities, as reported elsewhere (Cluver et al., 2016). By including ART-initiated adolescents who were no longer engaged in care or who were considered to be lost to follow-up in care, this study ensured the inclusion of more vulnerable adolescents within the treatment-initiated population. At baseline, 95% of participants were receiving a household cash transfer grant, 22% reported not having enough to eat in the past week, 19% lived in informal

housing, and 44% and 30% were maternally and paternally orphaned, respectively. These rates reflect the high levels of deprivation prevalent in the study context and reaffirm the applicability of the study's findings to adolescents facing similar levels of deprivation in other sub-Saharan African contexts.

Second, because study recruitment of ART-initiated adolescents ended in December 2015, only adolescents who had met eligibility criteria for ART initiation before 2016 would have been included in the study. In January 2015, following WHO recommendations, the South African National Department of Health expanded ART eligibility criteria for adolescents to patients with CD4 count ≥500 cells/mm^3; any patients co-infected with TB or hepatitis B virus (HBV); and any patients who were pregnant, breastfeeding, or within one year post-partum (National Department of Health, 2015). Only from September 2016 did South Africa adopt universal treatment into its national health policy, expanding ART eligibility criteria to all patients living with HIV, regardless of CD4 count (South African National AIDS Council, 2017). Hence, only adolescents who were vertically infected or who had comparatively worse or complicated clinical histories would have been initiated on ART by 2015 and therefore eligible for study inclusion. In contrast to the first source of sample selection bias, this sampling may have biased results towards worse health outcomes at baseline.

This sampling approach excluded ALHIV who were newly initiated on ART in the included healthcare facilities from 2016 onwards, including those who only became eligible for treatment under the universal test and treat policy. Hence, despite staggered entry into the Mzantsi Wakho study during the first wave of interviews from 2014-2015, Mzantsi Wakho is a fixed cohort of ART-initiated

adolescents, defined using a cross-sectional sampling approach of the underlying dynamic cohort of all ART-initiated adolescents in the health district (Szklo and Nieto, 2019). This fixed cohort design enabled the study to conduct community tracing and longitudinal follow-up for each adolescent participant.

Nevertheless, findings from this study provide key insights into adolescent HIV care in South Africa in the post-universal treatment context. By evaluating clinical records through December 2017, this study examines how adolescents experience and manage their HIV care within a system that is adapting to the large influx of newly eligible patients, who must also be initiated and maintained on ART. Effectively, this research addresses the question of what HIV care looks like for adolescents within a large decentralised healthcare system in the era of universal test and treat.

Furthermore, because prior ART initiation was an eligibility criterion for participation, this study was not positioned to evaluate the uptake of HIV testing, linkage to HIV care, and subsequent ART initiation for adolescents in South Africa. As demonstrated in Chapter 7, almost one third of ART-initiated adolescents in the Mzantsi Wakho cohort had initiated ART in primary care clinics, reflecting that decentralisation of HIV care has already been well integrated in the South African context. Yet, by 2013, only an estimated 14% of 15-24 year olds living with HIV in South Africa had initiated ART, and by 2016, only 57% of patients aged 1-19 who had entered HIV care had initiated ART (Zanoni et al., 2016; Maskew et al., 2019). With the switch to universal testing and treatment, the gap between those eligible for ART initiation (all persons living with HIV) and those on ART could potentially widen if sufficient human and physical resources

are not made available in South Africa. Decentralisation of HIV care, including ART initiation, is one strategy to close that gap.

For instance, rapid point-of-care HIV testing allows patients to know their HIV status within the same visit that they present for testing, reducing delays between testing, status disclosure, and subsequent linkage to care and ART initiation. A 2016 study conducted among youth in Kenya found that rapid point-of-care testing for HIV-1 RNA facilitated earlier linkage to care and ART initiation among patients testing positive, and the use of testing for HIV-1 RNA enabled greater detection of acute and early HIV infections (Sanders et al., 2019). In November 2019, the WHO officially recommended that countries shift from longer laboratory-based HIV testing to rapid diagnostic tests that can be used at point of care (World Health Organization, 2019b). As highlighted in Section 6 of this chapter, future research should consider how point-of-care HIV and viral load testing can be employed to improve rates of adolescent ART initiation in decentralised healthcare systems.

Defining decentralisation of HIV care

This dissertation does not evaluate the effect of decentralisation of HIV care beyond healthcare facilities and into community-based care models. Data collected from clinical records did not indicate whether adolescents were participating in community-based care models, such as community ART groups or medication pick-ups through central chronic medicine delivery and dispensing programmes (CCMDD) programmes (Kipp et al., 2012). As a result, analyses of clinical outcomes presented in this thesis were not able to specifically evaluate the

effect of decentralising HIV care into community models. However, through South Africa's models for differentiated service delivery, patients would only be eligible for community-based HIV care if they met sufficient patient stability criteria (International AIDS Society, 2017). Patients meeting these clinical criteria would simultaneously experience decentralisation of their facility-based care from higher-level healthcare facilities into primary care clinics, where they would still be expected to present for at least annual viral load testing and clinical consultations (Southern African HIV Clinicians Society, 2017). Moreover, facility-based decentralisation remains the primary and most commonly implemented mode of decentralisation, both within South Africa and across sub-Saharan Africa (Sharer et al., 2019). Additionally, South African models of differentiated service delivery for clinically stable adolescents include facility-based teen adherence clubs, which are organised by healthcare workers (International AIDS Society, 2017). Furthermore, in South Africa, only adult patients ≥18 years old are officially eligible for medication pickup through CCMDD programmes (National Department of Health, 2016).

Nevertheless, as ART delivery programmes scale up in sub-Saharan Africa with the expansion to universal ART, decentralised care with significant community-based care components is likely to become an increasingly prevalent mode of differentiated service delivery (Ehrenkranz et al., 2019). As discussed in Section 6, future research should evaluate how receiving different modes of community- and facility-based ART care impacts adolescents' clinical outcomes.

Non-epidemiological study design

The Mzantsi Wakho study was designed as a social science study, and, accordingly, the data collection conducted in the clinics and community does not reflect a traditional epidemiological cohort study. The clinical arm of data collection was done as a sub-study within the larger social science project and was subject to financial and temporal constraints for the amount of clinical data that could be collected. At each healthcare facility, data on viral loads and CD4 counts were only extracted for the participant's first and most recent results (by the end 2015 and 2017 for Round 1 and Round 2, respectively, or the date of data extraction if earlier). Effectively, for a given facility, each patient could only have a maximum of three viral load or CD4 results available by the end of data collection, assuming no missing data. Adolescents attending more than one facility could have more than three data points, because files would be available at multiple facilities. As a result, the data presently available in this study is not suited to in-depth longitudinal analysis of biomarker data, which would require more continuous and regular outcome measurements. Hence, in Section 6, this candidate proposes further strategies for longitudinal clinical data collection for the Mzantsi Wakho cohort for subsequent longitudinal analyses, with linkage to South Africa's national database of laboratory test results. However, the present dissertation still provides a cross-sectional estimate of adolescents' most recent available viral load and CD4 measurements, as well as longitudinally traced loss to follow-up and mortality.

Determining sources of missing or outdated data

Participants with missing clinical records were known to have initiated ART because they had been listed on ART registries at their respective healthcare

facilities, but a lack of clinical records suggests that their patient file may have been lost. The absence of clinical records renders the precise viral loads for these adolescents unknown. However, combined with the lack of electronic records for these individuals, adolescents without clinical records or any viral load data were presumed to be disengaged from care and thus likely to have unsuppressed viral loads, in line with previous studies (Zanoni et al., 2016; Long et al., 2016).

Additionally, this study was unable to distinguish specific reasons for missing or outdated viral load results. Namely, this study could not determine whether issues arose from providers or patients themselves. As discussed in Chapters 6 and 7, provider-end issues could include missingness due to instances of invalid test results or test results that were lost between laboratory processing and record keeping in facilities. Patient-end reasons for missingness could include patients not attending clinic appointments for routine viral load testing.

Finally, precise dates of participant mortality were unavailable for all instances of death. Because the majority of instances of death were reported by the community, exact dates were unavailable. Instead, only approximate dates were available based on follow-up data collection and when research assistants were informed of the patient's passing upon attempted re-tracing into the community. Similarly, exact dates of loss to follow-up were unavailable in the current form of data collection. In some patient files, simply "LTFU" had been marked on the relevant files, without a precise date of status designation. Loss to follow-up would therefore only be known to be accurate through the date of data extraction for patient files. For these reasons, future research outlined in Section 6

proposes to apply a life-table approach for analysis, which enables survival modelling with predetermined time intervals.

Mobility of cohort

Although this thesis traced patients' clinical records across 52 healthcare facilities of the Amathole Health District, it was unable to trace patients to facilities beyond this network. In particular, this thesis could not determine instances where patients had transferred into private care or into facilities outside the geographical catchment area, such as Cape Town, Johannesburg, or Durban. Reasons for patient mobility beyond the Amathole Health District could include residential mobility, clinic-initiated transfers of care, or self-transfers for care-seeking. However, in future research plans outlined in Section 6, this candidate proposes to link Mzantsi Wakho data with the South African National Health and Laboratory Services to identify instances of such transfers.

4. Implications for Policy and Programming

Findings from this DPhil provide key implications for policy and programming to improve HIV care for adolescents in decentralised healthcare systems of sub-Saharan Africa. These key messages have also been incorporated into policy and programming dissemination led by this candidate, as outlined in Section 5.

These implications include the following: (1) Accounting for adolescent patient mobility in clinical data management; (2) Closing information gaps between adolescents' true health status and clinical records available at healthcare facilities; (3) Acknowledging adolescents' agency in HIV care-seeking; (4) Characterising context-specific frameworks for adolescent transitions in HIV care; (5) Identifying practical approaches for facilitating adolescent transitions in

HIV care; (6) Leveraging decentralisation of HIV care to strengthen healthcare systems; and (7) Considering the impact of COVID-19 on adolescent access to HIV care in South Africa.

Accounting for adolescent patient mobility in clinical data management

Through an intensive data collection strategy, this dissertation identified a high rate of multiple-clinic attendance among ALHIV in South Africa. Decentralisation of HIV care delivery exponentially increases patient inter-facility mobility among adolescents, who already demonstrate significant residential mobility (Laoire et al., 2010; Schuyler et al., 2017).

Therefore, it is essential for policy and programming to account for the high degree of adolescent patient mobility and to develop strategies for improving communication and linkage of HIV care across facilities. South Africa's current system relies on patients' arriving at new care facilities with an official transfer letter that contains a summary of their health history and status. This dissertation provides strong evidence that this communication system must be improved to provide patient-centred HIV care and monitoring.

The WHO recommends the use of unique patient identifiers to address these challenges, thereby improving patient safety, programme monitoring and evaluation, and appropriate allocation of health resources (World Health Organization, 2017b). The South African National Department of Health has developed a Health Patient Registration System (HPRS) in the Western Cape to allocate unique patient IDs in the public healthcare sector, but it has not yet been operationalised nationally (Mazanderani et al., 2018).

A key recommendation from this dissertation is to underscore the importance of this programme and to urge for a rapid national rollout of unique patient IDs, particularly in lower resourced provinces such as the Eastern Cape. Even if centralised electronic records are not feasible across all clinics in the Eastern Cape, the availability of a unique patient ID for each adolescent would certainly facilitate information sharing between facilities and enable more accurate analysis of data for monitoring and evaluation. Given the lack of national unique patient IDs, the National Health Laboratory Services of South Africa have undertaken several research collaborations to link individual patient records using probabilistic algorithmic matching methods for more accurate estimates of national care outcomes, as further discussed in Section 6 (Bor et al., 2018).

Until national unique patient IDs are available, it is crucial to develop stronger referral systems between healthcare facilities within the same health district, including regular information exchanges between nearby sites who may share patients. Additionally, patient navigator programmes can specifically include patient education on how to manage clinical mobility. This recommendation also highlights the importance of supporting programmes for patient navigators within healthcare facilities, and the potential to leverage these auxiliary staff in strengthening information sharing across facilities. None of these interventions would necessitate centralised electronic medical records and may be more feasible in other resource-limited settings across sub-Saharan Africa.

Without improved communication across facilities, misidentification of adolescents as lost to follow-up due may encourage disengagement from care due to negative reactions from healthcare providers (Ware et al., 2013). Silent

transfers without patient linkage may also result in double counting the number of patients initiated on ART, which would artificially inflate estimates of programmatic success and progress towards the UNAIDS Fast-Track targets (Etoori et al., 2020; Maskew et al., 2019). Finally, through silent transfers to new facilities, treatment-experienced adolescents may be misclassified as ART-naïve and initiated on a regimen that is no longer therapeutically effective, potentially resulting in higher rates of transmitted drug resistance (Castro et al., 2012).

Closing information gaps between adolescents' true health status and clinical records at healthcare facilities

Findings from this dissertation indicated that adolescents' clinical records both significantly underestimated mortality rates and demonstrated a paucity of recent viral load data. Additionally, if the high rate of viral suppression among ART-initiated youth in South Africa's 2017 national survey is truly representative, the large gap between findings from the national survey and from routine clinical records is of great concern (Human Sciences Research Council, 2019).

Based on these findings, this candidate recommends that national health databases actively engage in information sharing with decentralised primary care clinics, to improve the accuracy of information in patients' records and to identify potential gaps in clinical care management. For instance, where community tracing of patients lost to follow-up is not feasible, regular information exchange with national vital registries can improve the accuracy of mortality recording in clinics. Underreported mortality can both overestimate loss to follow-up rates and

underestimate the failures of HIV care programmes (Fox et al., 2018; Van Cutsem et al., 2011).

Further research is required to determine the extent to which routine viral load reporting for adolescents are incomplete, relative to information available in the South African National Health and Laboratory Service database, where results from all viral load tests are stored. If viral load tests are being performed at least annually in accordance with national guidelines—but these results are not reflected in clinical records—there is a crucial gap of communication or recording between the central laboratory services and individual facilities (Euvrard et al., 2019). In this situation, information systems must be optimised to streamline the sharing of information to ensure that healthcare providers can provide appropriately tailored HIV care for adolescents, which is often determined by viral load results (Southern African HIV Clinicians Society, 2017)

In parallel, guidelines should support the development of robust viral load testing infrastructures (Euvrard et al., 2019; Cissé et al., 2019). Point-of-care viral load testing offers one potential approach to simplify testing, with the rapid return of test results in remote and decentralised facilities that may improve accuracy of routine clinical records (Drain et al., 2019).

Acknowledging adolescents' agency in HIV care-seeking

By increasing the number of available healthcare facilities, decentralising HIV care has also expanded adolescents' agency in their own HIV care-seeking. One factor motivating patient mobility for ALHIV is the ability to self-specialise, or "shop," for their healthcare needs across facilities. For instance, healthcare providers

interviewed in the Mzantsi Wakho study noted that ALHIV would often return to specific healthcare facilities where they had good relationships with providers, even if they had been told to transfer to another clinic. Indeed, in the Mzantsi Wakho cohort, shorter travel time to clinic was not associated with retention in care for ALHIV, contrary to what the theory of change for decentralisation might suggest (Cluver et al., 2018).

Therefore, policy and programming must acknowledge that ALHIV are also agents in differentiating their own care. Recommendations and guidelines for healthcare provision in decentralised healthcare systems should aim to align both paths of care differentiation—by the healthcare providers and by the ALHIV themselves. For example, as reported in Chapter 7, while nurses determined which patients were eligible to transition out of paediatric care, adolescents were given a range of primary care clinics from which to select their destination facility. Thus, empowering ALHIV to become actively involved in their care decisions, including patient education, may have increased their sense of ownership and contributed to successful post-transition outcomes.

Furthermore, ALHIV must be actively engaged in guiding the formation of HIV policies that affect their care (Denison et al., 2018). Although much research attention has been paid to “adolescent-friendly” services, there is a clear lack of consensus around what these care packages might entail. In each care context, regular and continuous input from ALHIV is essential for determining which services are actually perceived as adolescent-friendly and should be implemented. These may include separate clinic hours (before or after school) or days for youth regardless of HIV status, separate spaces for youth, longitudinal

peer support networks, integrating sexual and reproductive health into HIV care, and training healthcare providers in youth-friendly care (Williams et al., 2017; Ritchwood et al., 2020; Zanoni et al., 2019).

For instance, ALHIV in sub-Saharan Africa have expressed preferences for facilities with spaces that ensure privacy during check-in and clinical evaluations, to minimise risk of stigma (Williams et al., 2017). Conversely, for some patients, facilities with separate days, units, or waiting areas for people living with HIV were also highly stigmatising, as community members could easily identify patterns in the clinic's schedule and physical set-up (Kolawole et al., 2017). Additionally, ALHIV perceived facilities that used colour-coded patient files to identify patients living with HIV to be highly stigmatising, posing greater risk for disclosure within the clinic (Ritchwood et al., 2020).

Characterising context-specific frameworks for adolescent transitions in HIV care

A key lesson from this dissertation has been the importance of first identifying and describing the complex reality of HIV care in the specific country context (Judd and Davies, 2018). Through this inductive approach, Chapter 7 of this dissertation demonstrated the need to understand adolescent transitions out of paediatric HIV care in South Africa beyond the framework developed in Western contexts.

Policy and programming efforts to improve adolescent HIV care must consider the multiple new pathways for adolescent HIV care created by decentralisation, such as down-referral transition to primary care clinics (Dahourou et al., 2017). However, this dissertation also emphasises the need to think of adolescents *beyond* paediatric care, as many never experience

specialised paediatric HIV care within South Africa's decentralised healthcare system. This, in turn, suggests that all healthcare providers in South Africa must be trained to manage the health needs of ALHIV, regardless of specialty or facility tier (Southern African HIV Clinicians Society, 2017). Furthermore, for those ALHIV who begin in paediatric HIV care, transition must be understood as a desired outcome in of itself, as ALHIV navigate life-long treatment (Kung et al., 2016).

Therefore, before developing guidance to facilitate adolescent care transitions, it is essential to first characterise the real-world HIV care context, as has been done by this dissertation for South Africa and by others for Nigeria (Badejo et al., 2018).

Identifying practical approaches for facilitating adolescent transitions in HIV care

Considering the successful outcomes of adolescents who experienced down-referral transition in the Mzantsi Wakho cohort, the informal protocols used by healthcare providers in these facilities offer key recommendations for reducing the risk of negative post-transition outcomes. Some key practical approaches include the following (Masese et al., 2019; World Health Organization, 2014a; Kung et al., 2016; Sharer and Fullem, 2012):

- Determine transition readiness and willingness through a developmentally appropriate, global assessment of the adolescent's clinical stability and likelihood to succeed in non-paediatric care—beyond age as an absolute indicator
- Ensure that adolescents are aware of their HIV status before transition to a new service model or healthcare site

- Frame conversations surrounding transition as a continuous, two-way dialogue that begins years before transition is set to take place
- Strengthen communication between adolescent clients and healthcare providers, including an understanding of why adolescents are being asked to transition out of paediatric care
- Engage adolescents and their caregivers throughout the transition process to encourage active decision-making by the adolescent, such as selecting destination facilities from a range of options (where possible)
- Create standardised procedures for each transition pathway, including transfer of clinical records and patient history, and ensure the adolescent is aware of what happens in each step in the process
- Strengthen communication between paediatric and non-paediatric care providers, including healthcare staff at primary care clinics, to establish continuity of care
- Ensure that receiving healthcare facilities are expecting and can accommodate the adolescent
- Consider transitioning adolescents as a group to facilitate peer support through this process, or creating support groups for adolescents approaching transition
- Train healthcare staff at all facilities to provide youth-friendly care, as contextually relevant
- Where possible, create multidisciplinary teams to support adolescent transition, including psychological and social support services

Importantly, these recommendations reflect that, in decentralised healthcare systems, infrastructure must be strengthened at both paediatric and non-paediatric healthcare facilities to facilitate transitions in care for ALHIV (Katusiime et al., 2013).

Leveraging decentralisation of HIV care delivery to strengthen healthcare systems

Although decentralisation of the public healthcare system in South Africa was motivated by the need to rapidly scale up HIV testing and treatment, decentralisation bears critical relevance to the management of other diseases and chronic illnesses (South African National AIDS Council, 2017). Decentralised primary care clinics function outside of the realm of HIV care and provide daily care to patients with and without HIV for a wide range of services.

Accordingly, lessons learned from decentralising HIV care delivery in South Africa can be applied to expanding other forms of clinical care, including TB treatment, sexual and reproductive health, non-communicable diseases (NCDs), and mental health. Effectively, decentralisation of HIV care can operate as a historical precedent for scaling up care for other illnesses in resource-limited contexts (Rasschaert et al., 2011). Indeed, the ultimate goal of the HIV/AIDS medical community is for HIV to be treated as one of multiple manageable chronic illnesses (Deeks et al., 2013).

Particularly as the double burden of disease rises across sub-Saharan Africa, integrating HIV and NCDs into routine, chronic care through decentralisation will be critical to ensure universal health coverage (Campbell et al., 2013). For instance, management of cardiovascular disease and diabetes can

adopt principles of decentralisation, with routine monitoring of cholesterol and blood glucose carried out at primary care clinics, alongside clinical counselling.

Considering the impact of COVID-19 on adolescent access to HIV care in South Africa

This section considers how the outbreak of the novel coronavirus (COVID-19) potentially impacts healthcare access for ALHIV and how South Africa's decentralisation of HIV care may inform the national response. Given that information about COVID-19 is continually evolving at the time of this dissertation, this section does not provide specific recommendations. Rather, it reflects on how decentralisation of adolescent HIV care is relevant to emerging recommendations for maintaining HIV care services during the COVID-19 pandemic.

The first case of COVID-19 was declared in South Africa on 5 March 2020, and by 21 July 2020 the South African Ministry of Health reported 373,628 confirmed cases within the country. The effects of the COVID-19 pandemic are continually evolving and far-reaching, with severe consequences for mental and physical health, poverty, food security, and economic growth. As the number of COVID-19 cases continues to grow, health systems around the world are at risk of becoming overwhelmed. In South Africa, the health system was already under immense pressure before COVID-19 due to the large population of patients living with HIV, TB, and a growing number of non-communicable diseases. Hence, a critical priority at this time must be ensuring that people living with HIV can continue accessing ART and other vital health services (UNICEF, 2020).

This challenge is particularly crucial for ALHIV, who already demonstrate the lowest rates of accessing ART and greatest difficulty maintaining adherence outside of the COVID-19 context. As COVID-19 increases the risk of service disruptions and reduced access to care, ALHIV are particularly vulnerable to disengagement from care, with potentially fatal consequences (Nyoni and Okumu, 2020). Conclusive evidence on the risk for COVID-19 infection among people living with HIV is still emerging (UNAIDS, 2020c). However, people living with HIV who are not on ART or who demonstrate poor adherence are at greater risk of being immunocompromised and therefore have higher risk of co-infections, which could include COVID-19. The low rate of ART uptake and adherence among ALHIV places this group at particular risk, although risk for COVID-19 infection must also account for their younger age. Furthermore, ALHIV in South Africa are more likely to be socioeconomically vulnerable and living in settings like informal settlements where social distancing is infeasible (Zar et al., 2020).

Lockdowns and social distancing requirements to curb the COVID-19 pandemic may impede access to HIV care for a range of reasons. Lockdown measures may generate confusion about whether and where patients can access care, as has been demonstrated in China, and travel restrictions can prevent ALHIV from reaching clinical care sites (Nyoni and Okumu, 2020). Social distancing requirements may also disrupt community-based psychosocial support strategies that promote ART adherence for ALHIV, including support groups and adherence clubs—aside from regular interactions with family and peers (Nyoni and Okumu, 2020). Financial insecurity resulting from lockdowns and the economic impact of COVID-19 may also result in an inability to pay for transport to

healthcare services and increase food insecurity, which is a key barrier to ART adherence (Singer et al., 2015). Finally, COVID-19 may overwhelm the already overburdened healthcare system in South Africa, both in terms of human and physical resources within facilities and the medication supply chain. In China, patients living with HIV faced difficulties accessing ART medication and experienced treatment delays due to hospitals' being overwhelmed with COVID-19 patients (Jiang et al., 2020).

Indeed, a modelling group convened by UNAIDS and the WHO estimated that a 6-month disruption of ART could result in over 500,000 extra deaths from AIDS-related illnesses in sub-Saharan Africa from 2020-2021 (Hogan et al., 2020). These excess deaths would reverse progress on reducing AIDS-related mortality to levels reported in 2008, with an annual average excess in deaths of 40% for the next five years (Hogan et al., 2020). Moreover, disrupted ART services would also reduce rates of virological suppression, resulting in higher rates of onwards transmission and HIV incidence. This could potentially reverse progress in prevention of mother-to-child transmission, resulting in a growing number of child HIV infections and, eventually, a significantly larger population of vertically infected ALHIV.

However, a series of policy recommendations have been developed by UNAIDS, UNICEF, and PEPFAR to minimise the disruption of HIV care services for people living with HIV, including ALHIV, during the COVID-19 pandemic. These policy recommendations reveal how decentralised service delivery, including decentralisation of HIV care, can be leveraged to support continued ART

delivery and other HIV care services throughout this pandemic. A few key elements of these recommendations are as follows:

- *Rapid scale-up of multi-month dispensing of ART and other medications for comorbidities, including drugs for TB treatment and prevention.* UNAIDS, UNICEF, and PEPFAR have all recommended multi-month prescriptions and dispensing of 3-6 month supplies, where medication stocks allow (UNAIDS, 2020c; UNICEF, 2020; Meeting Targets and Maintaining Epidemic Control (EpiC), 2020). These multi-month supplies would enable patients to maintain ART adherence without regular clinic attendance while facilities are overwhelmed with COVID-19 cases and also reduce risk of COVID-19 exposure or transmission. In turn, case management and peer navigator teams would need to be trained on how to support clients engaging in this new model of care delivery (Meeting Targets and Maintaining Epidemic Control (EpiC), 2020). In May 2020, South Africa's Department of Health announced that the central chronic medicine delivery and dispensing programme will provide 6- and 12-month extensions of ARV prescriptions (UNAIDS, 2020c). This policy expands eligibility for the decentralised central chronic medicine delivery and dispensing model for patients <18 years old in South Africa, including most ALHIV. However, dispensing programmes must ensure that appropriate supply management and storage availability are ensured (UNICEF, 2020).

  Prior to COVID-19, decentralisation of HIV care in South Africa increased the number of healthcare facilities where ALHIV could receive care and

pick up medications. In decentralised care models, primary care clinics have been sites for low-intensity medication pick-ups, which can easily translate to the pick-up of multi-month supplies in the context of COVID-19. The increased proximity of decentralised clinics to the homes of ALHIV may also mitigate the heightened financial and temporal difficulties associated with travel during the pandemic. To adhere to physical distancing recommendations, healthcare facilities should relocate refill/pickup locations to areas outside the facility building itself and ensure that distance is maintained between patients in queues (Wilkinson and Grimsrud, 2020). However, stigma-related concerns may persist and dissuade ALHIV from attending nearby clinics, even for medication pickup.

Under previous models of decentralisation, only clinically stable ALHIV were technically eligible for multi-month supplies with reduced clinical contact. However, given the context of COVID-19, recommendations include the provision of 6-month prescriptions for not yet clinically stable ART patients, with a minimum 3-month ART supply (Wilkinson and Grimsrud, 2020). This would ensure that these particularly vulnerable ALHIV are still able to access medication, while the longer prescription would provide the flexibility for patients to avoid a second visit to the healthcare facility if it becomes inappropriate after three months (i.e. patient becomes stable or clinics not accessible to patient).

- *Decentralisation of medication pick-up beyond the clinic.* Where clinics and other healthcare centres are unable to provide clinical care or medication supplies, alternative distribution plans must be considered, including decentralised community distribution (Wilkinson and Grimsrud, 2020; Meeting Targets and Maintaining Epidemic Control (EpiC), 2020). Some approaches could include community-based pickup points (e.g. churches and post offices), automated lockers near clinic buildings, pop-up pharmacies with pick-up windows, and home deliveries (where feasible, acceptable, and minimally stigmatising) (Meeting Targets and Maintaining Epidemic Control (EpiC), 2020).

- *Implementing feasible digital health interventions.* In several high-income settings, health systems have shifted the majority of patient care to telemedicine and virtual visits with healthcare providers (Wood et al., 2020; Barney et al., 2020). In many sub-Saharan African settings, including South Africa, telemedicine is not a truly viable alternative for patients in the public healthcare system, with limited access to the internet and mobile data (Mendelsohn and Ritchwood, 2020). Instead, patients arriving at public hospitals and clinics in South Africa are screened for acute respiratory symptoms before entry (Mendelsohn and Ritchwood, 2020). However, digital interventions can be harnessed to maintain continuity of psychosocial support services that improve ART adherence. For instance, peer support and routine adherence counselling can still continue through text messaging and phone calls (Meeting Targets and Maintaining

Epidemic Control (EpiC), 2020; Nyoni and Okumu, 2020). Moving peer support groups and adherence clubs to mobile messaging-based services may offer an alternative to in-person meetings. For these digital interventions to become feasible, healthcare systems must provide airtime and mobile plans for healthcare workers conducting remote support (Meeting Targets and Maintaining Epidemic Control (EpiC), 2020). However, the privacy and confidentiality of ALHIV must be carefully considered when shifting to these platforms (UNICEF, 2020).

- *Prioritising routine viral load testing for the most vulnerable patients.* PEPFAR recommends delaying routine viral load testing until laboratory services resume normal capacity and prioritising viral load testing for at-risk sub-populations. These groups would include pregnant women and those who were recently initiated on ART as well as those experiencing adherence challenges, developing opportunistic infections, or indicating treatment failure despite enhanced adherence support (Meeting Targets and Maintaining Epidemic Control (EpiC), 2020). This change to viral load testing guidelines may result in significant gaps in data coverage for patient monitoring and research activities that consider data from 2020 onwards, including future research activities planned by this candidate.

In sum, the recent changes and emerging recommendations for maintaining HIV care in South Africa amid COVID-19 are leveraging the expanded healthcare infrastructure developed by the decentralisation of HIV care. Even if

COVID-19 treatment is only provided at secondary and tertiary facilities in South Africa, the wider network of community health centres and primary care clinics can relieve stress from these centralised sites by maintaining treatment for other critical chronic illnesses. These decentralised care sites also offer pick-up points for multi-month drug supplies, in settings where community-based distribution models are infeasible or unacceptable by ALHIV clients.

5. Dissemination and Impact

Knowledge exchange, impact generation, and local capacity building have been core values of this thesis. With the present research, this candidate sought both to generate real-world impact in adolescent HIV care and to ensure local ownership of knowledge, through collaboration with local research assistants and partner healthcare facilities. Audiences for dissemination from this thesis can be divided into three categories: academic, policy, and programming.

Academic dissemination

From this DPhil, two first-authored papers have been published in peer-reviewed journals, and a third first-authored paper is currently under review. Additionally, through collaboration with other members of the Mzantsi Wakho research team, this candidate has co-authored one peer-reviewed publication, and two further co-authored manuscripts are currently in preparation. This candidate has presented findings from her dissertation at (1) international academic conferences and workshops, (2) research seminars with the Centre for Evidence-Based Interventions at the Department of Social Policy and Intervention, University of Oxford, and (3) research seminars for the Implementation Science Working Group

at the Centre for AIDS Research, University of California San Francisco. A full list of presentations and publications arising from this thesis are presented in Chapter 1.1.

Policy dissemination and impact

This candidate developed the third paper of this dissertation (Chapter 7) in close collaboration with the UNICEF Eastern and Southern Africa Regional Office HIV/AIDS Programme. Through this collaboration, this candidate has presented this dissertation research at webinars for the UNICEF Eastern and Southern Africa Regional Office, attended by UNICEF representatives from country offices. Additionally, this work has resulted in a UNICEF policy brief on adolescent transitions in HIV care, which this candidate has developed as part of a larger UNICEF policy brief series with Mzantsi Wakho on adolescent HIV care in sub-Saharan Africa. This policy brief is currently being finalised with UNICEF and highlights key messages from DPhil Papers 1 and 3.

Furthermore, findings from this dissertation were presented at workshops and webinars led by the Elizabeth Glaser Paediatric AIDS Foundation, as part of the New Horizons Advancing HIV Care collaboration. These meetings were attended by representatives from the Ministries of Health from several sub-Saharan African nations. Based on the expertise developed through this dissertation, this candidate was selected as a member of the Technical Working Group to co-develop the Elizabeth Glaser Paediatric AIDS Foundation's Adolescents Living with HIV Transition Toolkit. This toolkit aims to guide multi-disciplinary teams in the successful implementation of transitions in adolescent HIV care and treatment, across facility settings. In January 2020, this toolkit

underwent validation at a meeting with stakeholders in Uganda and is currently available at https://www.pedaids.org/resource/adolescent-and-youth-transition-of-care-toolkit/.

Finally, the Mzantsi Wakho team drafted the 2017 South African National Adolescent & Youth Health Policy (National Department of Health, 2017). In writing this policy document, members of the Mzantsi Wakho team conducted evidence reviews, including and beyond findings from the Mzantsi Wakho research project, and consultations with stakeholders, including adolescents themselves.

Programming dissemination and impact

The primary mode of local dissemination was feedback of findings to the healthcare facilities included in Mzantsi Wakho, particularly during this candidate's fieldwork in the Eastern Cape. All 52 healthcare facilities were provided with a one-page summary of Mzantsi Wakho research progress and preliminary findings, which was updated as new findings emerged. Additionally, at larger healthcare facilities, the clinic-based research team, led by this candidate, provided presentations to facility staff to discuss research findings and implications. By April 2018, presentations had been delivered to seven healthcare facilities, attended by over 68 healthcare providers in total. Preliminary findings from this dissemination were also shared with local NGOs, such as Beyond Zero and Kheth'impilo, which provide support for HIV, TB, and STI prevention and treatment.

From this candidate's experience, these dissemination efforts were consistently well-received and appreciated by healthcare staff, particularly nurses.

This dissemination approach, including direct communication with the healthcare facilities as stakeholders, acknowledged the ethical imperative to share emerging findings with local implementors in a timely manner.

At the provincial level, preliminary findings were shared in presentations to the Eastern Cape Department of Health Provincial Health Research Committee and the Eastern Cape AIDS Council. Additionally, while fieldwork was active, updates on research findings were provided to the Eastern Cape Department of Health once every three months.

Local capacity building

During this candidate's year of fieldwork project management, a key priority was a genuine effort to build the local capacity of research assistants, including but not limited to technical skills training. Accordingly, this candidate trained three members of the clinic-based research team on data entry in SPSS and one member on basic data analysis in SPSS. Additionally, this candidate trained ten members of the local Mzantsi Wakho research staff on advanced Excel skills in large files used to guide data collection strategies.

Finally, this candidate sought to empower and lift the voices of local staff to lead on discussions and presentations of study findings. For this candidate, it was critical to genuinely engage in sustainably developing capacity to lead and conduct health research among local research staff in South Africa (Franzen et al., 2017). Accordingly, during her year of project management, this candidate provided trainings and guidance to local research assistants on presenting findings to a range of stakeholders. As a result, presentations to included healthcare facilities as well as the provincial Department of Health were led by the

local clinic-based research assistants, with guidance and support from this candidate. Two members of the research staff (Vuyiseka Luke and Amanda Mbiko) presented clinical study findings at the Public Health Association of South Africa conference in September 2017. One member (Amanda Mbiko) also presented clinical findings at the South African AIDS Conference in June 2017, based on analyses that she conducted herself using SPSS, with the support of this candidate.

Figure 18. Senior Research Assistant Vuyiseka Luke rehearsing her presentation for the Public Health Association of South Africa Conference at project office in East London

Source: DPhil candidate

Figure 19. Clinic Research Assistant Amanda Mbiko presenting study findings at the Public Health Association of South Africa Conference in Johannesburg

Source: DPhil candidate

6. Directions for Future Research

Beyond the implications for policy and programming outlined in Section 4 of this chapter, this thesis highlights several key research questions for future work. This section highlights future research already planned for subsequent analysis by this candidate using data from the Mzantsi Wakho study as well as questions requiring further investigation.

Future analyses planned by this candidate with the Mzantsi Wakho cohort

Rates and predictors of adolescent mortality and loss to follow-up in HIV care
In her first post-doctoral paper, this candidate will estimate rates and predictors of mortality and loss to follow-up from HIV care within the Mzantsi Wakho cohort, corrected using community-traced methods. As demonstrated in Chapter 6, mortality and loss to follow-up estimates from clinical records alone can result in

significantly inaccurate estimates of retention in care, due to unrecorded transfers in care and deaths.

For this first post-doctoral paper, this candidate will apply the life table approach for analysis, rather than the Kaplan-Meier method implemented by Fox et al. (2018). Because exact dates are unavailable for mortality and loss to follow-up within the current Mzantsi Wakho dataset, the life table approach would allow for survival analysis using discrete time intervals during the follow-up period (Smith et al., 2004). This candidate proposes defining time zero as the date of ART initiation and measuring time intervals in months since ART initiation. Adolescents who had initiated ART before the observation period (pre-2014) will be left-truncated, resulting in a post-ART initiation survival estimates during the 3 years of observation in this study.

Subsequently, predictors of loss to follow-up and mortality will be estimated using multivariate Poisson regression. Predictors will include both sociodemographic and treatment-related factors such as having experienced decentralised care and transition out of paediatric HIV care. This study will expand upon previous clinic-based studies of adolescent retention in HIV care in South Africa through the inclusion of sexually infected adolescents and by evaluating outcomes adjusted for deaths not reported in clinical records and for transfers to new healthcare facilities (Evans et al., 2013; Slogrove et al., 2018). Furthermore, this study would be the first to analyse the effects of decentralising HIV care and paediatric care transition on mortality and retention in care for a large cohort of adolescents in sub-Saharan Africa (Murray et al., 2017).

Linkage of manually traced adolescent clinical records to national laboratory database

As a follow-up of the Mzantsi Wakho cohort, this candidate has been a Co-Principal Investigator in the setup of a new longitudinal study in collaboration with the National Health Laboratory Services of South Africa (NHLS). This study is known as Understanding Predictors of Lifelong Initiation and Follow-up Treatment for Adolescents and Youth Living with HIV (UPLIFT).

Data from the NHLS warehouse includes the date and result for every laboratory test conducted for all patients in South Africa's public healthcare facilities, including and beyond HIV-related tests. Using probabilistic matching to link Mzantsi Wakho participants to laboratory results within NHLS databases, this study aims to create a lifelong longitudinal HIV cohort of ALHIV in South Africa.

Previous studies have developed and applied a linkage algorithm to identify unique patients across laboratory results within the NHLS data warehouse, establishing a longitudinal national HIV cohort that includes adolescents (Maskew et al., 2019; Fox et al., 2018; Bassett et al., 2018). However, this study will take a further step of linking the Mzantsi Wakho social science cohort and adolescents' self-reported data (2014-2018) to lifetime laboratory results from the NHLS. Hence, UPLIFT would allow for both more rigorous epidemiological analyses of adolescents' care outcomes and identification of experiences in the clinic, home, and community that can shape health outcomes.

Because South Africa does not currently have unique national patient IDs, Mzantsi Wakho participants will be linked to records in NHLS databases using the clinical records manually extracted from the 52 healthcare facilities as well as personal identifying information from the adolescent questionnaires (2014-2018).

This self-reported information includes full names, dates of birth, sex, healthcare facilities, and residential addresses. During the third wave of Mzantsi Wakho interviews, consent was obtained from all participants and caregivers to access data from NHLS. As of May 2020, this candidate has provided the NHLS team with the necessary Mzantsi Wakho data for linkage, and she is collaborating with their team to refine the adolescent matching algorithm.

If the matching yields a linked cohort of sufficient size, this study will enable a wide range of further analyses to understand the longitudinal trajectories of adolescents' HIV care outcomes in South Africa. This study will potentially increase clinical data coverage of adolescents' health outcomes by (1) including all lifetime test results and (2) linking adolescents' outcomes across all public facilities in the nation, in the event of care transfers beyond the Mzantsi Wakho catchment area. Data obtained through NHLS would also include test results that were unavailable in facilities' clinical records as a result of delays in recording or lost reports, among other reasons (Kaposhi et al., 2015). Additionally, this study will include results from all available laboratory tests—not just viral load and CD4 counts—such as tests of opportunistic infections, drug resistance, and renal function.

One previous study using the linked NHLS cohort focused specifically on ALHIV, but it only evaluated rates of ART initiation among this cohort (Maskew et al., 2019). Through the UPLIFT study, this candidate plans to apply a multistate framework to longitudinally evaluate clinical stability for the Mzantsi Wakho adolescent cohort. At each time point since ART initiation, a multidimensional outcome of patient stability would be constructed based on WHO definitions for

stability and South African national guidelines for clinical monitoring of adolescents on ART (Waldrop et al., 2016; Southern African HIV Clinicians Society, 2017). This analysis would provide a more nuanced understanding of patient stability over time for ART-initiated ALHIV in South Africa, as they navigate the decentralised public healthcare system. To this candidate's knowledge, this work would be the first to apply a comprehensive, multidimensional definition of patient stability for ALHIV that reflects the lived experience of lifelong ART, moving beyond retention in care or mortality.

Additionally, the UPLIFT study enables further analyses that examine the effect of adolescents' experiences in their homes, communities, and clinics on longitudinal health outcomes. Predictors for analysis would be sourced from adolescents' self-reported questionnaires and the clinic-level questionnaires. For instance, this candidate plans to analyse whether the availability of different "youth-friendly" services within healthcare facilities predicts better healthcare outcomes for adolescents, and, if so, which package of services are the most protective. This analysis constitutes a continuation of the Mzantsi Wakho collaboration with the UNICEF Eastern and Southern Africa Regional Office HIV/AIDS Programme on improving adolescent and youth HIV care. Other clinic-level predictors planned for future analyses include provider-to-patient ratios at healthcare facilities, attending support groups, and accessing peer support.

Key questions for further analysis beyond the Mzantsi Wakho cohort

Point-of-care HIV testing and viral load monitoring in decentralised settings
Because the Mzantsi Wakho cohort comprised adolescents already initiated on ART, this dissertation was not positioned to examine experiences surrounding

ART initiation or linkage to care. Previous studies have demonstrated that a critical challenge to the health of adolescents living with HIV in South Africa remains linkage to and initiation on ART. A meta-analysis of data from South African cohorts found that only 14% of all 15-24 year olds living with HIV had reached this first step of the treatment cascade by 2013 (Zanoni et al., 2016). Even with the adoption of universal ART in 2016, the most recent national survey reported that the rate of ART initiation was only 40% for 15-24 year olds living with HIV by 2017 (Human Sciences Research Council, 2019).

It is crucial that future research characterises linkage to care and ART initiation in the context of decentralised healthcare systems and universal ART. Subsequently, it is important to identify feasible interventions for improving ART uptake among adolescents in sub-Saharan Africa.

As mentioned in Section 3 of this chapter, point-of-care HIV testing has been recommended by the WHO as an intervention to improve uptake of HIV care and ART initiation. As this dissertation has highlighted, a large number of patients, including children and adolescents, are experiencing nurse-initiated ART in primary care clinics. Nurse- or community health worker-led rapid diagnostic testing for HIV and point-of-care CD4 testing have been proven to improve rates of ART initiation in decentralised clinics of sub-Saharan Africa (Vojnov et al., 2016; Stevens et al., 2017; Lecher et al., 2015). The few studies of point-of-care HIV testing specifically among youth in sub-Saharan Africa indicate its potential for improving rates of ART initiation for this population (Patten et al., 2013; Sanders et al., 2019). Yet, further research is required to determine if point-of-care HIV testing in decentralised sites (primary care clinics or the community) can

improve rates of ART initiation for adolescents in sub-Saharan Africa, especially for those with sexually acquired HIV in older adolescence.

Point-of-care viral load monitoring has emerged as a recent technology that enables the earlier detection of viraemia among patients living with HIV (Drain et al., 2019). Through earlier confirmation of viral load results, this technology may increase efficiency in healthcare services, help streamline ART monitoring, and ultimately improve rates of viral suppression (Drain et al., 2014; International AIDS Society, 2017; Phillips et al., 2015). Currently, there is no evidence for the effect of point-of-care viral load monitoring among adolescents in sub-Saharan Africa, although one study is currently underway in Uganda (Drain et al., 2019; Jain, 2018). Furthermore, evidence for the feasibility of point-of-care viral load testing in decentralised care sites is lacking for patients of any age (Nash et al., 2018). Any implementation of point-of-care HIV testing and viral load monitoring within decentralised healthcare facilities will require proper training of clinical staff and integration into care (Drain et al., 2019; Roberts et al., 2016). Future work should investigate the effect of point-of-care viral load testing on the uptake of adolescent viral load testing and subsequent viral suppression in the context of South Africa's decentralised healthcare system.

Further differentiation of decentralised adolescent HIV care

Among adolescents already decentralised to primary care clinics, a wide range of further differentiated HIV care models are available in South Africa, including services within and beyond healthcare facilities (International AIDS Society, 2017). Notably, "stable" patients ≥18 years old on ART in South Africa have the option to collect ART refills outside of the facility through CCMDD programmes

(Southern African HIV Clinicians Society, 2017). Some healthcare facilities in South Africa also provide youth clubs, in which adolescents and young people regularly meet to develop a peer support network through youth-friendly services, structured group activities, and access to healthcare services, including ART refills (Southern African HIV Clinicians Society, 2017; International AIDS Society, 2017). Other interventions focus on the provision of community-based treatment support in addition to facility-based care, particularly through psychosocial and peer support (International AIDS Society, 2017).

These further modes of differentiating HIV care are critical to ensuring that primary care clinics do not face unmanageably large patient burdens, even within decentralised HIV care systems. Although studies have demonstrated the effectiveness of facility-based adherence clubs for adults on ART in South Africa, evidence for adolescents remains mixed (Tsondai et al., 2017; Flämig et al., 2019; Grimsrud et al., 2016; Fox et al., 2019). One retrospective cohort analysis in Namibia reported no difference between those who did and did not receive “teen club” support at a paediatric ART clinic (Munyayi and van Wyk, 2020). By contrast, a nested case-control study in Malawi found that adolescents who attended a “teen club” within a tertiary referral hospital were more likely to remain in care than those who did not (MacKenzie et al., 2017). Given the current state of evidence, further research is required to understand how and for which adolescents these facility-based support groups can promote better health outcomes. This research should investigate not only longitudinal care outcomes but also how adolescents and healthcare providers navigate the different care

settings in a decentralised system—from hospitals to clinics and from clinics to groups within them.

The Zvandiri intervention in Zimbabwe was a cluster-randomised controlled trial that supplemented standard facility-based care with community-based peer support for ART-initiated adolescents (Willis et al., 2018). Those receiving the intervention were provided with peer-led adherence counselling and support at clinic visits, including follow-ups through text messages, phone calls, or home visits. Peer supporters received weekly supervision by nurses at clinics in addition to peer support within their own network. Findings from the study, conducted in 16 rural primary care clinics of Zimbabwe, indicated that those receiving the community-based peer support were less likely to demonstrate virological failure or mortality at 96 weeks (Mavhu et al., 2020). This intervention highlights the promise of pairing decentralised facility-based care with differentiated community-based peer support for ART-initiated adolescents in sub-Saharan Africa. Further research is required to evaluate its scalability and efficacy in other decentralised care contexts, including rural and urban areas of South Africa.

7. Conclusion

Decentralisation of HIV care delivery is being rapidly scaled up globally to attain treatment targets to end the AIDS epidemic by 2030. This is the first quantitative study to evaluate how decentralising HIV care delivery has shaped the health outcomes and experiences for adolescents living with HIV in sub-Saharan Africa, who remain a vulnerable key population in the epidemic. This dissertation consists of a systematic review and a longitudinal primary research study, which is the

largest known community-traced cohort of adolescents living with HIV in sub-Saharan Africa to date.

This dissertation evaluates the decentralisation of HIV care delivery in South Africa for adolescents as a mode of differentiating service delivery and therefore considers how services could be better tailored to the needs of adolescent patients. Findings from this DPhil suggest that ART-initiated adolescents living with HIV demonstrate low rates of viral suppression and lag far behind UNAIDS treatment targets for 2020. Significant progress is required in both tailoring HIV care for adolescents and strengthening health data monitoring systems for adolescents to reach the 2030 treatment targets. This DPhil also provides the first study to characterise pathways of adolescent transitions out of paediatric HIV care in the context of a decentralised health system and identifies feasible protocols being implemented in South Africa to facilitate these transitions. Although more research is urgently required to increase longitudinal coverage of health outcomes in decentralised HIV care systems, this DPhil provides a critical foundation for understanding the real-world context of HIV care for adolescents. Further research should also investigate potential interventions to tailor HIV care for this understudied population.

Although the empirical studies of this dissertation were based on a South African cohort, implications extend to decentralised adolescent HIV care in the rest of sub-Saharan Africa. Because South Africa houses the largest population of adolescents living with HIV, findings from this dissertation suggest “what works”—and what may not work—in settings under the greatest strain for patient care.

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