Patterns, predictors and outcomes of patient transfer in public sector chronic primary care services

by

Jasantha Odayar

ODYJAS001

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Faculty of Health Sciences, University of Cape Town

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Supervisor: Professor Landon Myer

Abstract

1.1.1 Background

To maintain long-term care, patients with chronic conditions may require transfers between health facilities, jeopardising continuity of care. High levels of geographic mobility in low- and middle-income countries mean that patients may require transfers between primary health care (PHC) facilities. In addition, with decentralisation of chronic care services in many settings there are increasing numbers of PHC facilities between which patients can transfer. However, research on transfers between PHC facilities is limited. This thesis investigated transfers between PHC facilities of stable patients with chronic conditions in South Africa using HIV and diabetes as exemplars.

1.1.2 Methods

First, national guidelines were reviewed for recommendations regarding transfers of people living with HIV (PLH). Second, routinely collected data from across the Western Cape were used to determine transfer incidence and outcomes among PLH and people living with diabetes (PLD). Third, at a PHC facility in Cape Town, medical records of PLH transferring in from any PHC facility in the province were reviewed to compare features of silent (health facility not informed of transfer, transfer letter not obtained) and official (health facility informed, transfer letter obtained) transfers. Fourth, in a trial of antiretroviral therapy (ART) delivery strategies among postpartum women, data were obtained from questionnaires (demographics and travel history) and in-depth interviews exploring barriers to transfer.

1.1.3 Findings

Recommendations regarding management of transfers between PHC facilities were limited, particularly for silent transfers. Transfers between PHC facilities occurred frequently among PLH and PLD and were associated with viraemia and raised HbA1c results respectively. Among PLH transferring into a PHC facility, 52% had interrupted ART and 30% had clinical concerns; these percentages were higher among silent than official transfers. Among postpartum women, poor relationships with healthcare providers led to silent transfers;

barriers to successful transfer included fear of community stigma and limited knowledge of transfer options and processes including for mobile women.

1.1.4 Conclusions

Considering the volume and outcomes of transfers among PLH and PLD, routine monitoring and reporting of the number of transfers and transfer outcomes should be considered. Research on interventions to improve transfer outcomes and on transfers among people with other chronic conditions is warranted.

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Preface

This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) in the Division of Epidemiology & Biostatistics, School of Public Health & Family Medicine, Faculty of Health Sciences, University of Cape Town. The work included in this thesis is original research and has not, in whole or in part, been submitted for another degree at this or any other university. The contents of this thesis are entirely the work of the candidate, or, in the case of multi-authored published papers, constitutes work for which the candidate was the lead author.

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

1. Odayar J, Phillips TK, Hennessey C, Myer L. Guidelines for the transfer of people living with HIV attending primary health care facilities in South Africa: A scoping review. *Under review at International Health.*
2. Odayar J, Chi BH, Phillips TK, Mukonda E, Hsiao NY, Lesosky M, Myer L. Transfer of patients on antiretroviral therapy attending primary health care services in South Africa. *J Acquir Immune Defic Syndr.* 2022;90(3):309–315.
3. Odayar J, Chi BH, Hsiao N-Y, Mukonda E, Myer L. Silent and official transfers between primary health care facilities of patients on antiretroviral therapy in South Africa. *Manuscript being prepared for submission to J Acquir Immune Defic Syndr.*
4. Odayar J, Rusch J, Dave JA, Van Der Westhuizen DJ, Mukonda E, Lesosky M, Myer L. Transfers between health facilities of people living with diabetes attending primary health care services in the Western Cape province of South Africa: a retrospective cohort study. Under review at *Trop Med Int Health*.

5. Odayar J, Phillips TK, Kabanda S, Malaba TR, Mukonda E, Hsiao N-Y, Lesosky M, Myer L. Mobility during the post-partum period and viraemia in women living with HIV in South Africa. *Int Health.* 2023;15(6):692–701).
6. Odayar J, Myer L, Kabanda S, Knight L. Experiences of transfer of care among postpartum women living with HIV attending primary health care services in South Africa. *Manuscript under review at Glob Public Health.*

In addition, the following published manuscript is directly related to the thesis and included as an appendix:

7. Odayar J, Malaba TR, Allerton J, Kabanda S, Huang D, Kalombo C, Lesosky M, Myer L. Virologic outcomes after early referral of stable HIV-positive adults initiating ART to community-based adherence clubs in Cape Town, South Africa: A randomised controlled trial. *PLoS One.* 2022; 17(11):e0277018.

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

Student Name: Jasantha Odayar Student number: ODYJAS001

Signed: Signed by candidate Date: 12 February 2024

Per university guidelines, the text of each publication is presented verbatim in this thesis. As such, there are minor discrepancies in terminology between papers; these have not been changed in order to reflect the publications. Minor changes have been made to style and to figure and table numbers to ensure consistency throughout this thesis.

List of abbreviations

AC	Adherence club
aIRR	Adjusted incidence rate ratio
ANC	Antenatal care
aOR	Adjusted odds ratio
ART	Antiretroviral therapy
ARV	Antiretroviral
CHW	Community health worker
CHC	Community health centre
CI	Confidence interval
DSD	Differentiated service delivery
EFV	Efavirenz
FDC	Fixed-dose combination
FTC	Emtricitabine
GEE	Generalised estimating equations
HbA1c	Glycosylated haemoglobin
HCT	HIV counselling and testing
HCW	Healthcare worker
HIV	Human Immunodeficiency Virus
HIVCS	HIV Clinicians Society
IDI	In-depth interview
IQR	Interquartile range
IRR	Incidence rate ratio
LMIC	Low- and middle-income countries
LTFU	Lost to follow-up
MDR-TB	Multidrug-resistant tuberculosis
MITT	Modified intention-to-treat
MOU	Midwife obstetric unit
NCD	Non-communicable disease
NDOH	National Department of Health
NHLS	National Health Laboratory Services

NVP	Nevirapine
OR	Odds ratio
PACART	Postpartum Adherence Clubs for Antiretroviral Therapy trial
PHC	Primary health care
PLD	People living with diabetes
PLH	People living with HIV
PMTCT	Prevention of mother-to-child-transmission
RCT	Randomised controlled trial
SD	Standard deviation
SOC	Standard of care
SOP	Standard operating procedure
TB	Tuberculosis
TDF	Tenofovir
TFI	Transfer-in
TFO	Transfer-out
TRAC	Timing of Referral to Adherence Clubs trial
UCT-HREC	University of Cape Town Human Research Ethics Committee
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	Viral load
WLH	Women living with HIV
WHO	World Health Organization
XTC	Emtricitabine or lamivudine
3TC	Lamivudine

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Chapter 1: Introduction

1.1 Overview of the thesis

This thesis investigates transfers between health care facilities of people living with chronic conditions, focusing on transfers between primary health care (PHC) facilities. Chronic conditions include communicable diseases e.g., HIV and tuberculosis, and non-communicable diseases (NCDs) e.g., diabetes (1,2). The prevalence of chronic conditions is escalating, particularly in low- and middle-income countries (LMICs) (2). These conditions require long-term and continuous care (1). PHC is considered best placed to provide such care but in many LMIC, PHC systems have developed to provide acute, episodic care and changes are required to enable the provision of care for chronic diseases (2–5).

Transfers between PHC facilities of people with chronic conditions are an aspect of long-term care provision that has been largely neglected. To remain in care over the long-term, patients may require care at multiple facilities over time, necessitating transfers between health facilities. Transfers could interrupt continuity of care, potentially affecting patient outcomes (6). Transfers include up-referrals i.e., from lower to higher levels of care and down-referrals i.e., from higher to lower levels of care (7). Patients may be up-referred to access specialised care, while down-referral is often to facilities in closer proximity to the homes of patients to improve access to care; down-referred patients may or may not require periodic visits to higher levels of care at pre-determined intervals. Lateral transfers occur between facilities at the same level of care e.g., between PHC facilities or between hospitals. Among adults with chronic conditions, research has focused on transfers to and from hospitals and transfers of acutely ill patients (8–17). However, high levels of mobility in many LMIC including South Africa mean that stable patients with chronic conditions may require transfers between PHC facilities to remain in care (18,19). In addition, health care services have been decentralised in many LMIC resulting in an increased number of PHC facilities between which patients can transfer (20,21). Despite this, research on transfers between PHC facilities is extremely limited. Using HIV and diabetes as exemplars, this thesis aims to improve our understanding of transfers of stable patients with chronic conditions between PHC facilities.

Transfers may be required across health conditions and population groups. There are also different types of transfers, depending on the characteristics used to classify them. In addition to categorising transfers based on the levels of health facilities involved i.e., up-referrals, down-referrals and lateral transfers, transfers may also be official or silent. Silent transfers occur when patients transfer without informing their health facility and do not obtain referral letters, and official transfers occur when patients inform their health facility and obtain a referral letter (21,22). Prior research on transfers has been done within specific categories e.g., down-referrals among people living with HIV (PLH) as part of decentralisation of care (23–25) and silent transfers of PLH (12,15,26) with little coalescence of data across categories. Among stable adult patients with chronic conditions, there may be similarities and differences regarding transfers based on various factors including the health conditions involved, reasons for transferring and types of transfers. Understanding and comparing these variations is vital to developing strategies for the management of transfers that are cohesive but account for specific patient needs. This thesis thus aims to investigate transfers across health conditions, population groups, and transfer types with the aim of developing a multi-faceted understanding of transfers. As such, it includes research involving two conditions, HIV and diabetes and different population groups including general adults and postpartum women. Regarding types of transfers, it includes data on both official and silent transfers. While the focus is on transfers between PHC facilities due to the lack of data on this topic and the potential importance of these transfers in LMIC, data on transfers from hospitals to PHC facilities and from PHC facilities to hospitals are included to improve our overall understanding of transfers involving PHC facilities.

As mentioned above, the thesis will focus on transfers among PLH and people living with diabetes (PLD). While PLH and PLD have high rates of multimorbidity (27–29), for this thesis, each condition is considered individually. Reasons for the focus on HIV and diabetes include the high prevalence of each condition in LMICs (30,31) as well as the numerous differences between the two conditions. While they are both chronic conditions that require long-term care, HIV is a communicable disease while diabetes is an NCD, and the two diseases have different risk factors and affect different population groups. In addition, there are differences in the models of care for HIV and NCDs in many countries (32). The scale-up of HIV services over the past three decades has resulted in the development of

vertical systems that are able to provide care to large numbers of patients and it may be possible to leverage some of the systems and strategies developed for HIV care when developing systems for care of various chronic conditions (32–38). Another reason for the focus on diabetes and HIV is the methodology that will be used in this thesis. Both HIV and diabetes require regular laboratory monitoring in the form of viral load (VL) and glycated haemoglobin (HbA1c) testing respectively (39,40). This allows the use of data on routine laboratory testing to monitor health facility attendance, assess the occurrence of transfers, and provide an indication of changes in disease control over time, as will be described in more detail below. Other highly prevalent chronic conditions such as hypertension and asthma are not included in the thesis as they do not require routine laboratory monitoring; identification of transfers between health facilities would thus not be possible using the proposed methodology. Among PLH, the thesis includes both general adults and postpartum women due to possible differences related to transfers between these two population groups. For example, reasons for transfers may differ as postpartum women are one of the few groups who undergo mandatory transfer: in many countries pregnant women obtain HIV care as part of antenatal care services and are transferred to general PHC antiretroviral therapy (ART) services post-delivery (41,42). Ultimately, by conducting these analyses in different populations, health conditions and transfer types, this thesis aims to compare transfers across these various axes and provide insights into how outcomes may occur.

1.2 Overview of this chapter

This chapter provides an introduction to the thesis. It begins by providing context regarding the rapidly increasing prevalence of chronic conditions in LMIC and the need for health systems to provide long-term and continuous care for people with chronic conditions. The topic of transfers between health care facilities is then introduced, with a discussion of types of transfers and the potential for transfers between health facilities to impact engagement in care. A brief overview of research on transfers is then provided for two common chronic conditions, HIV and diabetes, which serve as the exemplars of chronic conditions in this thesis. The aims and objectives of the thesis are then presented and the

sources of data used in the thesis are described. Lastly, this chapter sets out the chapters that follow, outlining the objectives covered and the papers presented in each one.

1.3 Background and overview of the literature

1.3.1 Prevalence of chronic conditions

Chronic conditions, by definition, are persistent health conditions and require healthcare over time (1,43,44). Highly prevalent chronic conditions include HIV and diabetes. Globally, approximately 734 million people were estimated to be living with diabetes in 2019 (45) and the number of PLH was estimated at 39.9 million at the end of 2023 (46). In LMIC, urbanisation and lifestyle changes have led to a rapidly increasing prevalence of NCDs; this is occurring alongside ongoing chronic infectious disease epidemics, leading to what has been referred to as "colliding epidemics" (47,48). While diabetes was previously thought to be rare in LMIC, four-fifths PLD globally are estimated to live in LMIC and this burden is projected to increase (49). In South Africa, the prevalence of diabetes is already increasing, from an estimated 7.1% in 2011 to 10.8% in 2021 and in 2019, the total number of adults living with diabetes in the country was estimated at 4.2 million (30, 50). Regarding HIV, Africa is disproportionately affected, with more than two-thirds of PLH globally residing in this region (51). South Africa has the highest overall burden of HIV globally, accounting for 7.6 million people living with HIV in 2022 (31). A large and increasing number of people are thus in need of long-term care globally, including in South Africa, and this is expected to increase further, placing a huge strain on health systems.

1.3.2 Engagement in care among people with chronic conditions

Chronic conditions require long-term adherence to treatment and retention in care to prevent complications (2). Adherence refers to the extent to which an individual's behaviours match recommendations agreed upon with a health care provider, including recommendations regarding taking medications and implementing lifestyle changes (52). A related term is retention in care, which means that the time since an individual missed a clinic visit or pharmacy pick-up has not extended beyond a specified duration. It is often difficult to apply and differentiate these two concepts in practice. Retention in care is a requirement for adherence to treatment, but in patients who are not retained in care,

information on adherence behaviours is rarely available. As both adherence to treatment and retention in care are required to maintain health, the term engagement in care is used to encompass both concepts in the HIV literature (53). While the prevalence of chronic conditions is increasing rapidly in LMIC, healthcare systems in LMIC are structured to provide acute care, and provision of chronic care is one of the biggest challenges currently faced by these systems (2).

Universal initiation of ART for all PLH has been recommended by the World Health Organization (WHO) since 2016 (54) and substantial progress has been made in initiating people on ART. To realise the benefits of ART, sustained adherence to treatment and retention in care are required to achieve and maintain viral suppression which is associated with reductions in morbidity, mortality, and HIV transmission (55–57). As the numbers of people on ART has increased, maintaining engagement in care has become increasingly important (58,59). Targets for NCDs are provided by the Sustainable Development Goals which aim to reduce mortality attributable to NCDs by one third by 2030 (60); long-term engagement in care among people with NCDs is a pre-requisite to achieving these goals. For PLD, good adherence to treatment is required to improve glycaemic control, reduce microvascular and macrovascular complications, and reduce mortality (61,62). In LMIC, rates of loss to follow-up are high among PLD and there is evidence of poor glycaemic control indicating suboptimal adherence to treatment (63). For both HIV and diabetes, understanding the factors affecting engagement in care is thus vital.

1.3.3 Patient transfers between health facilities

To maintain long-term and continuous care, people with chronic conditions require continuous care that is provided across time, health care facilities and providers (1), which may necessitate transfers between health facilities. Transfers may be categorised in a number of ways including based on the levels of care of the facilities involved. Transfers may also be made between private and public services. However, the majority (>80%) of people in South Africa use public sector services (64) and movement between the public and private sector is expected to be minimal. This thesis will focus on transfers between health care facilities within the public sector.

In South Africa, higher levels of care include district, regional, tertiary, and central hospitals. PHC services include community- and home-based care, differentiated service delivery models, clinics, and community health centres (7). Transfers may be from lower to higher levels of care e.g., from PHC facilities to hospitals, referred to as up-referrals. Patients with complex medical conditions are typically up-referred for specialised care. Transfers may also occur from higher to lower levels of care e.g., from hospitals to PHC facilities, called down-referrals. Down-referrals may occur as part of decentralisation, which is the process of moving care from hospitals to PHC facilities to improve access to care (65). Patients who are down-referred may require visits to higher levels of care at pre-determined intervals. Transfers between facilities at the same level of care e.g., from PHC facility to PHC facility are referred to as lateral transfers. Patients may transfer laterally for reasons that include geographic mobility (66). Levels of mobility are high in LMIC and people migrate for employment, education, family, cultural reasons and health care access (18). Other reasons for lateral transfers include personal preference and stigma.

Silent and official transfers are categories of transfers that have been recognised among PLH (67). Official transfers occur when patients inform their health facility of the transfer and obtain a referral letter. Silent transfers which are also referred to as unofficial or self-transfers occur when patients do not inform their original health facility of the transfer and do not obtain a referral letter. In the case of silent transfers, patients may be classified as lost to follow-up (LTFU) at the original facility, while attending a different facility (22,67). Further, patients who silently transfer may be started on ART as new patients at the facilities to which they transfer, leading to an overestimation of the numbers ever started on ART (68).

Different types of transfers may have different characteristics and outcomes. The overview of literature on transfers among general adults living with HIV, postpartum women living with HIV and PLD that follows will thus include discussion of what is known about different types of transfers. A framework used to assess the quality of family planning services was adapted to assess the quality of transfer services in Chapter 8 and is used here and throughout the thesis to guide thinking about the components required to provide quality transfer care services and the relationships between these components (Figure 1.1) (69). The framework emphasises the effects of *programme effort* which includes *policy support* as

a factor affecting the elements making up transfer services which, in turn, affect *impacts* including *patient health*, *engagement in care*, *patient knowledge* and *patient satisfaction*. The overview which follows will include summaries of literature on each of these components for general adults living with HIV, postpartum women living with HIV and PLD.

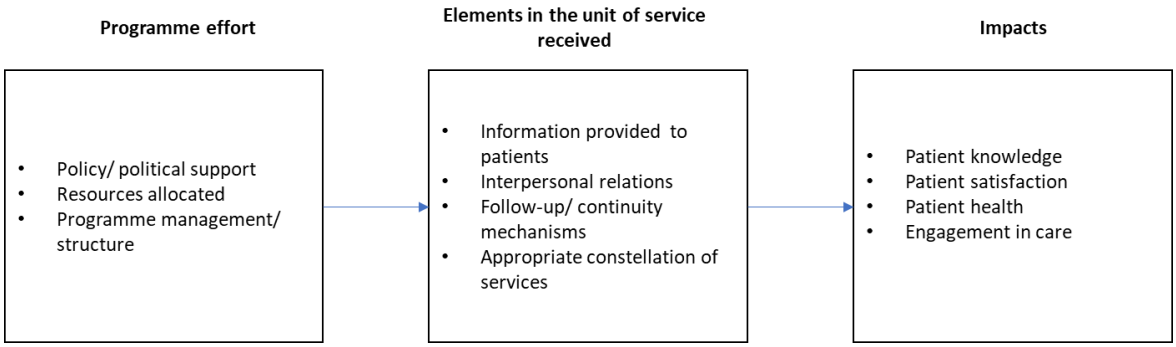

Figure 1.1 Framework assessing the quality of transfer services adapted from Bruce's framework assessing the quality of family planning services (69)

1.3.4 Transfers among general adults living with HIV

The importance of monitoring engagement in care is well-recognised within HIV care programmes. A cascade of care framework is typically used for this purpose (70–72), reporting the numbers tested for HIV, diagnosed with HIV, initiated on ART and virally suppressed. In addition, the number of patients officially transferred out are reported as part of the cascade framework. However, the outcomes of official transfers are not assessed or reported. In addition, silent transfers are often misclassified and reported as LTFU while in care at a different facility, leading to overestimation of the number of people out of care and underestimation of the number of transfers (68,71,73). Further, patients who silently transfer may be started on ART as new patients at the facilities to which they transfer, leading to an overestimation of the numbers ever started on ART (74).

Data on the frequency of transfers are provided by a number of research studies. An analysis in South Africa found that >50% of patients on ART transferred over a six-year period but the types of facilities involved and whether these were official or unofficial transfers was unknown (74). A study at a PHC facility in Cape Town used clinic records to determine that 13% of patients officially requested a transfer out to another PHC facility

over approximately 2.5 years of follow-up but patients were not followed up beyond the transferring facility (20). Importantly, this same study showed that the probability of transfer-out increased substantially with more recent calendar year of starting ART, from 1.4% in those starting ART in 2002-2004 to 8.9% in those starting ART in 2009 (20). In addition to official transfers, silent transfers have been shown to occur frequently among PLH. Numerous studies have physically traced all or a proportion of patients who are lost to follow-up and determined the proportion who had silently transferred to another facility (21,67,75–81). A systematic review of studies in LMICs included 10,806 patients who were successfully traced and estimated that 19% had silently transferred (21), but types of facilities involved were not specified. One study that did categorise transfers based on the types of facilities included 4,176 PLH on ART in Cape Town and found that 2,797 individuals transferred one or more times for a total of 14,849 transfers of which 33% were between PHC facilities, indicating that transfers between PHC facilities occur frequently in that setting (82).

Outcomes of transfers between facilities including between PHC facilities are unclear. In South Africa, the risk of mortality was three times higher in the short-term post-transfer among PLH on ART who transferred compared to those who did not transfer but hospitals and PHC facilities were not differentiated (83). HIV VL measurement is currently the method recommended by the WHO to monitor treatment response among PLH on ART (84), but the association between transfers and VL outcomes post-transfer has not been investigated among PLH on ART. In a recent study in Cape Town, PLH on ART who transferred were three times as likely to experience a disengagement compared to those who did not transfer (85). Disengagement is associated with viraemia and poor HIV treatment outcomes, but the relationship between transfers, disengagement and clinical outcomes including viraemia is not well understood, including for transfers between PHC facilities.

Based on the number of patients on ART who transfer and the potential risks, numerous interventions to improve post-transfer outcomes among PLH have been proposed. However, data to inform the development of interventions are limited. In particular, the reasons for poor outcomes in people who transfer between facilities are unclear. In South Africa, patients have described administrative and logistical barriers to successful transfer

between facilities (86). Per Figure 1.1, policies and guidelines are an important factor affecting the delivery of services which, in turn, affects patient outcomes (69). However, little is known about policies and guidelines regarding the management of transfers. Further, provision of services and outcomes may differ for people who transfer silently vs those who transfer officially; people who silently transfer do not have transfer letters and this may exacerbate the effects of transfers on continuity of care but silent and official transfers have not been directly compared.

1.3.5 Transfers among postpartum women living with HIV

A body of work among postpartum women living with HIV has highlighted specific considerations regarding transfers in this subgroup. As with all PLH, the number of women on ART has increased substantially in recent years. However, rates of disengagement from care are high, particularly in the postpartum period (18,42,87–90). In many countries, including South Africa, HIV care is integrated with antenatal care at antenatal clinics, meaning that women are transferred out to general adult PHC ART facilities for ongoing HIV care post-delivery (41). An analysis in South Africa showed that almost one-quarter of women transferred out from an integrated PHC antenatal/ART facility post-delivery did not attend the general PHC ART facility (18). Further, among women who did attend the PHC ART facility after transferring out, additional transfers to other PHC ART facilities occurred frequently over 30 months postpartum and were associated with viraemia (18). Understanding the factors that affect viral load outcomes in women who transfer is vital. As mentioned above, Figure 1.1 illustrates the effect of guidelines and policies on the transfer services that are provided which, in turn, affect outcomes (69). A lack of guidelines for the management of pregnant and postpartum women transferring between facilities has been described in a number of African countries (91) but guidelines have not been reviewed in South Africa. Further, a better understanding of transfer services and processes is required to understand how outcomes may be improved in this population. In South Africa, levels of geographic mobility are high in postpartum women, with many travelling from urban areas to their rural family homes post-delivery (92,93) and this has been posited as one of the reasons for frequent transfers between PHC ART facilities in the postpartum period. Research on how mobility affects outcomes, how mobile women access care, including through transfer, and an understanding of the constellation of services provided to

postpartum women is required. Lastly, while viraemia has been associated with transfers in this population, other outcomes relevant to the provision of high-quality care including the patient experience of and satisfaction with transfer services and patient knowledge of transfer services have not been well investigated. Ultimately, strategies to improve outcomes including viral load outcomes in postpartum women who transfer are required.

1.3.6 Transfers among people living with diabetes

Despite the risks that have been documented in PLH who transfer, data on transfers among patients with other chronic conditions are limited compared to among PLH. For diabetes, most countries do not have systems that routinely monitor patient engagement in care, including transfers (94–96). One of the few studies among adults with diabetes documenting the frequency of transfers included 457,975 elderly patients in South Korea and showed that almost 9% transferred at least once over one year of follow-up, with 53% of those who transferred moving between PHC facilities (97). This indicates that transfers between PHC facilities among adults with diabetes does occur. Insufficient availability of monitoring equipment and medications for diabetes have been documented in numerous LMICs (35) and improved planning to ensure adequate stock at facilities is required. Transfers affect the numbers of patients seen at specific facilities and, if transfers are not considered, estimates of the total numbers of patients in care may be inaccurate. Understanding the number of transfers is thus vital to inform resource allocation and improve access to care including monitoring and treatment.

Outcomes of transfers in adults have mostly been investigated post-hospital discharge, with PLD found to be at risk of readmission and mortality (13,14,98–101). A few studies among adults with diabetes have assessed the association between continuity of care and clinical outcomes among PLD. However, most have been conducted in high income countries. Further, most have used measures based on the number of providers seen by the patient (6,26,102–104). Fewer studies assessing continuity of care used measures of transfers between facilities (105). HbA1c testing provides an indication of average blood glucose levels in the preceding two to three months and raised HbA1c levels are associated with cardiovascular disease, stroke and mortality (106). While not directly measuring the number of transfers, a study in the United States, found that patients with a usual site of

care were more likely to have an HbA1c <8% compared to those without a usual site of care (107). Overall, the frequency of transfers and the association between transfers and patient outcomes among PLD are unclear in LMIC including for transfers between PHC facilities.

1.4 Problem statement and rationale

The prevalence of chronic conditions is increasing rapidly (1,2). Many LMICs are experiencing escalating rates of NCDs while simultaneously battling high levels of chronic communicable diseases (47,48). Chronic conditions require continuous care over time to prevent morbidity and mortality. However, health systems in LMIC are geared towards provision of acute care and chronic care services remain suboptimal. In South Africa in 2022, among approximately 7.6 million PLH, 75% were on ART and 69% had suppressed VLs (31) indicating gaps in the provision of care. Among adults with diabetes attending PHC facilities in sub-Saharan Africa, retention has been estimated at 40% (108). Changes to health systems in LMICs are required to improve and maintain engagement in care for chronic conditions. However, research to improve chronic care services is predominantly from high-income countries and studies from LMIC settings including South Africa are urgently required (2,109).

One largely neglected key aspect of chronic disease management is the transfer of stable patients with chronic conditions between PHC facilities. Transfers between health care facilities may interrupt continuity of care and affect patient outcomes. Most research thus far on transfers among people with chronic conditions has focused on acutely ill patients transferring to and from hospitals. However, transfers of stable patients between PHC facilities are relevant in LMIC including South Africa where high levels of geographic mobility mean that patients may require access to care at multiple locations and decentralisation of health care services has led to increasing numbers of PHC facilities between which patients may transfer (20,22). Transfers between PHC facilities occur frequently among general adults and postpartum women living with HIV and have been associated with viraemia among postpartum women. Data on transfers between PHC facilities for other chronic conditions including diabetes are extremely limited.

Health systems in LMIC are under pressure to adapt to provide continuous and co-ordinated care for NCDs and many authors have suggested that lessons be learnt from the scale-up of HIV care (32,33,35–37). Considering the frequency and potential risks associated with the transfer of stable patients between PHC facilities among PLH, the frequency and risks of transfers in people living with other chronic conditions including diabetes should be investigated. Among PLH, a better understanding of outcomes post-transfer and reasons for poor outcomes are required to develop strategies to maintain long-term engagement in care. Ultimately, transfers between PHC facilities require attention if we are to provide chronic care services that address patient needs, facilitate long-term engagement in care and improve outcomes in LMIC.

1.5 Aims and objectives

The overall aim of this thesis is to improve our understanding of the transfer of individuals accessing chronic care services at public sector PHC facilities for different chronic conditions, populations, and types of transfers.

Specific objectives are as follows (Table 1.1):

1. To review current national policies and guidelines for the transfer of adults living with HIV on ART attending PHC facilities in South Africa.
2. Among adults living with HIV on ART
    a. To describe and characterise the transfer of adults living with HIV on ART attending PHC facilities across the Western Cape Province of South Africa.
    b. To assess and compare VL outcomes in adults on ART who do and do not transfer.
    c. To compare the characteristics, management, and outcomes of PLH on ART who officially and silently transfer.
3. Among adults living with diabetes
    a. To describe and characterise the transfer of adults living with diabetes attending PHC facilities across the Western Cape Province of South Africa.
    b. To assess and compare HbA1c outcomes in adults living with diabetes who do and do not transfer.

4. To examine the relationship between travel, transfer and viraemia in postpartum women on ART.
5. To explore the experience of the transfer process and identify potential barriers to successful transfers among postpartum women on ART.

Table 1.1 Summary of thesis results chapters with objectives, manuscript titles and data sources

Chapter	and objectives	Manuscript title and status	Data source
3	**Objective 1**: To review current national policies and guidelines for the transfer of adults living with HIV on ART attending PHC facilities in South Africa.	Odayar J, Phillips TK, Hennessey C, Myer L. Guidelines for the transfer of people living with HIV attending primary health care facilities in South Africa: A scoping review. *Under review at Int Health.*	NA
4	**Objective 2a:** To describe and characterise the transfer of adults living with HIV on ART attending PHC facilities across the Western Cape Province of South Africa. **Objective 2b:** To assess and compare VL outcomes in adults on ART who do and do not transfer.	Odayar J, Chi BH, Phillips TK, Mukonda E, Hsiao N-Y, Lesosky M, Myer L. Transfer of patients on antiretroviral therapy attending primary health care services in South Africa. *J Acquir Immune Defic Syndr.* 2022;90(3):309-315.	NHLS
5	**Objective 2c:** To compare the characteristics, management, and outcomes of PLH on ART who officially and silently transfer.	Odayar J, Chi BH, Hsiao N-Y, Mukonda E, Myer L. Silent and official transfers between primary health care facilities of patients on antiretroviral therapy in South Africa. *Being prepared for submission.*	Data abstraction of patient medical records
6	**Objectives 3a:** To describe and characterise the transfer of adults living with diabetes attending PHC facilities across the Western Cape Province of South Africa. **Objective 3b:** To assess and compare HbA1c outcomes in adults living with diabetes who do and do not transfer.	Odayar J, Rusch J, Dave JA, Van Der Westhuizen DJ, Mukonda E, Lesosky M, Myer L. Transfers between health facilities of people living with diabetes attending primary health care services in South Africa: a retrospective cohort study. *Under review at Trop Med Int Health.*	NHLS
7	**Objective 4:** To examine the relationship between travel, transfer and viraemia in postpartum women on ART.	Odayar J, Phillips TK, Kabanda S, Malaba TR, Mukonda E, Hsiao N-Y, Lesosky M, Myer L. Mobility during the postpartum period and viraemia in women living with HIV in South Africa. *Int Health*. 2023;15(6):692–701.	PACART trial
8	**Objective 5:** To explore the experience of the transfer process and identify potential barriers to successful transfers among postpartum women on ART.	Odayar J, Myer L, Kabanda S, Knight L. Experiences of transfer of care among postpartum women living with HIV attending primary health care services in South Africa. Under review at Glob Public Health.	PACART trial
10	**Appendix supporting objective 1**	Odayar J, Malaba TR, Allerton J, Kabanda S, Huang D, Kalombo C, Lesosky M, Myer L. Virologic outcomes after early referral of stable HIV-positive adults initiating ART to community-based adherence clubs in Cape Town, South Africa: A randomized controlled trial. 2022;17(11):e0277018.	The timing of referral to adherence clubs trial
10	**Appendix supporting objective 1**	Frequency and outcomes of transfers among people living with HIV based on the levels of facilities involved.	NHLS

1.6 Data sources

This thesis has three data sources: routine laboratory records from the National Health Laboratory Service (NHLS); a randomized controlled trial, the Postpartum Adherence Clubs for Antiretroviral Therapy (PACART) study (ClinicalTrials.gov NCT03200054); and data abstraction from patient medical records. Objectives 2a, 2b, 3a and 3b used data from the NHLS. Objective 2c was addressed with data obtained through patient record data abstraction. Objectives 4 and 5 used data from the PACART study.

1.6.1 NHLS data

The NHLS conducts all public sector VL and HbA1c testing in South Africa and results are stored in a database administered by the NHLS. Data for objectives 2a and 2b included all VL tests conducted at public sector health facilities in the Western Cape province (WCP) for the period 2008-2018. Data for objectives 3a and 3b included all HbA1c tests conducted at public sector health facilities in the WCP for the period 2008-2022.

Based on clinical guidelines, PLH on ART should have VL assessments at six months on ART, 12 months on ART and then at least yearly (110). PLD require HbA1c testing at least annually (40,111,112). The data for both objectives were supplied as long data, with separate records for each test, even if done in the same individual. Identifiers were thus required to link multiple tests to individuals. Linking was done through probabilistic matching, creating a longitudinal cohort (113).

Variables in both the VL and HbA1c datasets included patient name, folder number, sex, facility name, test date and test result. The availability of the facility at which the test was conducted allowed transfers to be assessed as follows: participants with successive tests at different facilities were considered to have transferred. The longitudinal nature of the data allowed assessment of multiple transfers in individuals. The VL and HbA1c results allowed assessment of the association between the occurrence of a transfer and subsequent viraemia or raised HbA1c.

1.6.2 PACART data

The PACART study was a randomised controlled trial comparing strategies for the delivery of ART to postpartum women living with HIV who had initiated ART in pregnancy in Cape Town, South Africa (114,115). The trial was conducted from January 2016 to December 2019 at a large PHC facility which includes a midwife obstetric unit (MOU) providing antenatal, obstetric and postnatal care services integrated with HIV care.

Consecutive women attending postnatal care at the MOU were screened for trial eligibility. Women who were over 18 years of age, within 10 weeks postpartum, and virally suppressed with no medical conditions requiring regular clinical follow-up were eligible for inclusion. Per routine care, women on ART are transferred from integrated antenatal and ART care services to general adult PHC ART facilities for ongoing HIV care post-delivery. In this setting, the adherence club (AC) model is the predominantly implemented differentiated service delivery model. As part of routine care, all patients attending the PHC ART facility who are on ART for at least six months and are clinically stable are potentially eligible for referral to the ACs, but women are not referred directly from the MOU to the ACs. In this trial, participants who were otherwise eligible for referral to the ACs were randomised to be referred to either the PHC ART facility (the control arm) or the ACs (intervention arm) directly from the MOU.

Participants in the trial were followed through 24 months postpartum. Study measurement visits were conducted by research staff at 3, 6, 12, 18 and 24 months postpartum at a research office at the same site as the PHC facility but separate from routine care services. Study measurements included questionnaires regarding demographic information, medical history and travel history that were administered at every visit. HIV VL testing was also conducted at each visit. Clinical care was provided by routine care services using government protocols.

As part of the PACART study, qualitative one-on-one in-depth interviews (IDIs) were conducted with equal numbers of women randomised to the AC and PHC ART facility arms. IDIs were conducted by trained research assistants using semi-structured interview guides and explored participants' experience of care at ACs and PHC ART facilities and their experience of transfers between facilities in both arms.

Women enrolled in the PACART trial were included in the analysis for objective 4. A structured questionnaire was administered to participants attending the 3, 6, 12, 18 and 24-month visits and assessed the history of travel since the preceding study visit. Plasma HIV VL was measured at each study visit, separate to routine care. These data were used to assess the association between travel and VL outcomes through 24 months postpartum.

Women enrolled in the qualitative aspect of the PACART study were included in the analysis for objective 5. The analysis focused on reasons for transfer, the experience of transfer and potential barriers to successful transfer.

1.7 Ethical approvals

Ethical approval for this thesis was obtained from the University of Cape Town Human Research Ethics Committee (HREC-REF Number 503/2020) and has been renewed on an annual basis. The original approval is provided in Appendix 10.1.1 and the current approval is provided in Appendix 10.1.2.

A waiver of informed consent was requested and obtained for the analyses using NHLS data as the analyses would not be practicable without the waiver and it involved no more than minimal risk to participants. The main risk was loss of confidentiality. Identifying information including name, surname and date of birth were required to link records of separate tests in the same individual. To protect against loss of confidentiality, all electronic data were stored in password protected files on University of Cape Town servers which are firewall protected. All electronic communications of study data were through password-protected, encrypted files. Once all analyses were complete, the identified data were deleted.

The PACART study received approval from the University of Cape Town Human Research Ethics Committee (HREC-REF Number 194/2015). Study progress was reviewed on an annual basis. The original ethical approval is provided in Appendix 10.1.3 and the final study closure report is provided in Appendix 10.1.4. All women enrolled in the PACART study were 18 years of age and older and all women provided written informed consent prior to enrolment. A separate written informed consent was administered and obtained prior to enrolment in the qualitative aspect of the PACART study.

1.8 Overview and structure of the thesis

In addition to this introductory chapter, this thesis includes a literature review, six results chapters, a discussion chapter and supporting appendices.

This introductory chapter provides context to the topic of the thesis, including background regarding the prevalence of chronic conditions and the challenges of providing long-term and continuous care, particularly in LMIC. It then provides a brief overview of current research on transfers of patients with HIV and diabetes between PHC facilities and what is known regarding the effect of transfers on engagement in care, the rationale for the thesis and lists the aims and objectives. As this thesis involves secondary data analysis, a description of the sources of data is provided.

Chapter 2 reviews the literature on transfers that is relevant to this thesis among general adults living with HIV, postpartum women living with HIV, and PLD. The review is not exhaustive but presents key aspects of the literature with a focus on the frequency, outcomes and reasons for transfer and transfer processes. Please note that part of the literature review was published as narrative review that was first authored by the candidate and published in the journal *International Health*.

Chapters 3–8 present the thesis results. Results are presented as manuscripts which have been published, have been submitted for publication or are being finalised for submission for publication and correspond to the objectives of the thesis:

- Objective 1 is addressed in Chapter 3. It presents a review of South African national guidelines regarding transfers of adults living with HIV attending PHC facilities and highlights areas that are not addressed in guidelines.
- Objectives 2a and 2b are addressed in Chapter 4 and Appendix 10.4. In Chapter 4, using NHLS VL data, the incidence rate of transfers among adults on ART attending PHC is calculated and the association between transfers and VL outcomes is investigated.
- Objective 2c is addressed In Chapter 5. Medical records of PLH transferring into a PHC facility are reviewed to determine the proportions who silently and officially

transferred and to compare characteristics and management for these two types of transfers.

- Objectives 3a and 3b are addressed in Chapter 6. Here, NHLS HbA1c data are used to calculate the incidence rate of transfers among PLD attending PHC and to assess the association between transfers and HbA1c outcomes.
- Objective 4 is addressed in Chapter 7. Using data from the PACART trial, the frequency of travel over 24 months postpartum is tabulated and the association between travel and VL outcomes is assessed. The frequency of transfers to facilities at the travel destinations is tabulated for mobile women.
- Objective 5 is addressed in Chapter 8. Results of analyses of qualitative data from the PACART trial are presented, exploring women's experiences of transfer processes and identifying possible barriers to successful transfers in this population.

Chapter 9 summarises the main findings of this thesis, discusses the results, provides recommendations for future research and considers the policy implications of this work. Chapter 10 presents supplementary materials including a publication that includes data on transfers of PLH on ART from a PHC ART facility to a differentiated service delivery model, as well as inserts from each of the results chapters.

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Chapter 2: Literature review

2.1 Overview

This chapter provides a review of published literature on patient transfers between health care facilities for people living with HIV (PLH), with a focus on general adults living with HIV, postpartum women living with HIV and people living with diabetes (PLD). It describes the current landscape of research of the topic, thereby contextualising the research questions and the thesis as a whole.

The review consists of five sections. Following this first section which provides an overview of this chapter, Section 2.2 provides a brief introduction to the topic of transfers among people with chronic conditions and discusses the different types of transfers and the importance of considering the type of transfer when investigating transfers. Sections 2.3, 2.4 and 2.5 discuss the literature on transfers among the three populations included in this thesis, general adults living with HIV, postpartum women living with HIV, and PLD respectively. For each of the populations, data on the frequency of transfers, outcomes of transfers, reasons for transferring and current transfer processes are presented.

A framework used to assess the quality of family planning services was adapted in Chapter 8 to assess the quality of transfer services and is used to further guide data collection for the review and to provide additional structure to the results (1). The framework emphasises the effects of *programme effort*, which includes *policy support*, as a factor affecting *elements in the unit of service received* which, in turn, affect *impacts* (Figure 2.1) (1). Based on this, literature on policies and guidelines related to reasons for transfers and current transfer processes are discussed for each population. Further, as part of the elements making up transfer services, the framework includes *information provided to patients*, *interpersonal relations*, *follow-up/continuity mechanisms* and an *appropriate constellation of services*. In the review, what is known about these elements is included for each of the three populations when available and is compared to the framework. Lastly, based on the outcomes delineated in the framework, research on *patient knowledge*, *patient satisfaction*, *patient health* and *engagement in care* related to transfers is discussed for each population.

The review concludes with section 2.6, which summarises the available literature and highlights the gaps which this thesis aims to address.

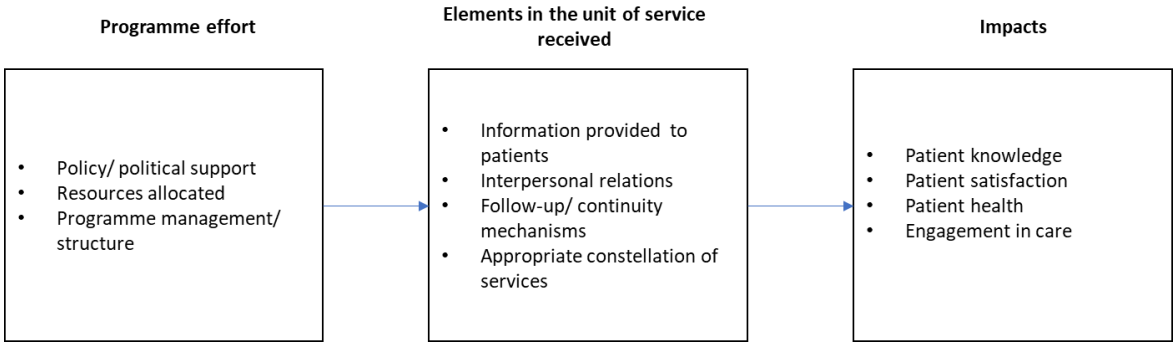

Figure 2.1 Framework assessing the quality of transfer services adapted from Bruce's framework assessing quality of family planning services (1)

A Pubmed search was conducted to identify the relevant literature, and reference lists were checked for additional publications. The review is not exhaustive but aims to provide an overview of the topic with a focus on literature relevant to the questions addressed by this thesis. The review focuses on studies from low- and middle-income countries (LMIC) i.e., low-income countries, lower-middle-income countries and upper-middle-income countries, with a particular focus on studies from sub-Saharan countries. Studies from high-income countries are included if there are no studies or few studies relevant to the areas covered by the review that were conducted in LMIC.

Aspects of this review were adapted into a manuscript that was published in the journal *International Health* as a narrative review (2). The review was conceived and authored by the candidate, with guidance from Professor Landon Myer.

2.2 Chronic conditions and transfers

Currently, the quality of care for chronic conditions is poor in many LMICs and levels of engagement in care are suboptimal (3–6). Understanding the factors affecting engagement in care is vital. Transfers between health facilities may disrupt continuity of care and this may negatively impact treatment outcomes. Transfers may take many forms and may be categorised in different ways. Different types of transfers may have different indications,

may be managed differently by the health care system and may have different outcomes. The type of transfer thus needs to be considered when investigating the effects of transfers on patient outcomes.

Transfers may be categorised based on the levels of care of facilities involved in the transfer: up-referrals are from lower to higher levels of care, down-referrals are from higher to lower levels of care and lateral transfers are between facilities at the same level of care e.g., between PHC facilities (7) (Figure 2.2). In South Africa, PHC facilities include community health clinics and community health centres (8,9). Hospitals include district, regional and tertiary hospitals. Patients seen at PHC facilities who require access to higher levels of care are up-referred to district hospitals, with additional referrals to regional and/or tertiary hospitals if more specialised care is required. Up-referrals may be urgent, semi-urgent on non-urgent. Patients at higher levels of care who are no longer in need of specialised care may be down-referred to a lower level facility for continued management (7). Down-referral may also be part of the process of decentralisation, which is the transfer of care from hospitals to PHC facilities to improve access to care (10,11). Down-referred patients may require visits to higher levels of care at pre-determined intervals. Lateral transfers between PHC facilities may occur due to patient request e.g., due to geographic mobility (12). As the clinical status of patients and the transfer services provided may differ for up-referrals, down-referrals and lateral transfers, including lateral transfers between PHC facilities, it is possible that these different types of transfers have different outcomes.

Level of Care at Referral and Receiving Facilities	Level of Urgency

• Transfer may be to or from facilities at different levels of care
  • Up-referrals: from lower to higher levels of care
  • Down-referrals: from higher to lower levels of care
  • Lateral referrals: between facilities at the same level of care
	• Transfer may be
	  • Urgent or emergent
	  • Semi-urgent
	  • Non-urgent

Reason for Transfer	**Method of Transfer**

• System initiated e.g.
  • Clinic closure
  • Decentralisation
  • Hospital discharge
• Patient initiated e.g.
  • Patient preference
  • Socio-economic factors
	• Official
	  • Known to and facilitated by original facility
	• Unofficial
	  • Patients attends a different facility without informing original facility ("self-transfer" or "silent transfer")

Figure 2.2 A typology of transfers for patients receiving care for chronic conditions from Odayar *et al* (2)

Transfers may also be categorised as initiated by the health care system e.g., due to decentralisation, or as initiated by the patient, i.e. based on patient request. Lastly, transfers may be official or silent. Research among PLH has identified the occurrence of silent transfers, which occur when patients transfer without informing the original facility or receiving a referral letter. Official transfers, on the other hand, occur when patients inform their health facility of their upcoming transfer and obtain a referral letter (13). As silent transfers do not have referral letters, it is possible that the effects on continuity of care are exacerbated, leading to worse outcomes than official transfers.

Each of these types of transfers may occur among people with chronic conditions. The indications, transfer services provided and outcomes for each type of transfer may differ. For this reason, as the literature is reviewed in the sections that follow, the types of transfers to which reported results apply will be specified.

2.3 Transfers among general adults living with HIV

2.3.1 Background

Antiretroviral therapy (ART) is lifelong and sustained engagement in care is required to achieve and maintain viral suppression, which is associated with reductions in morbidity,

mortality, and HIV transmission (14–16). Within HIV care programmes there is a strong emphasis on the monitoring of engagement in care and treatment outcomes (17,18). UNAIDS sets targets for HIV programmes related to the percentage of PLH who know their status, the proportion of people who know their status who are on ART, and the percentage of people on ART who are virally suppressed (19). A 'cascade of care' is commonly used to monitor and report these outcomes (20–24) (Figure 2.3). The proportions of patients who are lost to follow-up (LTFU) and who are transferred out at each step are indicated. By identifying the stages at which patients are LTFU, the cascade identifies points at which interventions may be needed to improve outcomes (17,25).

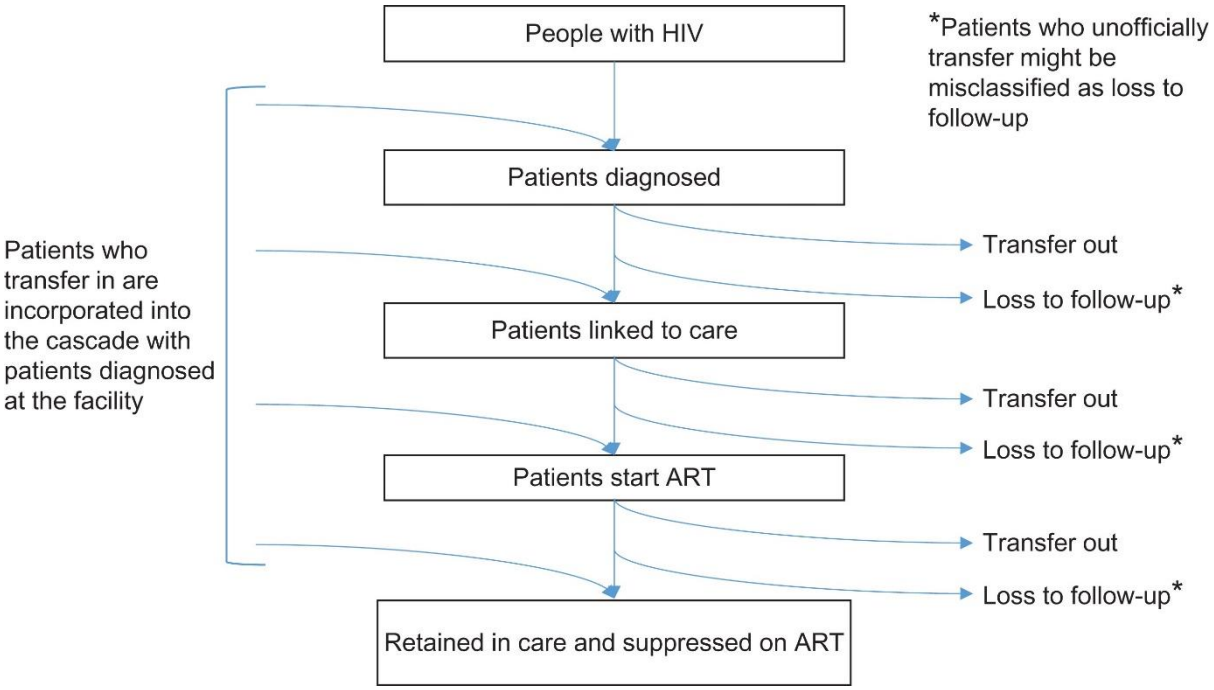

Figure 2.3 HIV cascade of care and patient transfers from Odayar *et al* (2)

Both within HIV programmes and HIV research, there has been a strong focus on preventing LTFU. A large body of work exists regarding defining and monitoring LTFU, determining outcomes of those who are LTFU, the development of statistical methods to correct for unknown LTFU outcomes and the development of strategies to maintain engagement in care and reduce LTFU (26–31). To maintain engagement in care through various steps in the

cascade, people may require transfers between health facilities. However, in comparison with LTFU, data on transfers between health facilities are limited (2,32,33) and the effect of patient transfers on patient and programme outcomes are less well understood.

A factor contributing to the relatively limited data on patient transfers is that research on transfers is operationally difficult to conduct. Patients who officially transfer out of health facilities may or may not link to care (34). Patients who silently transfer move from their original facility to attend a different facility, but this is unknown to the original facility where they are often recorded as LTFU (34–40). Identifying and tracing transfers is challenging, particularly as most health systems do not have linked electronic patient databases, and manual tracing of patients through telephone calls or home visits is required. Such tracing methods are expensive and labour intensive (21,32,41–43).

The traditional cascade of care described above reflects these difficulties. Cascades are reported at a local level but transfers may involve transferring out beyond the level of the cascade (20,25). Most ART programmes are not equipped to follow patients up to determine their outcomes (32,37,44). While the numbers of patients officially transferred out are reported as part of the cascade framework, the outcomes of official transfers are not assessed or reported. In addition, silent transfers are often misclassified and reported as LTFU while in care at a different facility, leading to overestimation of the number of people who are LTFU (21,45,46). Patients who silently transfer have also been documented to start ART as new patients at the facilities to which they transfer, leading to overestimation of the numbers of patients ever started on ART (43).

Over the last decade, however, transfers have been increasingly recognised as a point at which engagement in care may be disrupted. Many cohort studies on patient outcomes and/or disengagement report on the number of patients who transfer out (47–58). While these studies often censor participants who transfer out, they nevertheless provide a record of the proportions of PLH who transfer out in a few different settings. In addition, a number of studies tracing patients who are LTFU have documented the proportions who silently transferred but remained classified as LTFU at the original facility (35–39,59). In Uganda, Geng et al. pioneered a method in which a random sample of LTFU patients are traced to determine their updated outcomes including whether they silently transferred, and these

results are applied to the cohort using probability weights to obtain updated retention outcomes for the whole cohort (39). In addition, of late, the increasing use of electronic health records within health systems has allowed researchers to overcome some of the previous barriers to research on transfers: electronic medical records with unique patient identifiers allow patients to be linked across health facilities and facilitates tracking of patient movement between facilities (41,60,61). Over time, the importance of patient transfers among PLH has thus been increasingly recognised. Key publications related to current knowledge regarding transfers among adults living with HIV are discussed below.

2.3.2 Frequency of transfers

Studies reporting the proportions of patients on ART who transfer include studies reporting all transfers without differentiating the types of transfers (62,63), studies reporting official transfers only and studies reporting silent transfers only. An example of a study describing all transfers regardless of type includes a nation-wide study in South Africa which used National Health Laboratory Services (NHLS) data on viral loads (VLs) and identified transfers when individuals had successive VLs conducted at different facilities. While this study could not distinguish between silent and official transfers or between up-referrals, down-referrals and lateral transfers, it was able to demonstrate the high volume of transfers overall, with >50% of patients started on ART from 2004-2006 transferring one or more times over six years of follow-up (63). Further, this was likely an underestimate as visits at which VLs are not done are not recorded in the NHLS database.

When considering the proportions who officially transfer, estimates in South Africa have varied. In the Western Cape Province of South Africa, a study using electronic health records linked across health facilities in the province estimated that 2.5% of patients who attended a large peri-urban ART facility between 2013 and 2014 officially transferred out over 34 months of follow-up (48). However, this study defined transfers as patients moving to facilities in a different subdistrict; transfers have been shown to occur over short distances, meaning that this was likely an underestimate (64). At a PHC facility in Cape Town, Nglazi et al. used clinic records to determine that 13% of patients requested an official transfer to another PHC facility over approximately 2.5 years of follow-up (65). Studies in other countries include cohort studies in Ethiopia where 6.6% of patients on ART

officially transferred out by one year on treatment and in Kenya where 6% of patients officially transferred out over two years of follow-up (34,66).

In addition to official transfers, a number of studies have physically traced all or a proportion of patients who are LTFU and have found that large proportions of PLH who are categorised as LTFU have silently transferred to another facility (33,35–40,59,67). A systematic review of 28 studies from countries in sub-Saharan Africa included 10,806 patients on ART who were successfully traced after being categorised as LTFU at their original health facility and estimated that 19% had silently transferred (37).

Data on the frequency of transfers by the levels of care of facilities involved are limited. One study that did categorise transfers based on the types of facilities involved included 4,176 PLH on ART in Cape Town and found that 2,797 individuals transferred one or more times. Including repeat transfers among patients, there were a total of 14,849 transfers of which 33% were between PHC facilities, 27% were from a PHC facility to a hospital, 27% were from a hospital to a PHC facility and 6% were between hospitals. Transfers between PHC facilities were thus the most common type of transfer in this setting.

Overall, transfers occur frequently and the number of individuals on ART who transfer is thought to be increasing. In the study by Nglazi et.al. mentioned above, the proportions of patients officially transferring out by one year post-ART initiation increased from 1.4% for people starting ART in between 2002 and 2004 to 8.9% for people starting ART in 2009 (65). The proportion of people who silently transfer has also been shown to be increasing with calendar time (38). Possible reasons for the increasing numbers of transfers include decentralisation and universal ART initiation: decentralisation means that there are more PHC facilities between which people can transfer to obtain care, and universal ART initiation means that patients who are clinically well, and possibly more mobile, are being initiated on ART (34,37,65).

Most studies have followed patients until the first transfer out and censor patients at that point (47,48,50,66). Few studies have assessed the number of times that individuals transfer. One of the reasons that transfers occur is geographic mobility which, in addition to permanent migration, includes frequent travel and circular migration (68). It is thus possible

that geographically mobile patients may transfer numerous times. In Cape Town, patients who transferred into a PHC facility were more likely to officially transfer out (65). An analysis using data from the Western Cape Provincial Health Data Centre which links patient data across all public sector facilities in the province using a unique identifier (62) followed 4176 adults who initiated ART in an urban district of Cape Town for a median of 32 months and reported multiple transfers among individuals (64). Including up-referrals, down-referrals and lateral transfers, 2,797 (67%) individuals transferred one or more times for HIV-related care and patients transferred a median of 2 times (IQR 0–5). Including multiple transfers per individual, there were a total of 14,849 transfers involving 237 facilities. However, silent and official transfers were also not differentiated in this analysis. Overall, considering the proportions of individuals who transfer, the fact that these proportions are increasing and that patients transfer multiple times, it is clear that patient transfers are an important aspect of HIV care.

2.3.3 Reasons for transfers

There have been limited studies directly eliciting reasons for transfers from patients who have transferred. In the North-West province of South Africa, a study included 101 PLH who transferred in the first two years post-HIV diagnosis and found that the reason for transfer in the vast majority (77%) was geographic mobility (12). The study did not specify whether transfers were silent or official. While lateral transfers and transfers between PHC facilities were included, all transfers due to geographic mobility were between PHC facilities. Reasons for mobility include employment-related factors and cultural practices (69) and levels of mobility in LMIC including South Africa are high. Geographic mobility has long been recognised as a driver of HIV transmission in Africa and is now increasingly recognised as a factor affecting engagement in care (68,70).

Scale-up and decentralisation of ART services in many countries have increased the number of health facilities at which patients can obtain care in many LMIC (32,34,63,65,71,72). This allows patients to transfer for reasons of preference or convenience e.g., to facilities that are closer to home (73), are less congested, have friendlier staff or better quality of care (12,34).

A few studies have specifically assessed reasons for silent transfers (12,33,40). Geng et. al. interviewed patients in Uganda, Tanzania and Kenya who were LTFU, traced and found to be in care elsewhere (33). The most common reasons for silent transfers were structural i.e., related to access to care including distance to the facility and transportation. Psychosocial factors were also frequently cited including stigma, as were clinic-based reasons which were related to experiences at the facilities including waiting times (33). A qualitative study in Cape Town also raised factors related to patient experiences at health facilities: participants who had disengaged from care feared punishment from health workers when returning to the facility. To avoid this, patients described silently transferring to new facilities, sometimes even using a new name and retesting for HIV (44). Lastly, because migration can be unpredictable (34,63,64,74), patients may have difficulties obtaining transfer letters prior to travelling, leading to silent transfers (34,44).

Considering the reasons that people are geographically mobile including employment and cultural reasons, mobility and thus transfers will continue to occur. Developing strategies to manage these transfers, which may be silent, is thus vital. Avoidable reasons for transfers include poor quality of care at facilities and this should be addressed.

2.3.4 Outcomes of transfers

Yehia and colleagues adapted a behavioural model for PLH to understand how transfers may affect outcomes in this population (75). The original model illustrates the interplay between environmental factors (contextual and health care related), patient factors, health behaviours, and health outcomes but does not account for the dynamic effects of patient transfers (Figure 2.4). The adapted model emphasises the changes that patients go through as they transfer care including changes in socio-economic status, access to care, health information and care delivery and that these changes could affect adherence to ART, retention in care and risk-taking behaviours (Figure 2.5). These, in turn, could affect biological outcomes (including CD4 count, VL levels, clinical status and mortality) and public health outcomes (including HIV transmission), both of which will be discussed further below.

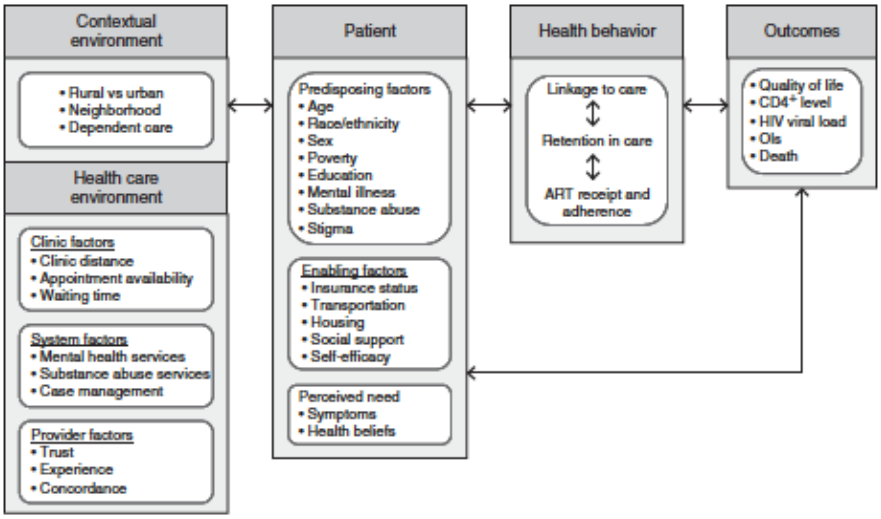

Figure 2.4 Revised behavioural model for people living with HIV from Yehia *et al* (75)

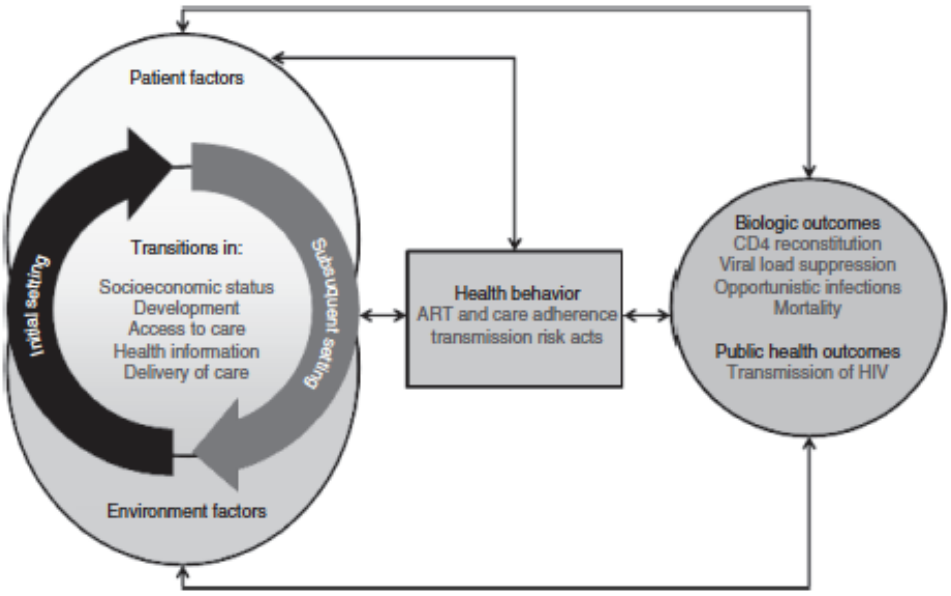

Figure 2.5 Dynamic behavioural model for people living with HIV from Yehia *et al* (75)

As mentioned above, many studies censor patients at the point of transfer-out, meaning that the outcomes of patients who transfer are not ascertained (47,48,63,66). Among the studies that have followed patients up beyond the point of transfer, outcomes that have been assessed include disengagement; this includes measures of whether the patient

attended the receiving facility and in those that did, whether a treatment interruption occurred. Among PLH on ART who have transferred, impacts on health that have been assessed include mortality.

Disengagement and LTFU are well-recognised threats to the success of HIV programmes and the various factors associated with disengagement have been well-researched (76). However, the relationship between transfers and disengagement has received relatively limited attention. A recent study in Cape Town, assessed the association between transfer of HIV care and disengagement: among 3821 adults who were initiated on ART between 2012 and 2016, transfer was associated with a three times increased rate of disengagement, defined as >180 days between visits (62). With PLH in South Africa receiving 3–6 months of medication at most, this suggests that treatment interruptions occur in many patients who transfer (62). This study, however, did not differentiate between up-referrals, down-referrals and lateral transfers and did not distinguish between official and silent transfers.

Down-referrals were assessed in a study in South Africa when patients were down-referred from a hospital-based ART facility to PHC facilities due to closure of the hospital-based facility: more than 99% of participants self-reported attending the receiving facility within 90 days, but among visits that were validated by record review, only 71% were confirmed (77). At a hospital in Malawi, the proportions of patients who died were significantly lower among those down-referred compared to those who remained in hospital care (72). In this study it was noted that those who were down-referred had less advanced disease compared to those who were not down-referred, likely explaining this association. In an analysis, assessing up-referrals, patients who were up-referred to a specialised HIV care centre in Uganda had a higher probability of being changed to a second-line ART regimen versus those initiated and retained at the centre (24). This likely reflects the fact that the patients transferring into the facility had clinical complications requiring specialised care. Few studies have assessed outcomes of lateral transfers between PHC facilities. One study that included 12,759 PLH in the United States found that attending multiple PHC facilities in a calendar year was associated with a 22% reduction in the odds of viral suppression but not all patients were on ART (78).

Outcomes have not been directly compared between silent and official transfers. A small study at a facility in Kenya traced patients who were categorised as LTFU and patients who officially transferred out to compare time to re-engagement. Among those who officially transferred out, the cumulative incidence of engagement at the receiving facility was 91% at three months. Among those who were LTFU, the cumulative incidence of reengagement in care was 14% and 60% at 3 and 6 months respectively but this included both patients who transferred to new facilities (silent transfers) and patients who returned to the original facility. In Zambia, 50% of patients who silently transferred had a raised VL (>1000 copies/mL), compared to 18% who were retained at facilities without transferring out but VL outcomes among official transfers were not assessed (36). Importantly, the study in Kenya described above showed that 26% and 43% of official transfers had a treatment interruption of <14 days and $\geq$14 days respectively, indicating that even official transfers are at risk of treatment interruptions. Further, in South Africa, 20% of participants requesting a transfer out from a PHC facility had a VL $\geq$1000 copies/mL just prior to transfer suggesting poor adherence around the time of transfer, but participants were not followed to their new facility. Risks among patients who officially transferred were also documented in a study in South Africa which compared mortality among patients who officially transferred versus those who did not transfer; those who officially transferred had a three times increased risk of mortality in the first three months post-transfer compared to those who did not transfer (32). These studies assessing official and/or silent transfers did not clearly differentiate between down-referrals, up referrals and lateral transfers between PHC facilities.

In addition to the effects on clinical outcomes, transfers may have programme level effects (75, 79). Accounting for health facility use and the number of transfers between facilities is important for planning and resource allocation (80,81). Both overestimation of the number of people on ART and misclassification of silent transfers as LTFU has implications for monitoring and planning of programmes. An example of the potential effects of misclassification of silent transfers as LTFU is provided by a study in Zambia. Among patients on ART, 72% were categorised as in care at two years on ART i.e., either at the original facility or officially transferred (36). A random sample of LTFU patients were then traced to identify those who silently transferred and findings from tracing were applied to the cohort using inverse probability weights. When patients who had silently transferred

were recategorized as in care, the total proportion of people in care increased to 91%. Misclassification of outcomes as described here can affect programme evaluation, drug forecasting and costing (37,79).

2.3.5 Transfer processes

Considering the possible negative outcomes of transfers, understanding current transfer processes and the services provided, and developing ways to optimise these processes is vital. Transfer is a potentially complicated process requiring co-ordination and communication between patients, health care workers and health facilities (2). The process of transfer also differs based on the type of transfer. Considering these intricacies, clear guidelines on the management of patients who transfer are necessary. Yet, data on current transfer guidelines and practices are limited.

Routine processes for official transfers were described in the methods of a few studies on patient transfer. At a PHC facility in Cape Town, patients transferring to other PHC facilities based on a request from the patient or as part of decentralisation were given referral letters, but no follow-up was done to confirm completion of transfers (65). Further details including the amount of treatment provided at transfer out were not specified. In a study at four large ART sites in South Africa (two in KwaZulu-Natal, one in the Western Cape and one in Gauteng province), patients requesting a transfer were provided with a transfer letter, a clinical summary and sufficient ART to last until their visit at the receiving facility (32). Patients were recorded as transferred out and did not receive any further follow-up. Interestingly, at one of the sites in KwaZulu-Natal, patients transferring to facilities in the same subdistrict were not categorised as transferred out. This was not the case at other sites, indicating differences in management of transfers at different locations.

A study in Malawi assessed processes for patients silently transferring. As part of the study, PLH who were LTFU were traced to identify silent transfers (35). However, it was found that some patients categorised as LTFU had officially transferred and had been misclassified as LTFU at the original clinic, indicating problems with data quality. Over half of all transferred patients were registered with new ART identifiers and received a new HIV test, indicating inefficient use of health care workers' time. Among silent transfers who had been on ART at the previous facility, 54% received ART at the first visit at the new facility, compared to 66%

of official transfers (35). There were thus problems with the management of transfers at the point of transfer out and transfer in.

Qualitative studies have provided some insight into the patient experience of transfer processes. In rural South Africa, PLH who had silently transferred described having to undergo the process of restarting treatment due to lack of paperwork (82). The process of transfer has also been described as confusing by patients. Mobile patients with a history of treatment interruption also described being unable to access care when travelling if they did not have a transfer letter (83). These studies indicate barriers to successful transfer introduced by health system processes. To assist patients who travel at short notice, national policy in Malawi allows patients on ART to collect an emergency supply of one month of ART from any other ART facility (84). However, the extent to which HCWs and patients are aware of this policy is unclear. A better understanding of policies and guidelines regarding transfer and how these are implemented is required in different settings to identify potential areas for improvement.

2.4 Transfers among postpartum women living with HIV

2.4.1 Background

With high levels of disengagement from care documented among postpartum women (85–88), understanding the reasons for disengagement and developing strategies to prevent disengagement in postpartum women are public health priorities (89). In many health care settings, pregnant and postpartum women living with HIV are required to transfer between general HIV care and prevention of vertical transmission services, which are part of maternal and child health care services, for ongoing HIV care (90). These transfers may disrupt the continuum of care. In addition to changes in the site of health care delivery, postpartum women undergo myriad other changes that may affect health behaviours including physiological, psychosocial, and/or economic changes (89). Further, women, particularly in the peripartum period, are known to be geographically mobile in many settings, including in South Africa, where those who have migrated to urban areas often travel to their rural homes post-delivery to obtain support from family (91,92). Because of these unique

circumstances, specific research to understand transfers and their effects on postpartum women is vital.

2.4.2 Frequency of transfers

Pregnant and postpartum women present a unique group with regard to transfer because, depending on the structure of health care services, they may be required to transfer between routine adult HIV care and maternal and child health care services to maintain HIV care. Previously, in most settings, pregnant women living with HIV (WLH) attending antenatal care who were eligible to receive ART were referred to general ART services for ART initiation (90). However, many women did not successfully link to general ART services and were thus not started on ART. HIV care was then integrated with maternal and child health care in many countries including South Africa and other sub-Saharan Africa countries, and this substantially improved rates of ART initiation among pregnant women (93). With current guidelines recommending universal lifelong ART initiation, WLH who attend antenatal care who are not on ART should be initiated on ART at integrated facilities and should be transferred out to general adult ART facilities post-delivery for long-term HIV care; the duration postpartum at which this is done varies by setting. Women who are already receiving ART at general ART facilities prior to pregnancy are transferred to maternal and child health care services for HIV care and antenatal, delivery and postnatal care. They are then transferred back to general ART facilities post-delivery (90); this may be to the original facility at which they were receiving care prior to pregnancy or to a different facility. In health care systems with integrated HIV and maternal and child health care, all women are thus required to transfer out from maternal and child healthcare services to general ART facilities postpartum.

Women who successfully transfer to a general ART facility post-delivery may subsequently transfer to another general ART facility for their own reasons including mobility and personal choice, and these transfers have been shown to occur frequently (93). In Cape Town, linked electronic health records were used to identify transfers between PHC facilities in 485 women who had successfully transferred out from an integrated PHC facility to a general ART PHC facility post-delivery. After attending the general ART PHC facility, 101/485 (21%) women then transferred again to a different PHC facility at least once over 30 months

of follow-up (93). Some women transferred multiple times; among the 101 women who transferred at least once, a further 16% transferred again. This included both silent and official transfers.

Analyses assessing silent transfers have shown that, similar to non-pregnant adults on ART, silent transfers occur frequently among postpartum women. In Johannesburg, a large city in South Africa, 38% of postpartum women who were LTFU from the facilities at which they initiated ART were found to be receiving care elsewhere (94). Similar findings were obtained in a rural South African setting; among 280 pregnant or postpartum women classified as LTFU at PHC facilities, 29% had silently transferred (95). In Malawi, 577 women who started ART in pregnancy and were LTFU were traced. Of the 229 who were successfully traced, 30% had silently transferred to another clinic (79). Overall, transfers occur frequently in the postpartum period including transfers between PHC facilities and silent transfers.

2.4.3 Outcomes of transfers

While integration of antenatal and ART care has led to increased uptake of ART among pregnant women, it requires transfer out from the integrated facility to general ART PHC facilities post-delivery and women are at risk of not linking to care. In Cape Town, 26% of 279 women on ART who were transferred out from an integrated PHC facility to a general ART PHC facility post-delivery did not have evidence of engagement at an ART facility post-transfer in the form of an HIV-related laboratory test conducted at a facility in the province by one year postpartum (96). Another study, also in Cape Town, followed 617 women initiated on ART in pregnancy who were transferred out of an integrated PHC facility post-delivery. Using linked electronic health data to assess engagement, this study found that 132 (21%) women did not have evidence of HIV care over a 30-month period (93). In the same analysis, among the women who successfully linked to the general ART PHC facility post-delivery, outcomes were compared among those who made additional transfers to other PHC facilities versus those who did not. Those with additional transfers had a 29% reduced risk of VL $\leq$50 copies/mL compared to those without additional transfers (93).

Transfers from routine care to differentiated service delivery models may also be associated with disengagement. Differentiated service delivery models aim to simplify care and

provide services based on patient needs (97,98). In South Africa, adherence clubs (ACs) are the predominant model (99,100): pre-packaged ART is provided to stable patients by community health workers (CHWs) at health facilities or community venues and postpartum women attending ACs have had good outcomes (101,102). However, 15% of postpartum women transferred from integrated antenatal/ART facilities to ACs did not attend their first AC visit.

2.4.4 Reasons for transfers

Mobility is thought to be a major factor associated with disengagement among postpartum WLH and may be one of the reasons that postpartum women require transfers between facilities. Women in sub-Saharan Africa including South Africa are increasingly mobile (69,103) and high levels of mobility have been documented among peripartum women in South Africa (91–94,104). In Johannesburg, nearly half of pregnant and postpartum women travelled or planned to travel in the peripartum period, particularly post-delivery, to obtain assistance and support with the baby from family (91). Travel destinations for women in this study included eight provinces in South Africa and four international countries. In rural KwaZulu-Natal, a substantial proportion of women migrated in the peripartum period (105).

Women who are mobile may be at higher risk of disengagement compared to those who are not mobile and transfers to facilities at the travel destination may be a way for women to access care. A study compared mortality among WLH in KwaZulu-Natal who were mobile and not mobile: peripartum WLH who moved away from home had an increased risk of maternal mortality compared to those who did not move, and this was hypothesised by the authors to be due to mobile women experiencing difficulties transferring to new facilities (105). In a qualitative study in Tanzania, women described running out of treatment while travelling leading to treatment interruption (106), suggesting that they did not transfer to facilities at their travel destination to obtain treatment. However, we were unable to find studies comparing treatment outcomes in women who are mobile and not mobile beyond the peripartum period. Considering the effect that mobility is thought to have on engagement in care among postpartum WLH, a better understanding of the relationship between mobility and treatment outcomes is required. Further to this, understanding the

role of transfers in women who are mobile and the transfer services that are provided will allow a better understanding of the care needs of postpartum women.

Other factors identified as leading to transfer include fear of accidental disclosure of HIV status and stigma, particularly if seen by neighbours or acquaintances at the clinic (94,104). In South Africa, many women have been found to transfer to facilities that are close to their original facilities. Referred to as 'clinic shoppers', these women are thought to move around local facilities to avoid inadvertent disclosure (94).

2.4.5 Transfer processes

A lack of guidelines regarding the management of pregnant and postpartum women being transferred between integrated antenatal/ART facilities and general ART facilities has been described in a number of African countries but this has not been assessed in South Africa (107). In South Africa, current processes for transfers from midwife obstetric units (MOUs) to PHC facilities postpartum have been described in the methods sections of a few manuscripts. According to these manuscripts, women are referred to one of a network of routine PHC ART facilities in the area that provide general adult ART services for ongoing HIV care (102). The choice of facility is based on proximity to the woman's home and personal choice (96). Women are counselled by nurse-midwives regarding ART adherence and infant care including HIV-related care and are given a referral letter. Women are also provided with a two-month supply of ART and told to attend the general adult PHC ART facility within two months. The extent to which these processes are implemented, particularly outside of the context of research studies, is unclear.

Regarding the experience of transfers, pregnant women in Malawi who silently transferred, often due to mobility, described being turned away from facilities (104). Some described being off treatment for prolonged periods and a number of women also described being retested for HIV and reinitiated on ART, indicating inefficiencies in the system. No studies documenting the experiences of transfers for postpartum women were identified. A better understanding of transfer guidelines, current transfer processes, transfer experiences including patient satisfaction with the process and identification of potential barriers to successful transfer could identify areas that need to be addressed.

2.5 Transfers among people living with diabetes

2.5.1 Background

In sub-Saharan Africa including South Africa, levels of engagement in care among PLD are suboptimal. Many PLD are undiagnosed and among those who are diagnosed, few remain in care and are controlled on treatment (4,108–115). Retention in care among PLD attending PHC in sub-Saharan Africa has been estimated at 55% at 12 months (116). PLD require continuous care, and poor outcomes are largely due to the episodic nature of the care currently provided, particularly in LMIC (117). Strategies to enable the provision of continuous care at PHC level and evidence to inform these strategies are urgently required to improve outcomes.

It has been suggested that policymakers and managers should leverage the systems that are already in place in LMICs for HIV and tuberculosis (TB) care when developing systems for the long-term management of NCDs (108,118–121). While transfers are increasingly recognised as a factor affecting long-term engagement in care among PLH, there is less research on transfers among general adults living with diabetes, particularly in LMIC.

For chronic conditions in general and diabetes specifically, more research has been conducted in the context of continuity of care, which may be affected by transfers. Continuity of care, or the extent to which health care is experienced as connected and interrelated over time, is one of the fundamental components of PHC (122–124). Types of continuity include relational, which refers to a sustained relationship between patient and provider; informational, which involves the use of patient history to inform decisions regarding care; and managerial, which refers to consistency in the approach to patient management (122). Transfers between health facilities could affect continuity of care by affecting any of these domains. Measures of continuity of care that are frequently used include measures of continuity with providers. An example is the usual provider continuity index which measures the proportion of all of an individual patient's visits that are made to the provider who is most frequently seen (125–130). Fewer studies assess continuity to the location of care and, as scales or indices are often reported in such studies, outcomes such as the numbers of transfers are not always discernible, as will be described further below.

2.5.2 Frequency of transfers

Unlike for HIV and TB, most countries do not have cohort monitoring and reporting systems for NCDs (117,131). It follows that data on the number of transfers among PLD are limited. A few studies evaluating the implementation of cohort monitoring systems have reported the number of official transfers out (132,133). For example, among 1,864 PLD registered over the course of a year in Malawi, 3 (0.2%) were recorded as officially transferred out by the end of the year, but not all visits were captured (132). In South Korea, all individuals are covered by a National Health Insurance programme, which has a database containing data on all health care service usage. Among 457,975 PLD with at least two health facility visits in one year, 33% were documented to have transferred between facilities over the course of the year, of whom 53% had transferred laterally between PHC facilities (134). In rural Uganda, patients attending diabetic clinics at two hospitals were asked about the number of facilities or providers attended over the course of their illness (135). A total of 295/496 (60%) participants had attended another provider prior to the hospital, including private clinics, health centres, neighbours or traditional healers. A study in the United Kingdom assessed the frequency of silent transfers by tracing outcomes in 47 PLD who were LTFU from a hospital outpatient facility. Of those LTFU, 39 (83%) had silently transferred and were accessing care elsewhere (136). These limited studies provide evidence that transfers do occur, including between PHC facilities, but further studies are required to understand the frequency of transfers, particularly in LMIC.

As mentioned in section 2.3.4 above, transfers need to be considered when planning health services and allocating resources. In sub-Saharan Africa, a lack of availability of basic diagnostic and monitoring equipment and treatments for diabetes has been documented (108). A better understanding of the volume of transfers is vital to informing efforts to improve access to diabetes care and the necessary treatments and equipment.

2.5.3 Reasons for transfers

Few studies have assessed reasons for transfers among PLD. A study in Kenya investigating how people with NCDs including diabetes, asthma and cardiovascular conditions cope with medicine stock-outs at health facilities, which occur frequently, found that moving between health facilities was one of the strategies used (137). Among PLD in Uganda who

transferred between facilities and providers including hospitals, private clinics, health centres, neighbours and traditional healers, reasons for transfers included better care and high costs of transport or treatment (135).

2.5.4 Outcomes of transfers

Among PLD, reduced continuity of care has been associated with lower levels of treatment adherence, impaired glycaemic control, increased health care usage and higher levels morbidity and mortality (125–128,138–141). This includes studies assessing continuity with providers and locations of care. Studies that measure continuity of the location of care do not always directly indicate whether a transfer occurred e.g., in the United States, Mainous et al. categorised patients as not having a usual site of care, having a usual site of care but no usual provider, or having a usual site of care and a usual provider (138). Having a usual site but no usual provider was associated with a 12-times increased relative odds of glycaemic control compared to no usual provider, while having a usual site and a usual provider was associated with 7-times increased relative odds of glycaemic control compared to no usual provider. Having a usual site of care thus appeared to improve outcomes.

Among the studies that have directly assessed outcomes of transfers, most focus on transfers between different levels of the health care system, particularly patients who are being discharged from hospital to PHC facilities, and most of these studies are from high income settings (142–148). For example, in the United States, 31% of PLD who were discharged from hospital did not attend outpatient follow-up (149). Studies have also assessed the risk of re-admission post-discharge from hospital among PLD and found that PLD are at a higher risk of readmission compared to people without diabetes (144,147). Studies assessing outcomes of transfers, including transfers between PHC facilities, are required in LMICs.

2.5.5 Transfer processes

Little is known regarding current transfer processes for PLD. Studies testing interventions to improve outcomes in patients who are transferring have been conducted in adolescents with diabetes transferring from paediatric to adult services including, for example, the use of transition coordinators who provide support and assist with the logistics of transfer (150).

For adults with chronic conditions including diabetes, studies have focused on movement between hospitals and PHC, in particular, how to improve outcomes post-hospital discharge (142,145,151–155). Medication errors occur frequently among PLD transferring between hospitals and PHC facilities and education of pharmacists was found to reduce medication errors in a non-randomised trial (142,156). In addition, patient education prior to discharge and follow-up at a transitional clinic 2–5 days post-discharge have been associated with improved outcomes (157,158).

2.6 Summary and gaps in the literature

As the prevalence of chronic conditions in LMIC increases, health systems are under pressure to provide long-term and continuous care. To remain in long-term care, patients with chronic conditions may require transfers between facilities and facilitating transfers is central to providing continuous care.

Transfers include up-referrals, down-referrals and lateral transfers e.g. between PHC facilities. Transfers between PHC facilities may be particularly important in LMIC where levels of geographic mobility are high, and a recent study in South Africa showed that transfers between PHC facilities occurred more frequently than transfers from hospitals to PHC facilities and from PHC facilities to hospitals (64). Transfers among general adult patients living with HIV have been associated with disengagement and mortality but these studies did not differentiate outcomes for up-referrals, down-referrals and lateral transfers and outcomes of transfers between PHC facilities among PLH on ART, including VL outcomes, are unknown. Transfers may also be silent or official. Both silent and official transfers occur frequently in LMIC and are associated with poor outcomes but the management, characteristics and outcomes of these transfers have not been directly compared. In postpartum women, transfers between PHC facilities occur frequently and have been associated with viraemia (93). Levels of mobility are high in postpartum women and this may contribute to the high number of transfers. Research on current transfer services and processes is required to identify barriers to transfers and understand how outcomes may be improved in this population, including for mobile women. For both general adult patient living with HIV and postpartum women, transfer processes may

contribute to the occurrence of poor outcomes, but little is known about current guidelines and policies informing these processes in the South African setting. Despite the high volume of transfers documented among PLH and the risk of poor outcomes, data on transfers for other chronic conditions including diabetes are limited, particularly in LMIC.

Based on the above gaps identified in this literature review, six areas were identified for further investigation in this thesis: 1) policies and guidelines for the management of transfers among PLH, 2) the association between transfers and viral load outcomes among adults on ART, 3) differences in the management and outcomes of silent and official transfers, 4) the frequency of transfers among PLD and the association between transfers and HbA1c outcomes, 5) patterns of mobility among women on ART in the extended postpartum period and the association between mobility and viraemia, and 6) barriers to successful transfers among postpartum women living with HIV.

2.6.1 Policies and guidelines for the management of transfers among PLH

Transfer processes are potentially complicated, involving multiple facilities, multiple health care workers as well as the patient and their family. Transfer processes may also differ based on the type of transfer. Based on Figure 2.1, policies and guidelines inform the elements making up the transfer service. However, despite the complexities of the transfer process, a lack of specific guidelines on the management of transfers has been noted for pregnant and postpartum women (107). Adults living with HIV have described transfer processes as confusing (82) but little is known regarding current policies and guidelines informing these processes. A better understanding of guidelines and policies on transfers between health care facilities is required to identify potential areas for improvement.

2.6.2 The association between transfers and viral load outcomes among adults on ART

While studies have documented disengagement from care and poor adherence during transfers between health facilities (62,65), the association between transfers and viraemia in general adult patients is unclear. Further, high proportions of patients who disengage and re-engage in care have advanced HIV disease and are clinically unwell (159) but the relationship between transfers, disengagement and clinical outcomes is not well

understood. Viral load is an objective marker of response to ART and research on virologic outcomes of transfers including transfers between PHC facilities in PLH who do and do not disengage from care is required. Understanding this relationship is vital to understanding the risks in patients who transfer and how transfers affect ART outcomes at a population level including levels of viraemia in the population.

2.6.3 Differences in the management and outcomes of silent and official transfers

Silent and official transfers both occur frequently among PLH (37,65). Reasons for silent and official transfers may differ and they are likely to be managed differently by the health system. Silent transfers may have worse outcomes than official transfers, but silent and official transfers have not been directly compared. Understanding the different types of transfers, including the transfer services provided for each and the risks involved, could help to identify those at highest risk of poor outcomes and could contribute to the development of appropriate management approaches.

2.6.4 The frequency of transfers among PLD and the association between transfers and HbA1c outcomes

Data on transfers between health facilities among PLD are extremely limited. Levels of retention in care and glycaemic control are suboptimal in LMIC (4) but it is unclear how patient transfers may contribute to this. Research on the frequency of transfers involving PHC facilities, including transfers between PHC facilities, and the association between transfers and HbA1c outcomes are thus required. In addition to clinical outcomes, patient transfers may affect programme planning. As the number of people requiring chronic disease care increases, a better understanding of the overall volume of transfers will inform health service planning including resource allocation and ordering of commodities and will inform further research.

2.6.5 Patterns of mobility among women on ART in the extended postpartum period and the association between mobility and viraemia

Geographic mobility is thought to be one of the main reasons for transfers between PHC health facilities in postpartum women on ART. Mobility may lead to disengagement, but the relationship between mobility and treatment outcomes including viraemia has not been

investigated in postpartum WLH. Research on the constellation of transfer services provided in the context of mobility is also required. Further, while breastfeeding is recommended for up to two years postpartum and beyond (159), most research on mobility has been done in the peripartum period. Research on travel and mobility in the extended postpartum period is needed.

2.6.6 Barriers to successful transfers among postpartum women on ART

Postpartum women on ART transfer frequently between PHC facilities, and transfers have been associated with disengagement and viraemia. Considering the risks associated with viraemia, the development of strategies to improve outcomes in women who transfer is vital. Currently reasons for poor outcomes among postpartum women who transfer are unclear. Research to understand women's experiences of transfer processes including the transfer services received, their knowledge of transfer processes and their satisfaction with the services received will help to identify barriers to successful transfers and inform possible interventions.

2.7 Conclusion

As the prevalence of chronic conditions continues to rise, improving the quality of chronic disease care services is a priority, particularly in LMIC. Transfers between health care facilities are a vital aspect of chronic disease care services that have been largely neglected to date. This thesis aims to improve our understanding of transfers across health conditions by including diabetes and HIV, and across population groups by including general adults living with HIV and postpartum women living with HIV. In addition, different types of transfers will be investigated to allow comparisons across these categories i.e., up-referrals, down-referrals and lateral transfers between PHC facilities, and silent and official transfers. In so doing, this thesis aims to develop a multi-faceted understanding of transfers and ultimately contribute to a consolidated approach to this vital health service function.

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Chapter 3: Guidelines for the transfer of people living with HIV attending primary health care facilities in South Africa: A scoping review

Odayar J, Phillips TK, Hennessey C, Myer L. Guidelines for the transfer of people living with HIV attending primary health care facilities in South Africa: A scoping review. *Under review at International Health.*

Relevance of this paper to the thesis:

Transfers involving primary health care (PHC) facilities, i.e., from PHC facilities to hospitals, from hospitals to PHC facilities and between PHC facilities, occur frequently among people living with HIV (PLH) and are associated with viraemia and disengagement. An understanding of the reasons for poor outcomes among PLH who transfer is required to identify areas for improvement. Transfer processes themselves may contribute to poor outcomes, with PLH in South Africa describing these processes as confusing. Yet, little is known regarding current guidelines and policies for management of transfers involving PHC facilities among general adult patients. This chapter presents the results of a scoping review of South African national guidelines and policies applicable to transfers of PLH and describes current recommendations, focusing on transfers involving PHC facilities, including lateral transfers.

Contributions of the student and co-authors:

JO conceptualised the review with guidance from TP and LM. JO developed the perspectives presented in the paper and drafted the manuscript. All authors reviewed the initial manuscript and provided conceptual and intellectual comment. All authors reviewed and approved the final manuscript.

3.1 Abstract

People living with HIV (PLH) may move between health facilities, also called transfer; this includes up- and down-referral based on clinical condition and lateral transfer, e.g., between primary health care (PHC) facilities for reasons such as geographic mobility or stigma. Transfers involving PHC facilities occur frequently and are associated with viraemia and disengagement, yet it is unclear how they are addressed in guidelines. We identified and reviewed national guidelines applicable to HIV care in South Africa for recommendations regarding transfer involving PHC facilities. Overall, 22/38 (58%) documents mentioned transfer, using the terms referral, linkage, transfer, transition, and handover. Linkage to care was defined as connecting individuals to care after HIV testing but other terms were not well defined, and all were used interchangeably. Documents emphasised transfers between different levels of the health system, and transfer between PHC facilities received limited attention. The transfer process was delineated for linkage to care, up- and down-referral but not for transfer between PHC facilities. Clinical management of patients transferring between PHC facilities and tracing of patients who requested transfers and missed their visits were not specified. Overall, transfers between PHC facilities were not well addressed and require attention to improve HIV treatment outcomes.

3.2 Introduction

Globally, approximately 28.7 million of the 38.4 million people living with HIV (PLH) were on antiretroviral therapy (ART) in 2021(1), including 5.5 million people in South Africa (1,2). Provision of long-term care to increasing numbers of people on ART is challenging, particularly in low and middle-income countries (LMICs) where health systems have developed to provide acute episodic care (3).

To maintain long-term care, PLH may require access to care at multiple health facilities over time (4). Movement between facilities, which we will refer to as transfer, could interrupt the continuum of care (5). Transfers may occur for numerous reasons. They may be health system-initiated: based on clinical condition, patients may be transferred from higher to lower levels of care (down-referral e.g., from hospitals to primary health care [PHC] facilities), or from lower to higher levels of care (up-referral e.g., from PHC facilities to hospitals). Transfers may also be patient-initiated e.g., in search of better clinic services (6,7), to avoid perceived stigma (5), or due to geographical mobility. These may include lateral transfers which are transfers between facilities at the same level of care e.g., between PHC facilities (8). With ongoing decentralisation of HIV care to PHC (3), transfers involving PHC facilities are increasingly important (9). However, transfers of adults on ART involving PHC facilities occur frequently, in multiple settings (9–15), and have been associated with viraemia (5), disengagement from care (16) and clinical deterioration (17). Understanding the reasons for poor outcomes among PLH who transfer is vital to improving outcomes.

Transfer processes themselves may affect outcomes. Transfers are potentially complicated, involving the patient and multiple health care workers from multiple facilities. The process of transferring has been described by PLH in South Africa as confusing and logistically complicated (18). Transfers can be either official or silent. Official transfers occur when patients inform their original facility of the transfer and obtain a transfer letter, while silent transfers (also called unofficial or self-transfers) occur when patients transfer without alerting the original facility or obtaining a transfer letter; these patients are often categorised as lost to follow-up (LTFU) at the original facility while attending another facility. Further, management processes may differ for up-referrals, down-referrals, and lateral

transfers between PHC facilities. While research has been done on up- and down referrals (19–25), there are limited data on transfers between PHC facilities. Despite the potential complexities of the transfer process, a lack of clear guidelines on transfer has been described for pregnant women living with HIV who may have to transfer between antenatal, postnatal and HIV care, (26) and it is unclear how transfers for general adults living with HIV are addressed in policies and guidelines. We reviewed national guidelines to describe recommendations regarding the transfer of PLH in South Africa, focusing on transfers involving PHC facilities, including lateral transfers between PHC facilities.

3.3 Methods

We conducted a scoping review to provide an overview of current guidelines. The review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) and was conducted according to the five stages described by Arskey and O'Malley (27,28).

The research question was formulated as follows: What are the national policies and guidelines regarding the transfer between health care facilities of adults living with HIV attending PHC?

3.3.1 Search strategy

We reviewed the South African National Department of Health (NDOH) website and contacted officials working at the Department to identify relevant documents. We also reviewed the HIV Clinicians Society (HIVCS) website which catalogues and provides access to NDOH guidelines related to HIV care. In addition, a literature search was conducted in Pubmed using terms for transfer identified in previous reviews on patient transfer (26,29). The search covered existing publications in English, had no time restrictions and was last conducted on 6 March 2023.

3.3.2 Screening and eligibility

Titles and abstracts were screened by one researcher (JO) who identified potentially relevant records. Full texts were obtained and read, and eligibility criteria applied. Policies, circulars, strategic plans, guidelines, standard operating procedures (SOPs), manuals, clinical decision-making tools and job aids that were authored and/or published by the NDOH were eligible for inclusion. Duplicates, provincial guidelines, frameworks, media releases, forms and patient education materials, draft guidelines, guidelines applicable to paediatric and adolescent populations only and documents published in languages other than English were excluded. Among potentially eligible documents, those that addressed any aspect of HIV testing, management or prevention were included; this included documents that also addressed management of other conditions. In addition, documents focused on health facility or health systems management that were applicable to HIV testing or management of PLH were included. Documents were included regardless of whether transfer was mentioned, to be able to assess how many addressed the topic. When a guideline had been updated over time, the most recent version was included.

3.3.3 Charting the data

Included documents were re-read iteratively and information was captured onto a data charting form that included how the document was accessed, year of publication, terms used to refer to transfer and their definitions, and recommendations regarding transfer processes. Information regarding transfers from PHC facilities to hospitals, hospitals to PHC facilities and between PHC facilities was extracted, and data related to transfers for HIV-specific care and for other care among PLH were included.

3.3.4 Analysis

Characteristics of the included documents were tabulated and expressed as frequencies and percentages, including terms used to refer to transfer and recommendations regarding transfer processes, which were categorised as related to the macro-level (policy level), meso-level (organisation and community level) or micro-level (patient interaction level) of the health system.

3.4 Results

Eligible documents were identified on the NDOH (n=15) and HIVCS websites (n=21; Figure 3.1). A Pubmed search identified 468 records; none were included as none were authored or published by the NDOH. An additional two documents suggested by an NDOH official were eligible for inclusion, making up 38 documents included in the final review.

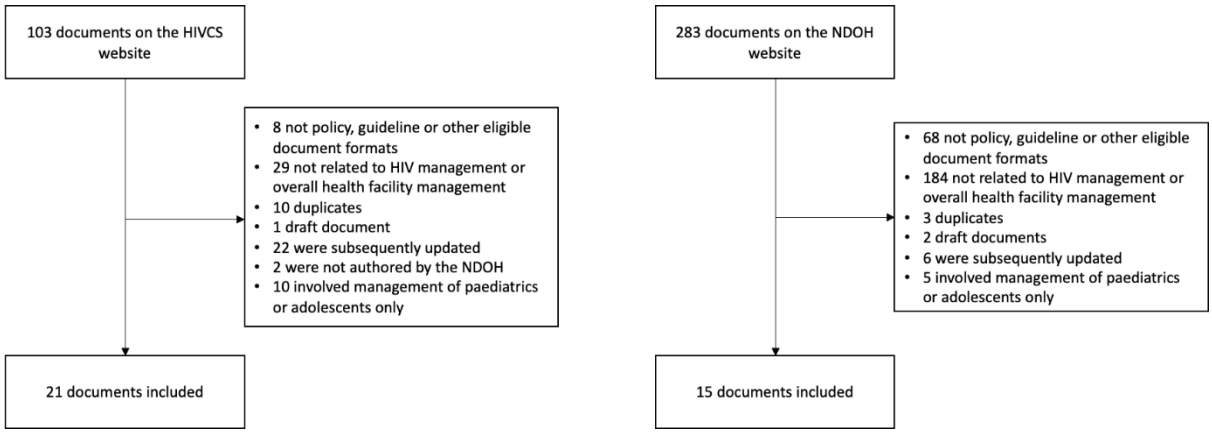

Figure 3.1 Eligibility of documents on the South African National Department of Health and HIV Clinicians Society websites

Of the 38 included documents, 19 (50%) addressed HIV testing, management and/or prevention (30–48), 3 (8%) addressed adherence among people with HIV, TB and/or NCDs (49–51) and 3 (8%) addressed clinical management of common conditions including HIV (52–54) (Supplementary table 10.2.1). Nine (24%) documents provided guidance regarding health facility or health system management that was applicable to HIV testing or management (55–63); of these, three formed part of the Ideal Clinic and Ideal Community Health Centre (CHC) programme which aims to improve quality of care at PHC facilities, and one focused on referral between health facilities (62). Four (11%) documents addressed management of specific patient populations, e.g., pregnant and postpartum women, and including management of HIV in these groups (64–67).

3.4.1 Terms and definitions

Documents used multiple terms when discussing transfer of PLH. Of the 38 documents, 21 (55%) mentioned refer/referral (46–55,57–62,64–68), 5 (13%) mentioned active referral (47,50,51,58,68), 16 (42%) mentioned links/linkages (38,46,47,49–52,54,57,58,62,64–68), 11 (29%) mentioned transfer (48–51,59–62,65,66,68), 3 (8%) mentioned handover (59,60,62) and 2 (5%) mentioned transition (50,65). While paediatric and adolescent populations were not included in this review, we note that two documents used *transition* to denote transfer of adolescents from paediatric to adult HIV services (58,64). Further, some of the above terms were used outside of the context of patient transfer, e.g., transition between drug regimens, but these uses were not tabulated. Five documents provided definitions of terms used: referral was defined in one document (62), active referral in three (47,50,68), transfer in one (62) and linkage in four (47,49,50,68). Neither transition nor handover were defined.

The South African referral policy defined *transfer* as the management process involved in moving a patient between facilities (Box 4.1) (62). The same document defined *referral* as "processes of professionals and institutions communicating and working together to protect, promote and restore the health of an individual", with upward, downward, and lateral referrals included as types of referrals. *Lateral referral* was defined as referral between hospitals for the same specialty, but movement between PHC facilities was not mentioned. The Ideal clinic and Ideal CHC manuals did not define referral or transfer, but use of *referral* related to ensuring access to a full range of health professionals and *transfer* to movement of patients between facilities and emergency medical services (59,60). *Transfer* thus appeared to denote the process of patient movement, while *referral* was used in terms of facilitating access to the care required to ensure patient health, but the distinction was not clear, and they were sometimes used interchangeably (54,61). *Active referral* was more clearly defined in three guidelines as initiation of the referral by the health care worker (HCW) including scheduling of the appointment (47), provision of a referral letter (68) and/or accompanying the patient to the appointment (47,50).

Text box 1 Definitions of terms used to refer to patient transfer

1. Transfer
   a. Referral policy for South African health services and referral implementation guidelines (35):
      - "A management process used to move a client from one facility to another."
      - In the same document transfer is also categorised as a type of referral and is defined as: "The clinical responsibility for patient management is transferred to the most appropriate practitioner as warranted by the patient's condition."

2. Link/linkage
   a. National Consolidated Guidelines for the Management of HIV in Adults, Adolescents, Children and Infants and Prevention of mother-to-child transmission of HIV (40) and National HIV testing Services: Policy (41):

      Process of actions and activities that support people testing for HIV and people diagnosed with HIV to engage with prevention, treatment, and care as appropriate for their HIV status.
      - For people living with HIV, it is the period from HIV diagnosis to enrolment in HIV care and treatment.
      - For people testing HIV negative, it is the period from HIV testing to enrolment in preventative health services.

   b. Adherence guidelines for HIV, TB and NCDs (23):

      Process of engaging a person with a disease to appropriate prevention, treatment, care and support services. It has two steps:
      - Screening to testing (screening may occur in community or health facilities) and testing to enrolment in care.
      - Once patients link to care, the next step is to start treatment.

   c. Adherence guidelines: Education on illness and treatment(22):

      Process of linking or connecting a person with a disease to appropriate prevention, treatment, care and support services.

3. Refer/referral
   a. National Consolidated Guidelines for the Management of HIV in Adults, Adolescents, Children and Infants and Prevention of mother-to-child transmission of HIV (40):

      Active referral: A referral in which the official referring the patient makes an appointment for the patient and provides a referral letter/form.

   b. Adherence guidelines for HIV, TB and NCDs, NDOH (23):

      Active referral: The official referring the patient makes an appointment for the patient or accompanies the patient to the appointment, including for co-located services, and enrolment into linkage to care. Appointment date should be at a convenient date and time and should be recorded in a database or logbook.

a. National HIV Testing Services: Policy (41):

Active referral: A referral where the person performing an HIV test makes an appointment for the client or accompanies the client to an appointment including an appointment for co-located services and enrolment into HIV clinic care

b. Referral policy for South African health services and referral implementation guidelines (35):

- Referral: processes of professionals and institutions communicating and working together to protect, promote and restore the health of an individual. This movement of a patient to another level of care could be internal, upward, downward or **lateral** for continuity of care.
- Lateral referral: Referral between hospitals for the same specialty

2. Transition and handover

Not defined

Abbreviations. NCD: non-communicable disease; TB: tuberculosis.

All four definitions of *linkage* involved connecting individuals to care after screening or testing for a disease (47,49,50,68). Two guidelines that were specific to HIV management defined *linkage* as connecting those who tested HIV-positive to HIV care and those who tested HIV-negative to preventative care (47,68). Two guidelines that applied to HIV, TB and NCDs defined *linkage* more generically as connecting someone diagnosed with a disease to prevention, treatment, and support services (49,50). However, in some documents, other terms were used for this concept including referral and transition (46). *Transition,* was also used in other ways, including to indicate movement between types of service delivery e.g., transition from postnatal to standard adherence clubs (65), while *handover* referred to the process of moving patients between health facility and transport staff, (59,60,62) and to handover of patients between staff at shift changes (60).

3.4.2 Recommendations

Recommendations regarding transfer were found in 22 documents and were grouped into macro-, meso- and micro-level recommendations.

3.4.2.1 Macro-level

The first South African referral policy was published in 2020 after the COVID-19 pandemic exposed difficulties with referrals between levels of the health system (62). It aimed to provide HCWs and managers with an approach to referral of patients to the appropriate health service, based on clinical condition, while ensuring timely access to comprehensive healthcare and maintaining continuity of care. Recommendations were made for referral processes in general, but processes for lateral transfers between PHC facilities were not mentioned.

3.4.2.2 Meso-level

3.4.2.2.1 Referral pathways

Five documents promulgated clear referral pathways to ensure access to higher or lower levels of care based on clinical condition (55,59,60,62,67). District-level SOPs describing the referral network including names and contact details of facilities providing specific services should be available, and a list of referral pathways should be displayed at facilities. Referral pathways between PHC facilities and availability of contact information for PHC facilities to which patients may request transfer were not mentioned.

3.4.2.2.2 Communication between facilities

The South African referral policy stated that all referred patients must receive a referral form with enough information for the receiving facility to continue care (62). Other documents emphasised use of referral forms for linkage to care among PLH, TB and NCDs (50,68) and for women living with HIV who are post-delivery and will receive ART elsewhere (65,68).

The South African referral policy also recommended scheduling of appointments with receiving facilities for patients being referred (62). Five additional documents

recommended scheduling of appointments (47,50,51,58,68) in specific situations: one applied throughout the continuum of care in patients with HIV, TB and NCDs with an emphasis on co-located services and linkage to care, three applied to linkage to care among PLH (47,58,68), and one applied to people with HIV, TB or NCDs being referred back to a facility after missed visits and to PLH being referred to community structures for support (51).

The adherence guideline for HIV, TB and NCDs recommended that appointment information for patients being linked to care be shared with the receiving facility (50) while the national ART guideline recommended this after HIV testing at community or work sites (68). Three documents suggested that, where feasible, patients being linked to care be accompanied to the receiving facility (50,58,68), with one specifying that patients be introduced to their new HCWs (58,68).

Regarding digital communication between facilities, the National Digital Health Strategy aims to establish an integrated platform for health information systems with a unique patient identifier used across facilities that will allow linkage of patient-level systems, development of a complete electronic health record, safe sharing of information between facilities and tracking of patient movement (56).

3.4.2.2.3 Recording and reporting

The Ideal Clinic and Ideal CHC manuals stated that all facilities should have a referral register to record transferred patients (59,60). Two documents stated that HIV counselling and testing (HCT) appointment registers should be used to monitor linkage to care and identify those who are LTFU (50,68).

The South African referral policy listed indicators to monitor referrals including hospital referral rate and down-referral rate but did not include transfers between PHC facilities (62). One document stated that patients categorised as LTFU patients who are traced and found to have self-transferred to another facility should have their classification changed to transferred out (68).

3.4.2.2.4 Training on transfer processes

Only the Ideal Clinic and Ideal CHC manuals addressed training on transfer, stating that all HCWs should be trained on referral processes (59,60). The content of training was not specified.

3.4.2.3 Micro-level

3.4.2.3.1 Indications for transfer

The South African referral policy stated that up-referral is required when the necessary care cannot be provided at the original facility (62). Six documents provided indications for up-referral (52–54,65,68,69). Two documents recommended down-referral to support adherence (52,53), and the referral of patients with chronic diseases who are stable to community-based services was emphasised (59,60). Regarding lateral transfer, the South African referral policy stated that patients who relocate may be referred to a facility at the same level of care, specifying referral from one tertiary facility to another as an example (62), and the adherence guideline included travel as a reason to obtain a referral letter (50). A counselling aid for use when counselling patients with HIV, TB and/or NCDs stated that patients should be told that if it becomes difficult to attend their health facility e.g., due to relocation, they should inform the facility and request a transfer letter (49). However, none of the full guideline documents included patient choice or request as a reason for transfer.

3.4.2.3.2 Clinical management

At least four documents stated that no-one who has run out of treatment should be denied care, regardless of whether they have a transfer letter or not (62,65,68,69). Clinical management of acutely ill patients being up-referred was described in a few clinical guidelines, including management prior to and during transfer (52,53). However, clinical management of patients who officially transfer or silently transfer between PHC facilities was not specified in any guideline.

3.4.2.3.3 Information provided to patients

Post-test counselling to facilitate linkage to care was emphasised (50,68). Linkage information was considered particularly important after HIV self-screening and HIV testing

in patients' homes by HCWs (46,47). For HIV self-screening, strategies to provide information included distribution of brochures with self-screening kits, a telephone hotline, mobile phone messages and community-based follow-up by CHWs.

Pre-ART counselling should include that patients should inform the clinic before travelling and receive a referral letter and/or sufficient treatment (50). If unable to do this, they should attend the nearest health facility as soon as possible after arriving at their destination with evidence of their diagnosis and treatment (50).

3.4.2.3.4 Patient support

Interventions to support linkage to care post-HIV testing included enhanced post-test counselling, patient accompaniment to ART initiation services, peer support, and additional psychosocial support for patients who require tracing before linking to care (47,50,68). If at increased risk of not linking to care for example patients who have previously delayed ART initiation, telephonic follow-up and/or home visits are recommended (47). Outside of linkage to care, provision of additional treatment was recommended for patients who are travelling, but there were minimal other interventions suggested for PLH on ART who transfer between PHC facilities.

3.4.2.3.5 Tracing and follow-up of transfer

Tracing of people who miss appointments would identify those who have or are in the process of silently transferring. Seven documents stated that patients who miss appointments should be traced, without mentioning transfer status (49–51,59,60,65,68): two applied to all patients attending PHC facilities, three to patients with HIV, TB or NCDs, one to PLH, and two to pregnant women (65,68).

Three documents mentioned tracing of officially transferred patients who miss their appointment at the receiving facility. Of these, two recommended tracing patients who did not link to care, of which one applied to all PLH (68) and the other to PLH, TB or NCDs (50). The third document recommended tracing of down-referred patients who missed their appointment (61).

3.5 Discussion

Numerous documents discussed transfer of PLH attending PHC facilities, emphasising transfer between different levels of the health system including linkage to care, up-referral, and down-referral to community structures. PLH may want to transfer between facilities for personal reasons, including lateral transfers between PHC facilities, yet patient request as an indication for transfer received minimal attention and the process of transfer between PHC facilities was not clearly outlined.

The terms referral, transfer and linkage were most frequently used. Most documents did not define the terms used. Overall, *transfer* related more to the process of patient movement, while referral related to HCWs facilitating access to the required care to ensure patient health, but the distinction was unclear, and terms were sometimes used interchangeably. *Linkage* was most often and consistently defined as connecting individuals to care after screening or testing for a disease; however, other terms were sometimes used in this context and linkage was also used in other contexts. Transition and handover were used but not defined. The lack of clear definitions may hamper access to and exchange of research and information regarding transfer (44,45). As further research regarding transfers is conducted, standardisation of terms is increasingly important.

Much of the focus of the reviewed guidelines was on linkage to care post-HIV testing, which is vital to ensure ART initiation in people testing HIV-positive. As the number of people on ART has increased, supporting adherence and retention has become increasingly important (70). Decentralisation of HIV care to PHC means that that there are increasing numbers of PHC facilities to which patients can transfer (9,15). In an analysis of people testing HIV-positive in an urban sub-district of Cape Town who started ART, 33% of transfers involving PHC facilities were from one PHC facility to another (71). Despite this, transfer between PHC facilities of PLH on ART received minimal attention in guidelines. Relocation and travel were mentioned as reasons for transfer in different documents and a counselling aid stated that patients should be told to inform their facility if it becomes difficult for them to attend that facility and request a transfer letter. However, patient request or preference was not mentioned as a reason for transfer in any of the full guideline documents. Clinical management of PLH on ART transferring between PHC facilities was not specified. Factors

such as regimen, previous blood results and disengagement may affect treatment, investigations, and follow-up (68) but these were not mentioned in the context of transfer. Guidelines for clinical management based on these factors are required. Importantly, numerous guidelines stated that individuals without transfer letters must not be refused care. However, further details regarding assessment and management of patients who silently transfer and do not have transfer letters was not discussed.

Disengagement has been documented in adults who officially transfer, albeit in a small study, and in adults who silently transfer (14,72). The South African referral guideline stated that all patients who miss visits should be traced; this would identify people who have or are in the process of silently transferring to another facility. We did not find mention of follow-up of patients who officially transfer, unless their visit at the receiving facility was missed, and this applied only to linkage to care and down-referred patients. Scheduling of appointments and sharing of appointment information with receiving facilities would allow identification of missed appointments by the receiving facility but these steps were not clearly specified for transfers between PHC facilities. Considering the risk of disengagement, follow-up of patients who officially transfer should be considered. In addition, research to better understand risks in patients who officially versus silently transfer is also required.

In the reviewed guidelines, it was not always clear whether recommendations applied to transfers between PHC facilities or not. For example, the South African referral policy recommended scheduling of appointments with receiving facilities, but this document focused on referrals between levels of the health care system (62). The adherence guidelines specified that appointments be scheduled throughout the continuum of care in patients with HIV, TB and NCDs but emphasised this for co-located services and linkage to care without mentioning transfers between PHCs (51). Overall, recommendations regarding transfers appear in different documents, applying to different types of transfers and situations, and a clear approach to management of all transfers, including transfers between PHC facilities is required.

This review focused on one country, South Africa, with specific mobility patterns and a health system which may differ from other countries. However, these findings may be relevant to other LMIC with high levels of mobility (26). The extent to which these

guidelines are implemented is unclear and, as these are national guidelines, there may be differences in implementation at a local level. Current transfer practices thus require investigation. Considering the prevalence of other chronic conditions in LMIC, transfer guidelines should be examined for other chronic conditions.

3.6 Conclusion

In summary, numerous terms are used to refer to transfer, many of which are not well defined and are used interchangeably. In addition, different types of transfers are managed differently, and aspects of transfer management are addressed in different documents, leading to a lack of clarity regarding when specific recommendations are applicable. Current guidelines focus on transfers between different levels of the health system i.e., up- and down referrals and linkage to care. Transfers between PHC facilities are not well addressed. Overall, clear guidance regarding transfers, including transfers between PHC facilities, and required.

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Chapter 4: Transfer of patients on antiretroviral therapy attending primary health care services in South Africa

Odayar J, Chi BH, Phillips TK, Mukonda E, Hsiao N-Y, Lesosky M, Myer L. Transfer of patients on antiretroviral therapy attending primary health care services in South Africa. *J Acquir Immune Defic Syndr.* 2022;90(3):309-315.

Relevance of this paper to the thesis:

As the number of people living with HIV (PLH) on ART increases, ensuring engagement in care and medication adherence to achieve and maintain viral suppression is a public health priority. With HIV care being decentralised in many countries including South Africa, understanding patient engagement in primary health care (PHC) services is vital. Transfers involving PHC facilities include transfers from PHC facilities to hospitals, hospitals to PHC facilities, and PHC facilities to PHC facilities. Transfers involving PHC facilities occur frequently and may disrupt continuity of care but the association between transfers and virologic outcomes is unclear. This chapter investigates the transfer incidence rate, predictors of transfer and viral load outcomes post-transfer among PLH attending PHC services in the Western Cape Province of South Africa. This chapter investigates all transfers involving PHC facilities and does not differentiate between transfers based on the types of facilities involved. Additional analysis focusing on the frequency and outcomes of transfers between PHC facilities is presented in Appendix 10.4.

Contributions of the student and co-authors:

JO conceptualised the analysis with guidance from BHC and LM. NYH oversaw laboratory testing. NYH and EM contributed to data management. JO conducted the analysis with guidance from ML. JO led data interpretation and drafted the manuscript. All authors reviewed the initial manuscript and provided conceptual and intellectual comment. All authors reviewed and approved the final draft of the manuscript.

4.1 Abstract

4.1.1 Background

Patients stable on antiretroviral therapy (ART) may require transfer between health care facilities to maintain continuous care yet data on the frequency, predictors and virologic outcomes of transfers are limited.

4.1.2 Methods

Data for all viral load (VL) testing at public sector health facilities in the Western Cape Province (2011–2018) were obtained. Participant inclusion criteria were a first VL between 2011-2013, age >15 years at ART initiation and >1 VL within 5 years of ART initiation, of which ≥1 was at a primary health care facility. Two successive VLs taken at different facilities indicated a transfer. We assessed predictors of transfer using generalised estimating equations with Poisson regression and the association between transfer and subsequent VL> 1000 copies/mL using generalised mixed effects. All statistical tests were 2-sided at $\alpha = 0.05$.

4.1.3 Results

Overall, 85,814 participants (median age at ART initiation 34 years, 68% female) were followed up for up to 4.5 years after their first VL: 34% (n=29,056) transferred at least once, and among these, 26% transferred twice and 11% transferred thrice or more. Female sex, age <30 years and first VL>1000 copies/mL were independently associated with an increased rate of transfer (adjusted rate ratio 1.24, 95% confidence interval [CI] 1.21–1.26; 1.34, 95% CI 1.31–1.36; and 1.42, 95% CI 1.38–1.45 respectively). Adjusting for age, sex, and disengagement, transfer was associated with an increased relative odds of VL>1000 copies/mL (odds ratio 1.35, 95% CI 1.29–1.42).

4.1.4 Conclusion

Approximately one-third of participants transferred and virologic outcomes were poor post-transfer. Stable patients who transfer may require additional support to maintain adherence.

4.2 Introduction

Substantial gains have been made in access to antiretroviral therapy (ART) globally (1,2). In 2019, 5.2 million of the 7.5 million people living with HIV (PLH) in South Africa were on ART making it the largest ART programme in the world (3). The benefits of ART require high levels of medication adherence and retention in care to achieve and maintain viral suppression (4,5), and as the number of PLH on ART increases, ensuring engagement in care and medication adherence has become a growing priority (6,7). To maintain long-term care, individuals may require access to care at multiple health care facilities over time (8). The process of moving between health facilities, referred to as transfer or transition of care (9), has the potential to interrupt the continuum of care. However, there are few data on HIV treatment outcomes in PLH who transfer.

Research on transfers is difficult to conduct. PLH may *officially transfer* out of health facilities (i.e., informs treatment facility and obtains a referral) and may or may not link to care (10). Alternatively, PLH may *silently transfer* (i.e., does not inform treatment facility or receive a referral) to a new facility and may be misclassified as lost to follow-up (LTFU) at the initial facility while in care elsewhere (11–17). Tracking these movements is notoriously difficult, particularly since most health systems lack integrated clinical information systems, and on-the-ground tracing efforts are resource-intensive and time-consuming (18). Further, the cascade of care framework traditionally used to monitor HIV treatment program outcomes is linear and does not directly account for PLH transferring between health care services (6,19,20).

Transfer may occur for numerous reasons (21). Geographically mobile patients might require access to care at multiple health facilities. In South Africa, people commonly move between rural and urban areas for multiple reasons including employment, education opportunities and health care access. Transfer may also be mandatory, e.g., postnatal transfer from maternal to routine ART services (22). Clouse et. al described “clinic shopping” among postpartum women on ART who were recorded as LTFU in South Africa; women silently transferred to clinics close to their original clinics, possibly due to stigma or fear of disclosure (23). Current evidence shows that transfers occur commonly; >50% of PLH started on ART from 2004-2006 in South Africa transferred between health facilities at

least once over a six-year period (24). Up to 36% of PLH categorised as LTFU have been shown to have transferred silently between health facilities, and this misclassification has implications for programme evaluation and resource allocation (15,25). There is evidence of suboptimal adherence to treatment and gaps in care at the time of transfer (10,22,26-29), but data on the association between transfer and VL outcomes in PLH on ART are few.

A better understanding of transfers is critical to ensuring comprehensive HIV services while accounting for outcomes on ART at the population level. To address the current gaps in the field we used routinely collected data from all public sector health facilities across the Western Cape Province of South Africa to determine the transfer incidence rate, predictors of transfer and viral load outcomes post-transfer.

4.3 Methods

4.3.1 Setting and data source

This is a retrospective cohort study conducted using routinely collected data from the Western Cape province of South Africa. There were an estimated 421,752 people living with HIV in the province in 2016 and this number has remained relatively stable in the years since (30). The province has one large urban district, the City of Cape Town, which has a high population density, and five rural districts (31). More than 70% of people living with HIV in the province reside in the Cape Town District (30).

Over 80% of the Western Cape population attend public sector health services (32), which consist of 52 hospitals and 354 primary health care (PHC) facilities across the province (33). South African antiretroviral treatment guidelines in 2010 recommended ART initiation at a CD4 count <200 cells/mm^3 and this was changed to a CD4 count <350 cells/mm^3 in 2012 (34,35). Supplementary table 10.3.1 illustrates ART regimen changes over the study period. All VL tests conducted in the public sector are processed by the National Health Laboratory Service (NHLS) and recorded in the NHLS database. Since 2010, guidelines have recommended VL testing at 6 and 12 months on ART and then annually (34).

For this analysis, data on all VL tests conducted at public sector health facilities in the Western Cape Province from 01 January 2011 to 30 September 2018 in individuals who had

their first VL in this period were obtained from the NHLS. Data included patient name, surname, sex, age, facility at which the VL test was taken and VL result. Data on each test were received separately and multiple tests in the same individual were not linked. A record linkage algorithm was used to match tests taken in the same individual, creating a longitudinal cohort. Due to the variable presence of reliable unique identifiers in the data a custom record linkage procedure using the Jaro-Winkler algorithm was used (36).

4.3.2 Inclusion criteria

All patients with their date of ART initiation (imputed as 6 months prior to the first VL) between 01 January 2011 and 30 September 2013 and who were older than 15 years at ART initiation were potentially eligible for inclusion in this analysis. All VLs taken within 5 years of ART initiation (or 4.5 years after the first VL) were included, and those with >1 VL in the follow-up period and at least one VL at either a clinic or a community health centre were included in the final sample.

4.3.3 Definitions

The ART initiation date was imputed as 6 months prior to the first VL. Each VL was considered evidence of a health facility visit. The visit interval was the time period between two consecutive visits in one participant (Figure 4.1). A transfer was defined as a VL documented at one facility with the subsequent VL documented at a different facility in an individual. As it is not possible to differentiate official and silent transfers using these data, this definition of transfer includes both types of transfer. When a transfer was documented, the date of transfer was calculated as the midpoint of the visit interval. A disengagement was considered to occur if a visit interval was >730 days (24 months). Participants who disengaged and had a subsequent VL in the study period continued to contribute person-time after the disengagement. South African guidelines for the management of HIV recommend intense adherence assessment and repeat VL testing in patients with a VL >1000 copies/m (34). Based on this, viraemia in this analysis was defined as a VL >1000 copies/mL.

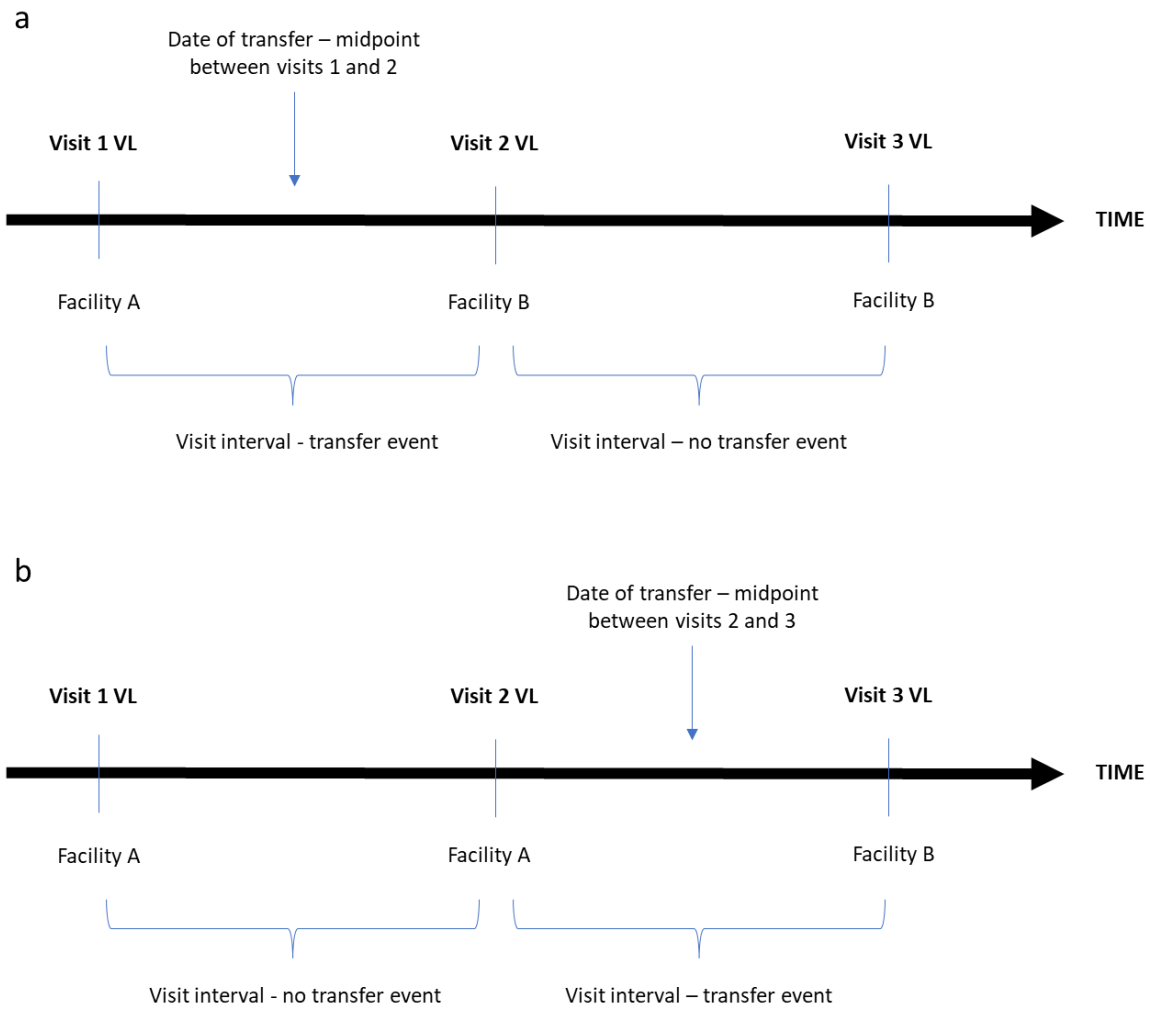

Figure 4.1 Hypothetical timeline of patient visits illustrating a transfer event between (a) visits 1 and 2 and (b) between visits 2 and 3.

4.3.4 Analysis

Data were analysed using STATA/SE version 14.0 (Stata Corporation, College Station, TX, USA). The proportion of participants who transferred at least once, the number of transfers per participant and the total number of transfers (including multiple transfers per patient) were counted. Frequencies and proportions, means with standard deviations (SD) or medians with interquartile ranges (IQR) were used to describe characteristics at ART initiation or at first VL in all participants, in those who did and did not transfer, and based on the number of transfers.

Transfer rates were calculated for all events that occurred from the first VL to the end of the study period, including multiple events per participant. Maximum possible duration of follow-up was 4.5 years for each individual. Participants with at least one VL between 2.5 and 4.5 years after the first VL were censored at 4.5 years after the first VL. Those who did not have a VL in this period were censored 12 months after the date of the last VL. To calculate transfer rate ratios, generalised estimating equations (GEE) under an unstructured working correlation with Poisson regression were used to account for repeated measures in participants. All statistical tests were 2-sided at $\alpha = 0.05$. Results are presented as crude and adjusted transfer incidence rate ratios (IRR or aIRR) with 95% confidence intervals (CI). Multivariable models were adjusted for age, sex, the location of the first VL (urban vs rural), year of ART initiation and first VL result which were identified *a priori* as potential confounders.

Generalised mixed effects models were used to assess the association between transfer during a visit interval and the occurrence of viraemia at the end of the interval (i.e. the first VL taken after the transfer, Figure 4.1), with results reported as odds ratios with 95% confidence intervals. Models were adjusted for age at ART initiation and sex as fixed effects and the occurrence of disengagement in the visit interval as a random effect. A sensitivity analysis was conducted, restricted only to visit intervals in which the preceding VL was <1000 copies/mL. Additional sensitivity analyses modelled alternate definitions of VL outcomes including VL <400 copies/mL and VL <50 copies/mL and alternate definitions of disengagement (VL >540 days [18 months] and >420 days [14 months]). Based on *a priori* hypotheses, we used stratified models to assess effect modification of the relationship between transfer and viraemia by the occurrence of disengagement in the visit interval.

4.3.5 Ethics

Ethical approval was obtained from the University of Cape Town Human Research Ethics Committee.

4.4 Results

A total 474,594 individuals had their first VL load at the NHLS in the Western Cape province between 01 January 2011 and 30 September 2018 (Figure 4.2). Among these, a total of 389,780 participants did not meet the criteria for our analysis in the following ways: 29% (n = 112,763) initiated ART before 01 January 2011, 3% (n = 11,747) were <15 years of age at ART initiation, 60% (n = 232,108) initiated ART after 30 September 2013, 6% (n = 23,564) had only one facility visit in the study period, and 2% (n = 8598) did not have a primary health care facility visit during the study period.

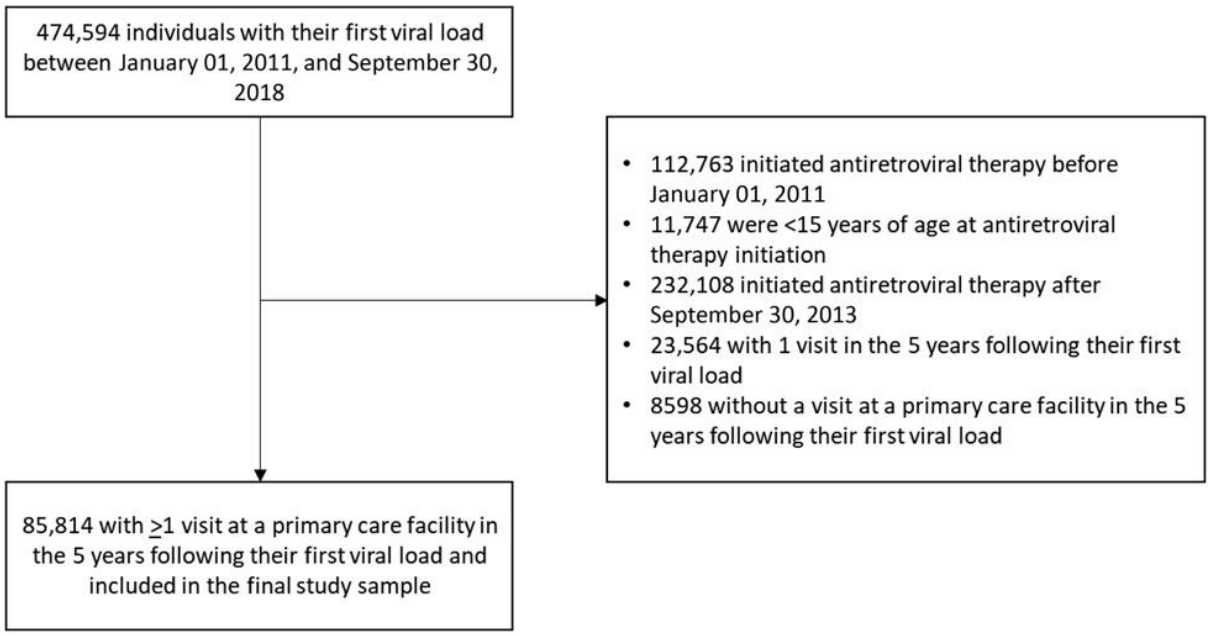

Figure 4.2 Flow diagram of the study cohort

The remaining 85,814 participants comprised the study cohort and contributed a total of 416,212 visits over 252,105 person-years of follow-up. Descriptive characteristics of the cohort are shown in Table 4.1. Median age at ART initiation was 34 (IQR 28–40) years and the majority of participants were female (n = 62,953, 68%). The first VL was conducted in a rural region of the province in 30% (n = 26,036) and was >1000 copies/mL in 15% of participants (n = 13,132). Median number of visits was 5 (IQR 4–6) and median duration of

follow-up was 4.5 years (IQR 4.5–4.5). Overall, 70% (n = 60,375) were virally suppressed throughout follow-up. Median duration between visits was 294 days (IQR 179–381). At the end of follow-up, 23% (n = 19,510) had not had a VL in the preceding two years and were classified as LTFU.

Table 4.1 Description of participants included in the analysis by whether a transfer occurred and by the number of transfers (n = 85,814)

	All participants	≥1 transfer	1 transfer	2 transfers	≥3 transfers	No transfer
Number of participants, n (%)	85,814	29,056	18,259	7580	3217	56,758
Age at ART initiation (yr), median (IQR)	34 (28-40)	32 (27-39)	33 (28-39)	31 (27-38)	31 (26-37)	34 (29-41)
Female, n (%)	58,724 (68.4)	21,046 (72.4)	12,794 (70.1)	5731 (75.6)	2521 (78.4)	37,678 (66.4)
Number of visits, median (IQR)	5 (4–6)	5 (4–6)	5 (3–6)	6 (5–7)	7 (6–8)	5 (3–6)
Duration of follow up (yr), median (IQR)	4.5 (4.5–4.5)	4.5 (4.5–4.5)	4.5 (4.5–4.5)	4.5 (4.5–4.5)	4.5 (4.5–4.5)	4.5 (4.5–4.5)
Type of facility at which first VL was performed						
Hospital	6289 (7.3)	6289 (21.6)	4676 (25.6)	1016 (13.4)	597 (18.6)	0 (0)
Primary health care facility by clinic size quartile						
≤7 patients	81 (0.1)	74 (0.3)	49 (0.3)	10 (0.1)	15 (0.5)	7 (0.01)
8 – 78 patients	425 (0.5)	279 (1.0)	187 (1.0)	51 (0.7)	41 (1.3)	146 (0.3)
79 – 600 patients	4413 (5.1)	1717 (5.9)	1099 (6.0)	436 (5.8)	182 (5.7)	2696 (4.7)
>600 patients	74, 606 (86.9)	20,697 (71.2)	12,252 (67.1)	6064 (80.0)	2381 (74.0)	53,909 (95.0)
First VL conducted in a rural region	26,036 (30.3)	9498 (32.7)	6611 (36.2)	2109 (27.8)	778 (24.2)	16,538 (29.1)
First VL >50 copies/mL	25,482 (29.7)	10,035 (34.5)	6210 (34.0)	2557 (33.7)	1268 (39.4)	15,447 (27.2)
First VL >400 copies/mL	14,689 (17.1)	6448 (22.2)	3986 (21.8)	1597 (21.1)	865 (26.9)	8241 (14.5)
First VL >1000 copies/mL	13,132 (15.3)	5801 (20.0)	3600 (19.7)	1421 (18.8)	780 (24.3)	7331 (12.9)
Year of ART initiation						
2011	27,701 (32.3)	9421 (32.4)	6418 (35.2)	2131 (28.1)	872 (27.1)	18,280 (32.2)
2012	31,737 (37.0)	10,216 (35.2)	6314 (34.6)	2775 (36.6)	1127 (35.0)	21,521 (37.9)
2013 (01 January–30 September)	26,376 (30.7)	9419 (32.4)	5527 (30.3)	2674 (35.3)	1218 (37.9)	16,957 (29.9)

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range; SD, standard deviation; VL, viral load.

4.4.1 Incidence of transfers and predictors of transfer

Approximately one-third of participants (n = 29,056, 34%) had evidence of transferring between health facilities at least once over the study period. The median duration from ART initiation to first transfer was 25.0 (IQR 17.0–32.5) months. Among the 29,056 participants who transferred at least once, more than one-third had evidence of multiple transfers: 26% (n = 7580) transferred twice and 11% (n = 3216) transferred three or more times. A total of 44,712 transfers events were documented (including repeat transfers) for a transfer rate of 12.71 (95% CI 12.59–12.83) transfers per 100 person-years (Supplementary table 10.3.2).

Of those who transferred, 72% were female, compared to 66% among those who did not transfer. Higher proportions of females were observed as the number of transfers increased: 70% (n = 12,794), 76% (n = 5731) and 78% (n = 2521) of those who transferred once, twice and three or more times respectively. Overall, 20% who transferred had a first VL >1000 copies/mL compared to 13% of those who did not transfer. A higher proportion of individuals who transferred three or more times had a first VL >1000 copies/mL (24%, n = 780) compared to those who transferred once (19%, n = 1421) or twice (20%, n = 3600). In a multivariable GEE Poisson model, female sex (aIRR 1.24, 95% CI 1.21–1.26), age under 30 years (aIRR 1.34, 95% CI 1.31–1.36) and a first VL >1000 copies/mL (aIRR 1.42, 95% CI 1.38–1.45) were associated with an increased rate of transfer (Table 4.2). There was no significant difference in the rate of transfer between those with their first VL conducted in a rural versus urban area. Compared to participants who started ART in 2011, those initiating ART in 2012 showed similar transfer rates (aIRR 1.00, 95%CI 0.98–1.03) while those initiating ART in 2013 demonstrated higher transfer rates (aIRR: 1.13, 95%CI: 1.11-1.16).

Table 4.2 GEE Poisson regression model assessing predictors of transfers (n = 85,814)

	Unadjusted models	Adjusted model
	IRR (95% CI)	IRR (95% CI)
Age category (yrs)		
- **≥30**	1 (ref)	1 (ref)
- **<30**	1.42 (1.39–1.45)	1.34 (1.31–1.36)
Sex		
- **Male**	1 (ref)	1 (ref)
- **Female**	1.32 (1.29–1.35)	1.24 (1.21–1.26)
First VL (copies/mL)		
- **≤1000**	1 (ref)	1 (ref)
- **>1000**	1.43 (1.40–1.47)	1.42 (1.38–1.45)
First VL in a rural or urban district		
- **Urban**	1 (ref)	1 (ref)
- **Rural**	0.99 (0.97–1.01)	0.99 (0.98–1.01)
Year of first VL		
- **2011**	1 (ref)	1 (ref)
- **2012**	1.00 (0.98–1.03	1.00 (0.98–1.03)
- **2013**	1.16 (1.13–1.18)	1.13 (1.11–1.16)

Abbreviations: CI, confidence interval; GEE, generalized estimating equations; IRR, incidence rate ratio; VL, viral load; yrs, years.

4.4.2 Transfer and viral load outcomes

Median duration between VL tests was 0.8 (0.49–1.04) years. The duration between VLs was similar for visit intervals in which a transfer occurred (0.79 years [IQR, 0.41 – 1.19]) and those for which a transfer did not occur (0.81 years [IQR 0.5 – 1.03]). Of the total 44,712 transfer events, 19% (n = 8397) were followed by a VL >1000 copies/mL at the end of the visit interval. In a mixed effects model adjusted for age, sex, duration on ART, whether the first VL was conducted in a rural or urban district and the occurrence of disengagement in the visit interval, the occurrence of transfer was associated with a 35% increase in the odds of VL >1000 copies/mL (adjusted odds ratio [aOR] 1.35, 95% CI 1.29–1.42) (Table 4.3). In addition, male sex (aOR 1.57, 95% CI 1.48–1.67), age <30 years (aOR 1.63, 95% CI 1.54–1.72), having the first VL done in a rural district (aOR 1.85, 95% CI 1.75–1.97) and the occurrence of disengagement (aOR 2.54, 95% CI 2.35–2.74) were associated with an increased odds of viraemia, while the odds of viraemia decreased with each additional year on ART (aOR 0.91, 95% CI 0.90–0.92). In sensitivity analyses assessing alternate VL

thresholds, the occurrence of transfer was associated with slightly higher odds of VL >400 copies/mL (aOR 1.39, 95% CI 11.33–1.45) and VL >50 copies/mL (aOR 1.48, 95% CI 1.42–1.53) compared to VL >1000 copies/mL. The association between transfer and VL >1000 copies/mL was not altered by changes in the definitions of disengagement (Supplementary tables 10.3.3 and 10.3.4). In a further sensitivity analysis restricted only to visit intervals in which the VL at the start of the interval was <1000 copies/mL, the increased odds of VL >1000 copies/mL in those who transferred compared to those who did not transfer persisted (aOR 1.53, 95% CI 1.47–1.60; Supplementary table 10.3.5).

Table 4.3 Results of generalised mixed effects logistic regression modelling the relative odds of VL >1000, VL >400, and VL >50 copies/mL. Presented as adjusted odds ratios with 95% confidence intervals.

	VL >1000 copies/mL	VL >400 copies/mL	VL >50 copies/mL
Transfer during visit interval			
- **No**	1 (ref)	1 (ref)	1 (ref)
- **Yes**	1.36 (1.30–1.42)	1.39 (1.33–1.45)	1.46 (1.41–1.52)
Sex			
- **Male**	1 (ref)	1 (ref)	1 (ref)
- **Female**	1.52 (1.43–1.62)	1.51 (1.42–1.60)	1.53 (1.46–1.61)
First VL in a rural or urban district			
- **Urban**	1 (ref)	1 (ref)	1 (ref)
- **Rural**	1.85 (1.75–1.97)	2.05 (1.93–2.17)	2.29 (2.18–2.41)
Age (yrs)			
- **≥30**	1 (ref)	1 (ref)	1 (ref)
- **<30 years**	1.49 (1.40–1.57)	1.46 (1.38–1.55)	1.36 (1.30–1.43)
Duration on ART (yrs)	0.91 (0.90–0.92)	0.94 (0.93–0.95)	1.10 (1.09–1.11)
Disengagement in the visit interval			
- **No**	1 (ref)	1 (ref)	1 (ref)
- **Yes**	2.76 (2.56–2.98)	2.75 (2.55–2.96)	2.67 (2.50–2.85)

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; IRR, Incidence rate ratio; VL, Viral load; yrs, years.
*Disengagement defined as >24 months between VL tests

In adjusted stratified analyses including only visit intervals in which a disengagement occurred (defined as >24 months between VLs), a VL >1000 copies/mL was more likely to occur at the end of a visit interval in which a transfer occurred compared to one in which a transfer did not occur (aOR 1.43, 95% CI 1.30–1.57; Supplementary table 10.3.6). In

comparison, when including only visit intervals in which a disengagement did not occur, the odds of a VL >1000 copies/mL was still significantly higher for intervals in which a transfer occurred compared to those in which a transfer did not occur, but the effect size was smaller (aOR 1.35, 95% CI 1.28–1.41). When the duration between VLs to define disengagement was decreased, the difference in odds ratios between strata increased. Defining disengagement as >14 months between VLs and including only intervals in which a disengagement occurred, the aOR for VL >1000 copies/mL after a transfer occurred compared to when a transfer did not occur was 2.56 (95% 2.04–3.22). The corresponding aOR for intervals in which a disengagement did not occur was 1.23 (95% CI 1.16–1.29).

4.5 Discussion

This analysis described transfers of PLH on ART attending primary health care services and assessed VL outcomes post-transfer. Approximately one-third of PLH observed here transferred between facilities at least once over the standardised follow-up period (i.e., 4.5 years), with female sex, younger age and a first VL >1000 copies/mL associated with an increased rate of transfer. After adjusting for age, sex and disengagement, transfer was associated with a 35% increase in the odds of elevated VL.

Current World Health Organization targets aim for 95% of PLH on ART to be virally suppressed (37). Considering the number of PLH on ART who transfer—and the risk of viraemia following the event— PLH who seek care at different facilities represent an important target group in the achievement of this goal. The finding that 34% of PLH transferred care at least once is lower than in a study by Fox et al., which used NHLS data from *across* South Africa (rather than in the Western Cape alone) to find that 56% of participants transferred at least once (24). However, in this previous study, children below 15 years of age were included—a factor that might contribute to the higher proportion of patients transferring, particularly as adolescents in South Africa transfer from paediatric to adult services (18). A number of other studies have documented lower proportions of patients on ART as transferring but duration of follow-up was shorter in these cases (26,38). Our result is similar to that of Bengtson et al. who used evidence of HIV-related health facility visits across the Western Cape to find that 31% of participants transferred at least once over three years of follow-up. Overall, most studies censor patients at the point of

first transfer (24,26,38). By tracking patients across health facilities over time we were able to ascertain that approximately one-third of PLH who transfer do so more than once, contributing to a total of 44,712 transfers events over the study period and an incidence rate of 12.71 (95% CI 12.59–12.83) transfers per 100 person-years. Numerous studies have shown misclassification of outcomes in patients who transfer, which affects programme evaluation and health care service planning (11,13,15). The sheer volume of transfers documented in this analysis reinforces the importance of tracking patient transfer across facilities to accurately ascertain patient and programme outcomes.

This is one of the first studies to assess the association between VL and transfer among adults on ART in a primary health care setting. We found that individuals with a VL >1000 copies/mL were 42% more likely to transfer than those with a VL <1000 copies/mL, suggesting poor adherence or interruption of treatment prior to the occurrence of transfer and that patients who transfer are at risk prior to the occurrence of the transfer. In addition, even in patients with a suppressed VL, the risk of viraemia was increased post-transfer, highlighting the need for additional support.

Further research is required to understand how to improve outcomes in patients who transfer. In this analysis we were unable to distinguish between silent and official transfers. It is possible that these two types of transfer have distinct characteristics and outcomes and may require different interventions. Future research should compare outcomes between silent and official transfers. In stratified analyses, the association between transfer and viraemia was stronger when a disengagement occurred compared to when a disengagement did not occur. In patients who disengage from care, South African guidelines recommend a VL at two to three months after restarting ART (34,39). This suggests that in this analysis, the risk of viraemia post-transfer in those who disengaged was increased even after treatment was restarted. Disengagement has previously been associated with transfer (29), and improving access to care and preventing disengagement in patients who transfer will thus be vital to improving treatment outcomes. In a qualitative study of 16 adults with HIV who silently transferred in South Africa, patients described the transfer process as confusing and difficult to navigate with numerous logistical barriers to transfer, including having to restart treatment at receiving facilities due to a lack of paperwork (40). Transfer processes themselves may thus contribute to poor outcomes and documentation of current processes

and an understanding of patient and provider experiences of transfer are required to understand how to improve services.

Strengths of this study include the use of medical records from public sector health facilities across the province which could be linked, allowing tracking of patient movement between facilities. Use of this central data source allowed us to follow a large number of PLH for a longer duration than many previous studies. We also note several limitations. First, the number of transfers may be underestimated. Not all visits are recorded in the NHLS database, only those at which VLs were taken. If transfers occurred but VLs were not done at the receiving facilities, these transfers would be undetected. In addition, individuals who were transferred out but never attended the receiving facility would not be counted in this analysis. Second, although the NHLS database provided a robust, centralised database, it contains only limited individual patient data; we were thus unable to consider some potentially important confounders such as socio-demographic descriptors. Third, these data covered only the Western Cape, meaning that inter-provincial transfers were not measured; however, more than 90% of transfers in the Western Cape are estimated to be intra-provincial (24). Finally, our data covered public healthcare facilities, but it is possible that participants had VLs taken at private sector facilities which would not be included in this dataset, although movement of PLH between public and private services is thought to be infrequent.

4.6 Conclusion

In summary, we found that approximately one-third of PLH on ART transferred one or more times over a 4.5-year period. The rate of viraemia increased after transfer, indicating that those who transfer may be in need of additional support to maintain treatment adherence. Additional research is required to understand how to improve viral load outcomes in stable PLH attending primary health care services who transfer.

4.7 References

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Chapter 5: Silent and official transfers between primary health care facilities of patients on antiretroviral therapy in South Africa

Odayar J, Chi BH, Hsiao N-Y, Mukonda E, Myer L. Silent and official transfers between primary health care facilities of patients on antiretroviral therapy in South Africa. *Manuscript being prepared for submission to J Acquir Immune Defic Syndr as a brief report.*

Relevance of this paper to the thesis:

Transfers may be official (referral letter obtained) or silent (health facility not informed and referral letter not obtained) and include up-referrals, down-referrals and lateral transfers. Chapter 4 showed that transfers among people living with HIV attending primary health care (PHC) facilities occur frequently and are associated with viraemia compared to no transfer. However, the analysis did not differentiate between silent and official transfers, nor between up-referrals, down-referrals and lateral transfers. The analysis in Chapter 4 used data on viral load (VL) tests from the National Health Laboratory Service which included the names of facilities at which tests were taken; patients with VLs at different facilities were identified as having transferred. However, the data did not include an indication of whether a transfer was silent or official. To differentiate silent and official transfers, a review of medical records was conducted; individuals from the dataset in Chapter 4 who transferred from any PHC facility in the Western Cape to the Gugulethu community health centre in Cape Town were identified. To further focus in on PHC, only lateral transfers from another PHC facilities were included. Transfers were categorised as silent (no transfer letter in file) or official (transfer letter in file), allowing comparison of their management and outcomes.

Contribution of the student and co-authors:

JO conceptualised the analysis with guidance from LM and BHC. JO conducted all data abstraction and analysis and wrote the first draft of the manuscript. All-co-authors reviewed the manuscript and provided conceptual and intellectual comment. All authors have been involved in the draft manuscript which is currently being prepared for submission to the *Journal of Acquired Immune Deficiency Syndromes*.

5.1 Abstract

5.1.1 Background

Transfers among people living with HIV (PLH) may be official (patient informs health facility and obtains referral letter) or silent (health facility not informed), but few studies have compared the two.

5.1.2 Methods

Data on viral load (VL) tests at public sector facilities in the Western Cape were used to identify transfers-in from primary health care (PHC) facilities to the Gugulethu Community Health Centre (CHC) in Cape Town from 2016–2018. Individuals with a VL at a different PHC facility and a subsequent VL at the CHC were considered possible transfers-in and their medical records were requested. Data abstraction was conducted if transfer-in was confirmed. Guidelines recommend the first VL at six months on ART; as all participants had a VL they were all considered to have been on ART. Transfers with and without referral letters were categorised as official and silent respectively. Clinical features at transfer-in were compared for each transfer type.

5.1.3 Results

Of 65 possible transfers, 35 records were located and 33 were confirmed eligible (median age 38.6 years, 70% female). Overall, 21/33 (64%) transfers were official and 12/33 (36%) were silent. Despite having prior VLs, 4/33 (12%) participants transferred in as newly diagnosed with HIV with no ART history. 6/18 (33%) official transfers and 8/12 (67%) silent transfers were off ART for at least a month at transfer-in. Among silent and official transfers, 5/11 (45%) and 3/18 (17%) respectively had clinical concerns requiring medical intervention at transfer-in.

5.1.4 Conclusion

Interventions to prevent disengagement and guidelines for management of transfers are required.

5.2 Introduction

Transfer of care between health facilities among people living with HIV (PLH) attending primary health care (PHC) occurs frequently and has been associated with disengagement and viraemia (1–3). Transfers may be official or silent. Official transfers are known to the health facility and occur when patients inform the original health facility and obtain a referral letter. Silent transfers are not known to the health facility and occur when patients transfer to another facility without informing the original facility or receiving a referral letter (4–6). Transfers affect continuity of care and this effect may be greater when patients silently transfer and do not have referral letters compared to when they officially transfer. However, most research on transfers has not differentiated between official and silent transfers or has not directly compared them (2–4).

In a previous analysis among PLH on antiretroviral therapy (ART) attending PHC in the Western Cape province (WCP) published in *JAIDS* in 2022, we found that one-third of participants transferred one or more times over 4.5 years of follow-up (1). Further, transfers were associated with a 35% increase in the relative odds of a VL >1000 copies/mL versus no transfer. However, the analysis included both silent and official transfers and did not distinguish between them. In addition, it included transfers between different levels of care (i.e., between PHC facilities and hospitals) and between facilities at the same level of care (i.e. between PHC facilities). People may transfer between PHC facilities for numerous reasons including geographic mobility (7). In a cohort of PLH on ART in Cape Town, 33% of transfers to other facilities in the WCP were between PHC facilities (8). While transfers between different levels of care have received some attention in the literature (9–16), many analyses of transfers among PLH do not clearly indicate the types of facilities involved (2,3) and data on transfers between PHC facilities are limited.

Understanding the different types of transfers—their management and associated risks—can help to improve outcomes. To address these gaps, we extended the analysis of transfers among PLH on ART in the WCP published in *JAIDS* in 2022 in a subset of participants to compare the characteristics, clinical management and outcomes of silent and official transfers between PHC facilities.

5.3 Methods

This work follows from a previous analysis which used data from the National Health Laboratory Service (NHLS) on all viral load (VL) tests conducted at public sector health facilities between January 2011 and September 2018. For the current analysis, we conducted a cohort study focused on one facility, the Gugulethu Community Health Centre (CHC). Participants transferring into this facility from other PHC facilities in the WCP were identified as described below and their medical records were requested for review.

5.3.1 Setting and data sources

The Gugulethu CHC is a large PHC facility in the City of Cape Town which includes an ART clinic. The facility serves a population of approximately 350,000 (17). Antenatal HIV prevalence in the City of Cape Town district was estimated at 22% in 2019 (18).

South African guidelines recommended ART initiation at a CD4 count <200 cells/mm^3 in 2010 (19). In 2012, this was changed to a CD4 <350 cells/mm^3 (20). Baseline investigations prior to ART initiation included serum creatinine, alanine transaminase and haemoglobin. Since 2010, VL testing has been recommended at 6 and 12 months on ART and then annually. All public sector VL tests are processed by the NHLS and recorded in a database administered by the NHLS. Regarding transfers, guidelines in 2020 stated that referred patients should receive a referral form from the referring facility with sufficient information for the receiving facility to continue care and that a copy of the letter should be kept in the patient medical record (21). Patients who have run out of treatment should not be denied care, regardless of whether they have a transfer letter (21–23).

In the previous analysis from which this analysis follows, participants with their first VL between 2011 and 2013, aged over 15 years at ART initiation and with $\geq$2 VLs within five years of initiation of which at least one was at a PHC facility were included. Because guidelines recommended the first VL at six months on ART, participants with a documented VL were considered to be on ART. Consecutive VLs at different facilities indicated a transfer. For the current analysis, we took all participants included in the previous analysis and identified potential transfers-in to the Gugulethu CHC from other PHC facilities between January 2016 and September 2018. Only transfers after 2016 were considered because

medical records of patients last seen at the CHC prior to 2016 were archived. Transfers-in from hospitals and MOUs were excluded. For identified participants, routine medical records which are paper-based were requested from the CHC and reviewed. Those confirmed to have transferred in in the stipulated time period were included in the final analysis.

Records were assessed for referral letters. Participants with and without referral letters were categorised as official and silent transfers respectively. Standardised data abstraction forms were used to abstract information from referral letters including clinical history. Data abstracted from clinical notes included clinical status at transfer-in. Participants documented to be off ART for at least a month at the point of transfer-in were categorised as disengaged from care. In addition, the occurrence of subsequent transfers and disengagement during follow-up were documented. Data were abstracted up to 62 months after transfer-in, allowing equal follow-up duration in all participants.

5.3.2 Analysis

Using STATA/SE version 14.0 (Stata Corporation, College Station, TX, USA), variables were summarised as frequencies and percentages, means with standard deviations or medians with interquartile ranges (IQR). Baseline characteristics, clinical features and outcomes were tabulated and compared for silent and official transfers.

5.3.3 Ethics

Ethical approval was obtained from the University of Cape Town Human Research Ethics Committee.

5.4 Results

Of 85,814 individuals in the original study from which this analysis follows, 63 were identified as potentially transferring into the CHC from a PHC facility in the WCP between January 2016 and September 2018. Medical records were located for 35/63 (56%) individuals, of whom 33 (94%) were confirmed to have transferred to the CHC in the stipulated time frame and were included in the final analysis. Data abstraction was conducted from December 2022 to March 2023. Despite having a VL prior to transfer-in,

4/33 (12%) participants transferred in as newly diagnosed with HIV with no prior history of ART. The remaining 29/33 (88%) participants were recorded as currently or previously on ART. Median age of all participants was 38.6 (IQR 33.7–47.4) years at transfer-in and 23/33 (70%) participants were female (Table 5.1). Referral letters were present for 21/33 (64%) transfers and these were categorised as official, with the remaining 12/33 (36%) categorised as silent. Of the 29 participants who transferred with a history of ART use, 18 (62%) transferred in officially and 11 (38%) transferred in silently. Of the four participants who transferred in as newly diagnosed with HIV, three (75%) transferred in officially and one (25%) transferred in silently.

Table 5.1 Characteristics of patients officially and silently transferring into the Gugulethu Health Centre, 2016-September 2018. Presented as n (%) unless otherwise specified.

	Official transfers (n=21)			Silent transfers (n=12)			All participants (n=33)
	History of ART use (n=18)	New Patient (n=3)	All official transfers (n=21)	History of ART use (n=11)	New Patient (n=1)	All silent transfers (n=12)	
Median age at transfer, years (IQR)	39.2 (34.4–52.3)	34.1 (30.4–47.3)	38.6 (34.1–47.3)	36.3 (32.1–47.4)	55.1 (55.1–55.1)	39.6 (32.9–48.3)	38.6 (33.7–47.4)
Female	12 (66.7)	2 (66.7)	14 (66.7)	8 (72.7)	1 (100.0)	9 (75.0)	23 (69.7)
Median duration between last VL and TFI visit at CHC, days (IQR)	428 (325–920)	1336 (954–1443)	547 (334–1019)	474 (387–1565)	393 (393–393)	454 (390–1241)	474 (366 – 1019)
Median duration between referral letter date and TFI visit at CHC, days (IQR)	31 (4.5–75.5)	11 (9–72)	26 (6–72)				
- **Missing**	2 (11.1)	0	2 (9.5)				
VL pre-transfer							
- **LDL**	13 (72.2)	2 (66.7)	15 (71.4)	7 (63.6)	0	7 (58.3)	22 (66.7)
- **20–400 copies/mL**	4 (22.2)	1 (33.3)	5 (23.8)	3 (27.3)	0	3 (25.0)	8 (24.2)
- **401–1000 copies/mL**	0	0	0	1 (9.1)	0	1 (8.3)	1 (3.0)
- **>1000 copies/mL**	1 (5.6)	0	1 (4.8)	0	1 (100.0)	1 (8.3)	2 (6.1)
Median duration between TFI CHC visit and first VL post-transfer, days (IQR)	44.5 (0–179)	120 (119–145)	116 (0–145)	128 (41–163)	139 (139–139)	128 (76.5–152)	119 (28–145)
VL post-transfer							
- **LDL**	11 (61.1)	2 (66.7)	13 (61.9)	7 (63.6)	1 (10.0)	8 (66.7)	21 (63.6)
- **20–400 copies/mL**	2 (11.1)	1 (33.3)	3 (14.3)	3 (27.3)		3 (25.0)	6 (18.2)
- **401–1000 copies/mL**	0		0	0		0	0
- **>1000 copies/mL**	5 (27.8)		5 (23.8)	1 (9.1)		1 (8.3)	6 (18.2)
Not on ART at TFI	6 (33.3)	3 (100.0)	9 (42.9)	7 (63.6)	1 (100.0)	8 (66.7)	17 (51.5)
Duration off ART in those not on ART at TFI, months (IQR)	11.5 (5–27)			9 (5–24)			

	Official transfers (n = 21)			Silent transfers (n = 12)			All participants (n=33)
	History of ART use (n=18)	New Patient (n=3)	All official transfers (n=21)	History of ART use (n=11)	New Patient (n=1)	All silent transfers (n=12)	
Clinical status at transfer-in							
- **Asymptomatic/mild illness, no multimorbidity**	12 (66.7)	3 (100.0)	15 (71.4)	5 (45.5)		5 (41.7)	20 (61)
- **NCDs, well controlled**	2 (11.1)		2 (9.5)	1 (9.1)		1 (8.3)	3 (9)
- **NCDs, not well-controlled**	2 (11.1)		2 (9.5)	2 (18.2)		2 (8.3)	4 (12)
- **TB diagnosed at TFI, not on ART**				1 (9.1)		1 (8.3)	1 (3)
- **Cryptococcal meningitis, recent hospitalisation, not on ART**				1 (9.1)		1 (8.3)	1 (3)
- **TB on treatment, on NVP-containing ART – reason unknown**	1 (5.6)		1 (4.8)				1 (3)
- **Disseminated TB on treatment**				1 (9.1)		1 (8.3)	1 (3)
- **MDR-TB on treatment for 2 weeks, not on ART**	1 (5.6)		1 (4.8)				1 (3)
- **Referred for hospital admission, not on ART**					1 (100.0)	1 (8.3)	1 (3)
TFO to a PHC facility requested during follow-up	7 (38.9)	1 (33.3)	8 (38.1)	4 (36.6)	0	4 (33.3)	12 (36.4)
- **Disengaged prior to TFO request**	2 (28.6)	1 (100.0)	3 (37.5)	1 (25.0)	0	1 (25.0)	4 (33.3)
Disengaged during follow-up	6 (33.3)	1 (33.3)	7 (33.3)	9 (81.8)	1 (100.0)	10 (83.3)	17 (51.5)

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range; LDL, lower than detectable limit; PHC, primary health care; MDR-TB, multidrug-resistant tuberculosis; NA, not applicable; NCD, non-communicable disease; NVP, nevirapine; TB, tuberculosis; TFI, transfer-in; TFO, transfer-out; VL, viral load.

5.4.1 Contents of referral letters for official transfers

Of the 21 referral letters, 20 (95%) had the patient's name, 19 (90%) had the referring institution's name and 19 (90%) had the referral date (Table 5.2). Lower proportions included the name of the receiving facility (n = 9/21, 43%) and the prospective date of the visit at the receiving facility (4/21, 19%). For official transfers with a history of ART, 15/18 referral letters (83%) had the date of ART initiation, 15/18 (83%) had the drug regimen, 12/18 (67%) had baseline blood results and 15/18 (83%) had monitoring blood results. All three participants who transferred in officially as newly diagnosed with HIV were reported to have tested positive for HIV in the preceding three months.

Table 5.2 Information included in referral letters. Presented as n (%).

	TFI on ART (n=18)	TFI as new patient (n=3)	All TFI (n=21)
Patient name	17 (94)	3 (100)	20 (95)
Date of referral	16 (89)	3 (100)	19 (90)
Name of referring institution	17 (94)	2 (67)	19 (90)
HCW name			
- Not included	2 (11)	0	2 (10)
- Signed but illegible	9 (50)	1 (33)	10 (48)
- Signed and legible	7 (39)	2 (67)	9 (43)
Name of receiving facility	7 (39)	2 (67)	9 (43)
Date of visit at receiving facility	4 (22)	0	4 (19)
Date of ART initiation	15 (83)	0	15 (71)
ART drug regimen	15 (83)	0	15 (71)
Baseline blood results	12 (67)	1 (33)	13 (62)
Monitoring blood results	15 (83)	0	15 (71)

Abbreviations: ART, antiretroviral therapy; TFI, transfer-in; HCW, health care worker.

5.4.2 Assessment at the point of transfer-in for official and silent transfers

For the 16 patients who officially transferred in with a history of ART use whose referral letters were dated, the median duration between the date of referral and attendance at the CHC was 31 days (IQR 4.5–75.5). Among the three participants officially transferred in as

newly diagnosed with HIV, median duration between referral and CHC attendance was 11 days (IQR 9–72).

Overall, 11/33 (33%) had a detectable VL prior to transferring, made up of 6/21 (29%) participants who officially transferred in and 5/12 (42%) who silently transferred in. More than half (n=17/33, 52%) of all participants had disengaged at the point of transfer-in and were not on ART. This included the four patients who transferred in with no history of ART, 6/18 (33%) who officially transferred in with a history of ART and 7/11 (64%) who silently transferred in with a history of ART. Median duration off ART in those who transferred in with a history of ART was 9 (IQR 5–24) months among silent transfers and 11.5 (IQR 5–27) months among official transfers. Among official transfers, 3/18 (17%) had clinical concerns requiring medical intervention, including a patient on multidrug-resistant tuberculosis (TB) treatment who was not on ART, compared to 6/11 (55%) participants who silently transferred, including two with undiagnosed TB who were not on ART. Among those transferred in as newly diagnosed with HIV, one required referral for hospital admission.

5.4.3 Follow-up of official and silent transfers

A total of 12/33 (36%) participants requested another transfer during follow-up. Of these, 4/12 (33%) had disengaged from the CHC and returned while not on ART to request a transfer-out. There were no obvious differences in the proportions who requested a transfer during follow-up between those who had officially and silently transferred in.

More than half of all participants (n = 17, 52%) disengaged during follow-up, including the four participants who disengaged as part of a subsequent transfer mentioned above. A higher proportion of participants who had silently transferred in (n = 10/12, 83%) subsequently disengaged compared to those who officially transferred in (n = 7/21, 33%).

5.5 Discussion

This analysis described the transfer-in of PLH at a large CHC in South Africa. Despite the relatively small number of participants, it demonstrated the risks involved for PLH who transferred between PHC facilities, both officially and silently, in this sample. More than

one-quarter of participants had clinical problems requiring intervention and more than half had disengaged and were not on ART at the point of transfer-in. More than one-third of transfers were silent and the proportions who had disengaged and who had potential clinical complications at transfer-in were higher among silent than official transfers.

Management and follow-up of patients who have interrupted ART and/or have clinical complications may be complicated and depends on many factors including the previous regimen and blood results (22). The proportions of patients transferring in who had disengaged and had clinical concerns were high for both silent and official transfers but were particularly high among silent transfers, amplifying the importance of clinical information in participants without referral letters. Current guidelines on management of transfers between PHC facilities, particularly silent transfers, are limited (21–23). In particular, there is minimal guidance on how to obtain clinical information in patients who silently transfer. Even among official transfers, information in referral letters was sometimes omitted or incorrect. The Western Cape has an electronic health system that integrates individual-level health information across public sector facilities and services (24). However, it is unclear how this system was used to access information for participants transferring in. Understanding it's use, for example through qualitative interviews with health care workers (HCW), could assist in identifying ways to improve management of transfers. Overall, additional guidance for assessment and management of transfers between PHC facilities, particularly silent transfers, is required.

Fifty-one percent of participants had disengaged and were not on ART at transfer-in and research to understand the reasons this occurs is vital to developing strategies to prevent it. After transfer-in, four participants disengaged from the CHC and subsequently returned to request a transfer letter. Patients without referral letters being refused care has previously been documented and it is possible that these patients returned to the CHC to obtain a referral letter for this reason, which could prolong disengagement (25,26). A number of patients who were previously on ART transferred-in as newly diagnosed with HIV and were not on ART. Transferring to a new facility as a new patient has been documented elsewhere and is hypothesised to be way for patients who have disengaged to access care while avoiding HCW judgement (27–29). Removal of barriers to care, including HCW attitudes and the need for transfer letters is required. Overall, 52% of all participants disengaged after

transfer-in, made up of 83% of participants who silently transferred in and 33% of participants who officially transferred in. Transfer-in, particularly silent transfer, may thus be a risk factor for future disengagement and this requires further investigation.

Strengths of this analysis include the long follow-up duration. We also note some limitations. First, the number of possible transfers identified from the NHLS data appears low. The NHLS has record only of visits at which VLs are taken, and transfers involving facilities at which VLs were not taken would thus not be identified. Second, a large proportion of requested medical records were not located. This is likely due to misfiling, which is likely to be random and should not bias findings. Lastly, the small number of participants, and the fact that transfers-in to only one health facility were included, limits the conclusions that can be drawn; however, we believe that these results provide a valuable illustration of the journeys of patients who transfer.

5.6 Conclusion

In this cohort who transferred between PHC facilities in South Africa, high proportions of participants had disengaged from care and had potential clinical complications at transfer-in. Strategies to prevent disengagement are required for both official and silent transfers. More than one-third of transfers were silent and the proportions off ART and with clinical complications were higher among silent versus official transfers. Detailed guidelines for the management of transfers, particularly silent transfers, are required.

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Chapter 6:Transfers between health facilities of people living with diabetes attending primary health care services in the Western Cape Province of South Africa: A retrospective cohort study

Odayar J, Rusch J, Dave JA, Van Der Westhuizen DJ, Mukonda E, Lesosky M, Myer L. Transfers between health facilities of people living with diabetes attending primary health care services in the Western Cape Province of South Africa: A retrospective cohort study. Under review at *Trop Med Int Health*.

Relevance of this paper to the thesis:

Most research on transfers involving primary health care (PHC) facilities has been conducted among PLH. A few studies in high-income settings have shown that people living with diabetes do transfer between health facilities including between PHC facilities and that transfers affect continuity of care but data in low- and middle-income countries (LMIC) are limited. The prevalence of diabetes is increasing rapidly in LMIC and levels of engagement in care are low. A better understanding of transfers among patients living with diabetes is vital to improving health care delivery and patient outcomes. This chapter investigates the transfer incidence rate, predictors of transfer and HbA1c outcomes post-transfer among people living with diabetes attending PHC services in the Western Cape Province of South Africa. This chapter thus broadens the discussion regarding transfers beyond HIV to other chronic conditions.

Contributions of the student and co-authors:

JO conceptualised the analysis with guidance from LM. JR, DJVDW and EM contributed to data management. JO conducted the analysis with guidance from ML. JO led data interpretation and drafted the manuscript. All authors reviewed the initial manuscript and provided conceptual and intellectual comment. All authors reviewed and approved the final draft of the manuscript.

6.1 Abstract

6.1.1 Objectives

Transfers between health facilities of people living with HIV (PLH) attending primary health care (PHC) including transfers between hospitals and PHC facilities and transfers between PHC facilities occur frequently, affecting health service planning. Transfers may also disrupt the continuum of care and are associated with disengagement and viraemia among PLH. In low- and middle-income countries, diabetes care is suboptimal, with low levels of retention in care and glycaemic control. With decentralisation of care, PHC facilities at which people can obtain care have increased but little is known about transfers of people living with diabetes (PLD) attending PHC. We assessed the transfer incidence rate of PLD attending PHC, and the association between transfers and subsequent HbA1c values.

6.1.2 Methods

We analysed data on HbA1c tests at public sector facilities in the Western Cape Province (2016–March 2020). Individuals with an HbA1c in 2016–2017 were followed-up for 27 months and included in the analysis if >18 years at first included HbA1c, >2 HbA1cs during follow-up and >1 HbA1c at a PHC facility. A visit interval was the duration between two consecutive HbA1cs. Successive HbA1cs at different facilities of any type indicated any transfer, and HbA1cs at different PHC facilities indicated a transfer between PHC facilities. Mixed effects logistic regression adjusted for sex, age, rural/urban facility attended at the start of the visit interval and disengagement (visit interval >14 months) assessed the association between transfers between PHC facilities and HbA1c >8%. All statistical tests were 2-sided at $\alpha = 0.05$.

6.1.3 Results

Among 102,813 participants, 22.6% had >1 transfers of any type. Including repeat transfers, there were 29,994 transfers (14.4 transfers per 100 person-years, 95% confidence interval [CI] 14.3–14.6). 6,996 (30.1%) of those who transferred had a transfer between PHC facilities. Visit intervals with a transfer between PHC facility were longer (349 days, IQR 211–503) than without any transfer (330 days, IQR 182–422). The adjusted relative odds of

an HbA1c >8% after a transfer between PHC facilities versus no transfer were 1.19 (95% CI 1.05–1.36).

6.1.4 Conclusion

The volume of transfers involving PHC facilities requires consideration when planning services. Individuals who transfer between PHC facilities require additional monitoring and support.

6.2 Introduction

In low- and middle-income countries (LMIC), the prevalence of chronic non-communicable diseases (NCDs) including diabetes is increasing rapidly, and this is occurring alongside ongoing chronic infectious disease epidemics including HIV (1,2). Approximately three-quarters of the 537 million adults with diabetes globally live in LMIC and the prevalence is projected to increase further (3,4). In South Africa, the prevalence of diabetes increased from 7.1% in 2011 to 10.8% in 2021, with 4.2 million adults estimated to be living with diabetes in 2019 (4,5). Chronic conditions including diabetes require long-term and continuous care to prevent complications and reduce mortality (6). However, health care systems in LMIC have developed to provide acute care, and provision of care for people living with diabetes (PLD) is suboptimal (7–9). In many LMIC including South Africa, high proportions of PLD are undiagnosed and, among those who are diagnosed, few are in care and controlled on treatment (10–18). Strategies to improve chronic care services in LMIC are urgently required.

It has been suggested that the systems developed in response to the HIV and TB epidemics in many sub-Saharan African countries be leveraged when developing systems for long-term NCD care provision (2,18–20). Within HIV programmes, the effects of transfers between health facilities on patient and programme outcomes are increasingly recognised (21). Transfers include up-referrals to higher levels of care for complex medical care and down-referrals to lower levels of care when specialised care is no longer required (22). Transfers may also be lateral, between facilities at the same level of care e.g., between primary health care (PHC) facilities; these may be due to geographic mobility or personal preference (23–25). PHC is central to chronic care provision in many settings (7) and among people living with HIV (PLH) in sub-Saharan Africa, transfers involving PHC facilities i.e., up-referrals, down-referrals and lateral transfers occur frequently (26,27). This may affect planning of services including drug forecasting and referral systems (28–32). Transfers may also affect patient outcomes by disrupting continuity of care. While previous research among PLH has focused on up-referrals (33–35) and down-referrals (36–39), recent analyses have shown that transfers between PHC facilities of PLH occur frequently and are associated with viraemia (30,40).

Among PLD, few studies have assessed the frequency of transfers involving PHC facilities, particularly in LMIC. Studies in high-income countries include one conducted in South Korea: among 457,975 PLD attending hospitals and PHC facilities, 33% transferred between facilities over a one-year period, of whom 53% transferred between PHC facilities (41). Among PLD, reduced continuity of care, has been associated with reduced adherence to treatment, worsening glycaemic control, increased diabetes-related complications and increased mortality (42–49). However, measures of continuity of care used in these studies include indices of continuity to specific providers and/or health facilities (46,50–53) and it is not always clear whether a transfer between health care facilities occurred. Research on outcomes of transfers among PLD have focused on up-referrals (54,55) and down-referrals (56–63). In particular, PLD who are discharged from hospital are at risk of loss to follow-up and readmission, and numerous interventions have been tested to improve outcomes (56–63). However, data on transfers between PHC facilities among PLD are limited.

Levels of geographic mobility are high in LMIC (141), meaning that PLD may require transfers between PHC facilities. In addition, decentralisation of chronic care services in many LMIC mean that there are increasing numbers of PHC facilities between which people can transfer (18). Transfers between PHC facilities among PLD are thus an important area for investigation. In addition to the effects on patient outcomes, transfers may affect planning of diabetes health services (31,32). Insufficient monitoring equipment and treatments for diabetes have been described in sub-Saharan Africa (18) and understanding the overall volume of transfers involving PHC facilities is vital to improving the availability of diabetes care at PHC level. To address these gaps, we used routinely collected data from public sector health care facilities across the WCP to investigate transfers among PLD including the frequency of transfers involving PHC facilities, the frequency of transfers between PHC facilities and the outcomes of transfers between PHC facilities.

6.3 Methods

6.3.1 Setting and data source

The study was conducted across public sector health care facilities in the WCP. The province is divided into six health districts and 32 sub-districts (65). Of the six districts, one is urban

and densely populated (the Cape Town Metropole) and five are rural (66,67). The Western Cape population was estimated at 6.3 million in 2016, with 64% residing in the Cape Town Metropole (68). Over 80% of the population in the province attend public sector health care facilities (69) which comprise 52 hospitals and 354 PHC facilities (70). Between 2012 and 2019, 64% of public sector health care facility visits by PLD in the province were in the Metropole (71).

The prevalence of diabetes in the province was estimated at 11.2% (95% confidence interval [CI] 8.3–15.0) in 2012, which was higher than the national prevalence of 9.5% (95% CI 8.0–11.2) (16). Approximately 18,000 people, of whom 60% are women, start diabetes treatment in the WCP each year. Most PLD are 40–65 years old (58%) and nearly one-third are >65 years old (72). In the WCP in 2010, almost 60% of people previously diagnosed with diabetes were not on treatment and 33% had raised random blood glucose measurements (73).

Each subdistrict has community-based, PHC and district hospital services (65,74). PHC facilities include community clinics and community health centres. Patients at PHC facilities who require more complex medical care are up-referred to district hospitals and, if necessary, to regional or tertiary hospitals, which are at the provincial level (74). Patients at higher levels of care who are no longer in need of specialised care may be down-referred to a lower level facility for continued management 22).

Patients attending PHC services are managed by nurse practitioners and PHC doctors (67). National guidelines for the diagnosis of diabetes and HbA1c monitoring at the time of the study are summarised in Supplementary table 10.5.1 (75–77). Diabetes was diagnosed in individuals with either a fasting plasma glucose $\geq$7.0 mmol/L, a two-hour plasma glucose during an oral glucose tolerance test of $\geq$11.1mmol/L, an HbA1c $\geq$6.5%, or symptoms of diabetes and a random plasma glucose $\geq$11.1 mmol/L. Recommendations for HbA1c testing frequency ranged from three to six monthly if treatment was changed, and from six to 12 monthly if treatment goals were met. Targets for HbA1c varied between guidelines, with some recommending individualised targets (77). Generally, <7% was considered optimal for most patients, with additional action recommended for an HbA1c >8%.

HbA1c testing in the province is conducted centrally by the National Health Laboratory Service (NHLS) using NGSP certified methods. Testing requires venous blood samples be taken and sent to the laboratory for analysis with laboratory request forms (78,79). Data from these forms are captured electronically and stored by the NHLS Corporate Data Warehouse. For this analysis, data on all HbA1c tests done at public sector health facilities in the Western Cape, including hospitals and PHC facilities, from 1 January 2016 to 31 December 2021 were obtained from the NHLS. A unique patient identifier is used in the province and multiple tests in the same individual can thus be tracked across health care facilities. Variables obtained included patient sex and age, the facility at which the HbA1c test was done, and the date and result of each test.

6.3.2 Inclusion and exclusion criteria

Individuals <18 years of age at their first included HbA1c test were excluded from the cohort. While data were available up to 31 December 2021, we censored data for this analysis at the end of March 2020 because facility attendance thereafter may have been affected by the national lockdown implemented in response to the COVID-19 pandemic (80). To allow equal duration of follow-up for all participants, individuals with their first HbA1C after 31 December 2017 were excluded, and those with an HbA1c done between 01 January 2016 to 31 December 2017 were censored 27 months after their first included test. Those with at least two HbA1c tests in the 27-month follow-up period were potentially eligible, and those without an HbA1c at a PHC facility in this period were excluded. Individuals with one or more HbA1cs conducted at private health care facilities, correctional facilities, and/or care facilities were also excluded.

6.3.3 Definitions

Each HbA1c test represented a health facility visit. A visit interval was defined as the time period between two consecutive visits in one participant (Supplementary figure 10.5.1). A transfer of any type was defined as successive HbA1cs documented at different facilities in one individual; this included all transfers regardless of the types of facilities involved i.e., hospitals and/or PHC facilities. Each transfer was then further categorised as occurring from a PHC facility to a hospital, from a hospital to a PHC facility, between PHC facilities or between hospitals based on the types of facilities at which each HbA1c was done. We were

unable to distinguish between silent transfers (when the individual does not inform the original facility of the transfer) and official transfers (when the individual informs the initial facility and obtains a transfer letter) using these data, and the above definitions include both types of transfer. With a maximum recommended duration between HbA1cs of 12 months, we defined a disengagement as >14 months between HbA1c tests for the primary analysis. As some guidelines recommended a maximum of six months between tests, we conducted sensitivity analyses with disengagement defined as >7 months between HbA1c tests. Based on South African National Guidelines at the time, a raised HbA1c was defined as ≥8%, with sensitivity analyses defining a raised HbA1c as ≥7%.

6.3.4 Analysis

Data were analysed using STATA/BE version 17.0 (Stata Corporation, College Station, TX, USA). Frequencies and proportions, means with standard deviations or medians with interquartile ranges (IQRs) were calculated to summarise quantitative variables. The proportions of participants with one or more transfers of any type were tabulated. Participant characteristics were described for the whole cohort, and for those who did and did not transfer. The number of individuals and with at least one PHC facility to PHC facility, hospital to hospital, PHC facility to hospital, and hospital to PHC facility transfer were determined.

Transfer rates were calculated for all transfer events from the first HbA1c to the end of the study period, including multiple events per participant. Maximum possible duration of follow-up was 27 months per individual. Participants with at least one HbA1c in the last 14 months of their follow-up (between 13 and 27 months after their first HbA1c) were censored at 27 months after their first HbA1c. Those without an HbA1c in this period were censored seven months after their last HbA1c.

To assess predictors of transfer, generalised estimating equations with an unstructured working correlation with Poisson regression were used to account for repeated measures in participants. All statistical tests were 2-sided at $\alpha = 0.05$. Potential confounders were identified *a priori*. Multivariable models assessing predictors of any transfer were adjusted for age, sex, location of the first HbA1c test (rural vs urban) and value of the first HbA1c test. Multivariable models assessing predictors of PHC facility to PHC facility transfers were

adjusted for age, sex, location of the first HbA1c test (rural vs urban) value of the first HbA1c test, and the occurrence of at least one hospital visit.

Generalised mixed effects logistic models assessed the association between the occurrence of 1) any transfer during a visit interval and an HbA1c ≥8% at the end of the interval and 2) the type of transfer during the visit interval (PHC facility to PHC facility, hospital to hospital, PHC facility to hospital, or hospital to PHC facility) and an HbA1c ≥8% at the end of the interval. These models were adjusted for sex as a fixed effect and age at the start of the visit interval, location of the visit at the start of the visit interval (rural vs urban) and occurrence of a disengagement during the visit interval (visit interval >14 months) as random effects. Sensitivity analyses were done to assess the association between the type of transfer and an HbA1c ≥8% when including only visit intervals in which the HbA1c at the start of the interval was <8%, and to assess alternate definitions of the outcome (HbA1c ≥7%) and disengagement (>7 months without an HbA1c). Lastly, we conducted stratified analyses to assess effect modification of the relationship between type of transfer and HbA1c by the occurrence of disengagement (visit interval >14 months) in the visit interval.

6.3.5 Ethics

Ethical approval was obtained from the University of Cape Town Human Research Ethics Committee.

6.4 Results

A total of 345,151 individuals had at least one HbA1c test in the Western Cape between January 2016 and March 2020 (Figure 6.1). Among these, 134,722 had their first HbA1c after December 2017 and were excluded. Of the 210,429 who had their first HbA1c between January 2016 and December 2017, 1,849 were <18 years of age at the point of their first included HbA1c and were excluded. Including 2 years and 3 months of follow-up per individual, 91,467 had only one HbA1c during follow-up, 14,205 did not have an HbA1c at a PHC facility, 64 attended a private health facility, 17 had an HbA1c at a correctional facility and 14 had an HbA1c at a care facility and were excluded from the study cohort.

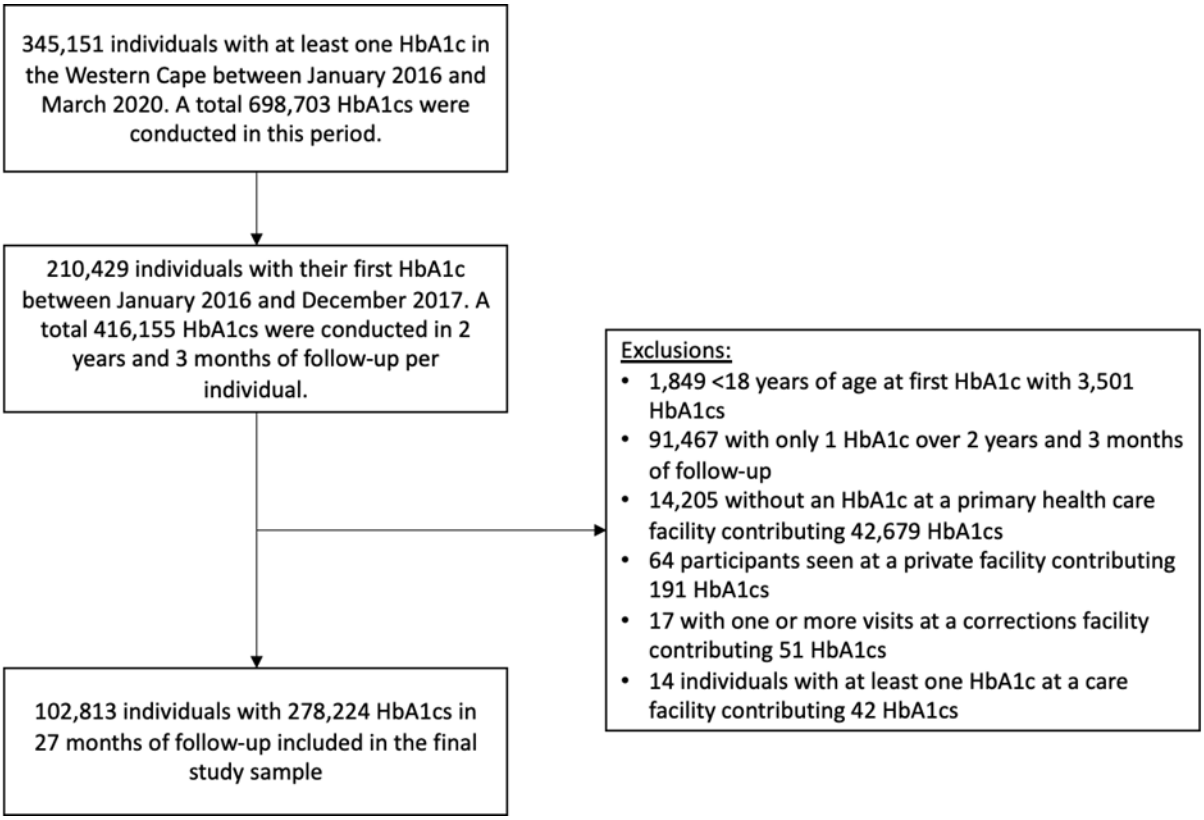

Figure 6.1 Flow chart of participant inclusion

The remaining 102,813 Individuals included in the analysis contributed 278,224 HbA1cs performed at 383 facilities over 208,030 person-years of follow-up. Median age at first HbA1c test was 56 years (IQR 48–64), approximately two-thirds of participants were female (n = 68,090; 66.2%) and approximately one-third (n = 35,443; 34.5%) had at least one HbA1c in a rural district (Table 6.1). Median number of visits was 2 (2–3) and median duration between visits was 321 (IQR 175–424) days. Across all visits, 68,151 (66.3%) participants had at least one HbA1c $\geq$8%.

Table 6.1 Patient characteristics overall and by transfer status (n = 102,813)

	All participants	≥1 transfer	No transfer
Number of participants, n (%)	102,813	23,277	79,536
Age at first HbA1c (years), median (IQR)	56 (48–64)	56 (46–65)	56 (48–64)
Female, n (%)	68,090 (66.2)	15,075 (64.8)	53,015 (66.7)
Number of visits, median (IQR)	2 (2–3)	3 (2–4)	2 (2–3)
Duration of follow up (days), median (IQR)	821.8 (821.8–821.8)	821.8 (821.8–821.8)	821.8 (821.8–821.8)
First visit in a rural region	34,730 (33.8)	6,370 (27.4)	28,360 (35.7)
At least one HbA1c conducted in a rural region	35,443 (34.5)	7,083 (30.4)	28,360 (35.7)
First HbA1c value (%), median (IQR)	8.4 (6.7–10.6)	8.7 (6.8–11.1)	8.3 (6.7–10.5)
At least one HbA1c ≥6.5%	88,126 (85.7)	20,341 (87.4)	67,785 (85.2)
At least one HbA1c ≥7.0%	80,934 (78.7)	18,858 (81.0)	62,076 (78.1)
At least one HbA1c ≥7.5%	74,326 (72.3)	17,571 (75.5)	56,755 (71.4)
At least one HbA1c ≥8.0%	68,151 (66.3)	16,345 (70.2)	51,806 (65.1)
At least one hospital visit	16,793 (16.3)	16,793 (72.1)	0

Abbreviations: HbA1c, glycated haemoglobin; IQR, interquartile range; n, number.

Overall, 23,277/102,813 (22.6%) participants transferred at least once (including all transfer types) during follow-up. Among the 23,227 participants who transferred one or more times, 5,542 (23.8%) had evidence of multiple transfers. Including repeat transfers per individual, a total of 29,992 episodes of transfer were documented for a transfer rate of 14.4 (95% confidence interval [CI] 14.3–14.6) transfers per 100 person-years. When considering the types of facilities involved in the transfer, 6,994/23,227 (30.1%) participants who transferred at least once transferred between PHC facilities, equating to 6.8% of the whole cohort. In comparison, a, 586 (0.6%) of the cohort transferred between hospitals one or more times, 9,959 (9.7%) transferred from a hospital to a PHC facility one or more times and 10,774 (10.5%) transferred from a PHC facility to a hospital one or more times during follow-up.

The median duration of visit intervals was shorter when any transfer occurred (275 days, IQR 143–436) in the interval compared to when a transfer did not occur (330 days, IQR 182–422; Supplementary table 10.5.2). However, visit intervals in which a transfer between PHC facilities occurred were of longer duration (349 days, IQR 211–503) compared to those in which no transfer occurred, or when the transfer was between hospitals (119 days, IQR 53–221), from a PHC facility to a hospital (240 days, IQR 123–404) or from a hospital to a PHC facility (257 days, IQR 134–421). Higher proportions of hospital-to-hospital transfers occurred between facilities in different districts and different subdistricts (n = 171, 25.6% and n = 553, 82.8%, respectively) compared to other types of transfers. Of a total of 7,933 transfers between PHC facilities 7,042 (89.3%) occurred within districts and 4,986 (63.3%) occurred within subdistricts.

In a multivariable GEE Poisson regression model modelling the occurrence of any transfer type, male sex (adjusted incidence rate ratio [aIRR] 1.04, 95% CI 1.01–1.06) and an HbA1c $\geq$8% (aIRR 1.21, 95% CI 1.18–1.24) were associated with an increased rate of transfers, while having at least one HbA1c in a rural district was associated with a decreased rate of transfers (Table 6.2). Similarly, an HbA1c $\geq$8% was associated with an increased relative rate of a transfer between PHC facilities (aIRR 1.19, 95% CI 1.14–1.25). However, the relative rate of a PHC facility to PHC facility transfer were lower in those with their first HbA1c in a rural district versus an urban district (aIRR 1.17, 95% CI 1.12–1.22). Further, the rate of a transfer between PHC facilities were lower in participants with at least one hospital visit compared to those without a hospital visit (aIRR 0.22, 95% CI 0.20–0.24).

Table 6.2 GEE Poisson regression model assessing predictors of any transfer among people living with diabetes attending primary health care (n = 102,813)

	Any transfer within primary care				PHC facility to PHC facility transfer			
	Unadjusted model		Adjusted model		Unadjusted model		Adjusted model	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Male	1.03	1.01–1.06	1.04	1.01–1.06	0.96	0.92–1.01	1.00	0.96–1.05
Age at first HbA1c (years)	0.993	0.992–0.994	0.994	0.993–0.994	1.001	0.999–1.003	0.999	0.997–1.000
Log first HbA1c value (%)	1.66	1.58–1.71			1.55	1.44–1.67		
First HbA1c ≥7.0%	1.17	1.14–1.20			1.30	1.24–1.37		
First HbA1c ≥8.0%	1.22	1.20–1.25	1.21	1.18–1.24	1.24	1.19–1.30	1.19	1.14–1.25
First HbA1c in a rural district	0.76	0.74–0.78			1.14	1.09–1.20		
At least one HbA1c in a rural district	0.86	0.84–0.88	0.84	0.82–0.86	1.35	1.29–1.42	1.17	1.12–1.22
At least one HbA1c at a hospital	-		-		0.21	0.19–0.23	0.22	0.20–0.24

Abbreviations: CI, confidence interval; GEE, generalised estimating equations; HbA1c, glycosylated haemoglobin; IRR, incidence rate ratio.

In a mixed effects logistic model, the adjusted relative odds of an HbA1c ≥8% when any transfer occurred in a visit interval versus no transfer were 1.02 (95% CI 0.95–1.10; Table 6.3). In a mixed effects logistic model adjusted for age, sex, whether the HbA1c at the start of the visit interval was conducted in a rural or urban district, and whether a disengagement (>14 months between HbA1cs) occurred in the visit interval, the relative odds of an HbA1c ≥8% for a transfer between PHC facilities, from a hospital to a PHC facility, a PHC facility to a hospital, and between hospitals, versus no transfer were 1.20 (95% CI 1.05–1.36), 0.92 (95% CI 0.84–1.02), 1.05 (95% CI 0.95–1.15) and 0.53 (95% CI 0.38–0.73), respectively (Table 6.4). Sensitivity analyses using an alternate definition of disengagement (>7 months between HbA1cs) did not substantially alter the odds of an HbA1c ≥8% for a PHC facility to PHC facility transfer (aOR 1.22, 95% CI 1.07–1.39; Supplementary table 10.5.3). Further, restricting the analysis to visit intervals in which the HbA1c at the start of the interval was <8% produced consistent findings regarding the association between PHC facility to PHC facility transfers and increased HbA1c percentage (aOR 1.21, 95% CI 1.08–1.36; Supplementary table 10.5.4).

Table 6.3 Results of generalised mixed effects logistic regression modelling the association between any transfer and HbA1c category (102,813 participants with 174,411 visit intervals)

	HbA1c ≥8.0%	**HbA1c ≥7.0%**
Occurrence of any transfer during the visit interval	1.02 (0.95–1.10)	0.96 (0.90–1.03)
Male sex	0.44 (0.39–0.49)	0.64 (0.60–0.70)
HbA1c at start of visit interval done at a facility in a rural district	2.25 (2.01–2.51)	2.67 (2.48–2.88)
Age at start of the visit interval (years)	0.89 (0.885–0.891)	0.96 (0.95–0.96)
Disengagement in the visit interval (>14 months between HbA1c tests)	1.12 (1.05–1.21)	0.97 (0.91–1.03)

Table 6.4 Results of generalised mixed effects logistic regression modelling the association between type of transfer and HbA1c category (102,813 participants with 175,411 visit intervals)

	HbA1c ≥8.0%	HbA1c ≥7.0%
Type of transfer during the visit interval		
- **No transfer**	Ref	Ref
- **Hospital to hospital**	0.53 (0.38–0.74)	0.54 (0.39–0.76)
- **Hospital to PHC facility**	0.92 (0.84–1.02)	0.94 (0.85–1.05)
- **PHC facility to hospital**	1.05 (0.95–1.15)	0.88 (0.80–0.97)
- **PHC facility to PHC facility**	1.20 (1.05–1.36)	1.17 (1.03–1.333)
Male sex	0.44 (0.39–0.49)	0.64 (0.59–0.69)
HbA1c at start of visit interval done at a facility in a rural district	2.25 (2.01–2.51)	2.68 (2.49 – 2.89)
Age at start of the visit interval (years)	0.888 (0.885–0.891)	0.955 (0.952–0.958)
Disengagement in the visit interval (>14 months between HbA1c tests)	1.12 (1.04–1.20)	0.96 (0.90–1.03)

The reduced relative odds of an HbA1c ≥8% after a hospital to hospital transfer were maintained in models including only visit intervals with an HbA1c <8% at the start of the interval (aOR 0.47, 95% CI 0.29–0.76), models defining disengagement as >7 months between visits (aOR 0.53, 95% CI 0.38–0.73) and models defining the outcome as an HbA1c ≥7% (aOR 0.54, 95% CI 0.39–0.76).

Compared to no transfer, PHC facility to hospital transfers were associated with a statistically significant reduction in the relative odds of an HbA1c ≥7% (aOR 0.88, 95% CI 0.80–0.97). Transfers from hospitals to PHC facilities were associated with a statistically significant increase in the adjusted relative odds of an HbA1c ≥8% (aOR 1.34, 95% CI 1.22–1.47) when including only visit intervals in which the HbA1c at the start of the interval was <8%.

In adjusted models stratified to include only visit intervals in which a disengagement occurred, the increased relative odds of an HbA1c ≥8% at the end of intervals in which a transfer between PHC facilities occurred versus intervals in which a transfer between PHC facilities did not occur persisted (aOR 1.13, 95% CI 1.03–1.23; Supplementary table 10.5.5).

Including only visit intervals in which a disengagement did not occur, the effect estimate remained above one but was reduced and was not statistically significant (aOR 1.05, 95% CI 0.90–1.23).

6.5 Discussion

This analysis demonstrated high numbers of transfers of PLD attending PHC facilities, including transfers between PHC facilities. Approximately 23% of participants transferred once or more over the study period, of whom 30% transferred between PHC facilities. Risk factors for PHC facility to PHC facility transfers included an HbA1c $\geq$8% at the first included visit and, compared to no transfer, transfers between PHC facilities were associated with a 19% increase in the relative odds of an HbA1c $\geq$8%.

The finding that almost one-quarter of individuals transferred at least once over the study period was slightly less than found in South Korea where 33% of individuals transferred one or more times (41). In India, 42% of individuals with diabetes living in an urban slum transferred between health facilities but the study included only 60 people (81). The overall transfer incidence rate over of 14.4 (95% CI 14.3–14.6) per 100 person-years was similar to the incidence rate of 12.7 per 100 person-years (95% CI 12.6–12.8) found among PLH attending PHC facilities in the Western Cape between 2011 and 2018 (40). The rate of transfer is thus similar in these two distinct diseases with differing disease profiles, suggesting that transfer should be investigated for other chronic diseases, including NCDs. The volume of transfers may have implications for health system planning. Consideration of use of health facilities and movement between facilities is important for planning and resource allocation (31,32). Previous research has described large proportions of PLD not in care (17,82) and has described insufficient monitoring equipment and medication in sub-Saharan Africa (18). Any efforts to improve access to diabetes care and availability of treatments and equipment at PHC level should consider the volume of transfers. Additional details on facility types and locations involved in transfers are required to facilitate planning.

The occurrence of any transfer in individuals attending PHC was not associated with a change in HbA1c percentage. However, this included up- and down referrals; patient characteristics, reasons for transfer and transfer processes likely differ for up-referrals,

down-referrals and lateral transfers, and outcomes of these types of transfers may thus also differ. When considering transfers between PHC facilities specifically, transfer was associated with an increased HbA1c percentage, and this was consistent across numerous sensitivity analyses. Worse outcomes among those who transferred between PHC facilities compared to those who did not transfer may be related to reduced continuity of care. Transfers may impair relational continuity which refers to an ongoing relationship between a patient and provider and has been associated with better quality of care for reasons that include better knowledge of the patient's history and better communication (46). Transfers may also affect informational continuity, which involves the use of information on past events to make care decisions, and managerial continuity, which refers to a consistent and coherent approach to patient management (51). Continuity is also associated with improved patient satisfaction (83), which may lead to improved adherence to medical recommendations. These results also indicate that the occurrence of disengagement among those transferring between PHC facilities may affect outcomes. In stratified analyses, the association between transfers between PHC facilities and an HbA1c $\geq$8% was maintained when a disengagement occurred, with a 12% increase in the odds of an HbA1c $\geq$8% when a transfer between PHC facilities occurred compared to no transfer. This association was somewhat reduced when a disengagement did not occur but was still increased, with a 9% in the odds an HbA1c $\geq$8% when a transfer between PHC facilities occurred compared to no transfer. However, this was not statistically significant. These results suggest that the effect of transfer on HbA1c is modified by the presence of disengagement. In this analysis, the duration between visits was longer when a transfer between PHC facilities occurred compared to no transfer. Improving access to care and developing strategies to prevent disengagement in people who transfer between PHC facilities may thus help improve outcomes.

Further research into reasons for transfers between PHC facilities, transfer processes, and possible reasons for increased HbA1c values in PLD who transfer between PHC facilities is required to develop strategies to improve outcomes. In addition, monitoring of overall transfer numbers and outcomes is relevant to programme evaluation. Both HIV and TB programmes use well-established cohort monitoring systems to monitor individual and programme level outcomes; however, neither system reports outcomes in people who

transfer (9,21). The importance of cohort analyses to improve the PHC response to the diabetes epidemic is well recognised and these results underscore the importance of monitoring transfers and transfer outcomes as part of chronic care programmes (84,85).

Strengths of this study include access to data from health facilities throughout the Western Cape. This, together with the use of a unique patient identifier in the province, allowed tracking of patient movement across facilities. HbA1c testing is an objective measure of disease control and is currently the standard of care monitoring test for PLD; we were thus able to monitor changes in disease control using an objective marker. Limitations of this analysis include that the data included only records of visits at which HbA1cs were taken. HbA1cs are not done at all visits, and the number of visits and the number of transfers will thus be underestimated. In addition, some patients may have had HbA1cs processed at private laboratories and records of these tests would not be included in the NHLS database, but this number is expected to be small. We were unable to differentiate between silent and official transfers and did not have data on a number of potential confounders including duration since diagnosis, the presence of multimorbidity, treatment and complications of diabetes. HbA1c can be used as a diagnostic test, and it is possible that some individuals in the analysis did not have diabetes. However, this number is likely to be small because at least two HbA1cs were required for inclusion in the cohort. In addition, 86% of participants had an HbA1c $\geq$6.5% which is diagnostic of diabetes. Lastly, these data are from one province of South Africa and research on transfer is required in other settings; however, we believe that these results may have relevance to other LMIC with high levels of mobility.

6.6 Conclusion

In conclusion, almost 23% of individuals attending PHC facilities transferred between health facilities one or more times during follow-up. Transfers between PHC facilities were associated with an increase in HbA1c percentage. Additional research is required to understand the reasons for transfer between PHC facilities and how to improve outcomes in patients who transfer between PHC facilities. Tracking of patient transfers should be considered as part of patient and diabetes programme monitoring.

6.7 References

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Chapter 7: Mobility in the postpartum period and viraemia in women living with HIV in South Africa

Odayar J, Phillips TK, Kabanda S, Malaba TR, Mukonda E, Hsiao N-Y, Lesosky M, Myer L. Mobility during the postpartum period and viraemia in women living with HIV in South Africa. Int Health. 2023;15(6):692–701.

Relevance of this paper to the thesis:

Postpartum women living with HIV are at high risk of disengagement from care. In South Africa, postpartum women are highly mobile, and this is thought to be a factor affecting engagement in care. However, the relationship between mobility and treatment outcomes including virologic outcomes has not been directly investigated in this population. Further, mobile individuals may require transfer between health facilities to maintain engagement in care, little is known regarding how mobile postpartum women access health care. To better understand their health care needs, this chapter describes travel patterns, health facility attendance while travelling and the association between travel and VL in a cohort of postpartum women on ART.

Contributions of the student and co-authors:

Contribution of student and co-authors: JO conceptualised the analysis with guidance from LM. LM conceptualised the study from which these data arise, was responsible for funding, study implementation and overall leadership. JO directed data collection with assistance from SK. NYH oversaw laboratory testing. EM was responsible for data management. JO conducted the analysis with guidance from ML. JO led data interpretation and drafted the manuscript. All authors reviewed the initial manuscript and provided conceptual and intellectual comment. All authors reviewed and approved the final manuscript.

7.1 Abstract

7.1.1 Background

We investigated the association between travel and viraemia in postpartum women with HIV on antiretroviral therapy (ART).

7.1.2 Methods

Data are from a trial of postpartum ART delivery strategies. Women who initiated ART during pregnancy, were clinically stable with viral load (VL)<400 copies/mL and <10 weeks postpartum were enrolled at a primary care antenatal clinic in Cape Town, South Africa. Study visits at 3, 6, 12, 18 and 24 months postpartum included questions about travel, defined as ≥1 night spent outside of the city, and VL testing. Logistic regression models using generalised estimating equations were used to assess predictors of travel and the association between travel and viraemia (VL ≥400 copies/mL). All statistical tests were 2-sided at $\alpha = 0.05$.

7.1.3 Results

Among 402 women, (mean age 29 years, 35% born in the Western Cape), 69% reported ≥1 travel event over 24 months. Being born beyond the Western Cape, (adjusted odds ratio [aOR] 2.03, 95% confidence interval [CI] 1.49–2.77), duration postpartum in months (aOR 1.03, 95% CI 1.02–1.05) and living with the child (aOR 0.60, 95% CI 0.38–0.93) were associated with travel. In multivariable analyses, a travel event was associated with a 92% increase in the odds of VL≥400 copies/mL (aOR 1.92, 95% CI 1.19–3.10).

7.1.4 Conclusions

Interventions to support women on ART who travel are urgently required.

7.2 Introduction

HIV is a chronic condition that requires lifelong adherence to treatment and retention in care (1). South Africa has the largest HIV epidemic in the world with an estimated 7.5 million people living with HIV in 2020, of whom almost two-thirds are women over the age of 15 years (2). While 78% of women living with HIV in South Africa were estimated to be on antiretroviral therapy (ART), there are ongoing concerns regarding disengagement from care (3). Risk of disengagement is particularly high in postpartum women, with less than two-thirds of women on ART retained in care at 24 months postpartum in one analysis (4,5). ART non-adherence contributes to HIV disease progression, virological failure, ART drug resistance and HIV transmission (6,7). Risk of HIV transmission continues throughout breastfeeding, and maintaining engagement in care in postpartum women is important to reduce vertical transmission during breastfeeding and improve maternal outcomes (3,8).

Mobility is a critical factor affecting engagement in chronic care services (9,10). Population mobility may take many forms, including permanent relocation, circular mobility (involving movement back and forth between multiple residences) and episodic travel (11,12). Population mobility is high in sub-Saharan Africa, including South Africa. In South Africa, people move for multiple reasons including employment, education and access to healthcare, and mobility is predominantly internal, with permanent or temporary relocation from rural to urban areas and frequent travel to homes in rural areas (11,12). Among women, mobility is increasing and is predominantly of a temporary and localised nature which may be difficult to measure (11-13). Postpartum women in South Africa are highly mobile, with many travelling to their rural homes post-delivery (5,14,15).

Mobile populations face numerous challenges to maintaining continuous HIV care. Mobility has been shown to impact ART adherence in general populations (10,15-18). Interruptions in medication supply may occur, particularly when trips are of longer duration (9,10) and mobile individuals may thus require access to care at multiple health facilities. However, transfer between facilities has been associated with an increased risk of viraemia in general adults and in postpartum women (19). Despite the risks of disengagement in mobile populations and evidence that travel occurs frequently immediately postpartum, there are few data on travel and viral load outcomes in the extended postpartum period. A better

understanding of travel patterns and the association between travel, health care usage and HIV treatment outcomes over the extended postpartum period is required to inform and target possible interventions. We assessed the frequency of travel, predictors of travel, health facility attendance while travelling and the association between travel and VL in a cohort of women on ART through 24 months postpartum.

7.3 Methods

7.3.1 Study design and participants

We hypothesised that travel may lead to non-adherence or treatment interruption which may lead to viraemia in postpartum women. To assess the association between travel and viraemia, we conducted a secondary analysis of data from a randomised controlled trial of differentiated service delivery for postpartum ART delivery (Postpartum Adherence Clubs for Antiretroviral Therapy [PACART] NCT03200054) in Cape Town, South Africa (20). The study was conducted at a large Community Health Centre (CHC) and associated Midwife Obstetric Unit (MOU) in Cape Town, South Africa. This public sector primary care facility serves a population of approximately 350,000 which is predominantly of low socioeconomic status (21). The MOU provides antenatal care (ANC), services to prevent vertical transmission of HIV, obstetric services and postnatal care to >4000 women annually. ANC uptake in the community is high (> 95%), as is antenatal HIV prevalence, estimated at 30% in 2013. The CHC includes an ART clinic which provides HIV care to the general adult population.

Women attending the MOU post-delivery were screened for participation in the parent trial between January 2016 and December 2017 and were enrolled if they were >18 years, had started ART in the preceding pregnancy, were <10 weeks postpartum, had an HIV VL<400 copies/mL in the preceding three months and had no medical conditions requiring regular clinical follow-up. All women started tenofovir (TDF) 300 mg, lamivudine (3TC) 300 mg or emtricitabine (FTC) 200 mg, and efavirenz (EFV) 600 mg taken once daily as a fixed-dose combination (FDC) in pregnancy. Participants were randomised to either the primary health care (PHC) ART clinic (the control arm) or the local differentiated service delivery model (adherence clubs [ACs], intervention arm). The ACs operate from a community hall located

approximately one kilometre from the antenatal clinic (22). Patients are provided with 1–2 months of treatment at PHC ART clinics with 3 months supplied at the end of year holiday period. At ACs, 2 months of treatment are supplied at routine visits with 4 months supplied at the end of year holidays. At the ACs, patients are allowed to send a representative, called a "buddy", to collect their treatment at alternate visits. As part of adherence counselling, patients on ART are advised to inform the health facility before travelling in order to receive a referral letter and sufficient treatment (23). VL testing is done annually at the AC and 6–12 monthly at the PHC ART clinic. Patients at the ACs with a VL>400 copies/mL are referred to the PHC ART clinic. At the ART clinic, together with adherence support, those with a VL between 400–1000 copies/mL have a repeat VL in 6 months and those with a VL >1000 copies/mL have a repeat VL in 2 months.

7.3.2 Data sources

Consecutive postpartum women who initiated ART during pregnancy, were within 70 days postpartum and met local differentiated service delivery eligibility criteria (clinically stable with VL <400 copies/mL in the preceding three months) were included in the parent trial. After enrolment, follow-up visits in the primary trial were conducted at 3, 6, 12, 18 and 24 months postpartum. Blood samples for VL testing were drawn at enrolment (this was separate to the screening VL) and at each subsequent visit. All study VLs were conducted separate to VLs done as part of routine care. Face-to-face interviews completed at all visits included questions regarding medical history, whether women had travelled outside of the City of Cape Town for at least one night since the last visit and the duration of travel. Questions regarding travel were implemented several months into the study and not all women attending the 3- and 6-month visits were asked about travel. Other questions included whether they attended an ART service visit at a facility at their travel destination, whether there had been any treatment interruptions since the last visit, which were defined as two-week periods without ART, and whether one or more doses had been missed in the 30 days preceding the visit. Regarding previous antiretroviral exposure, participants were asked whether they had taken short-course therapy for prevention of mother-to-child-transmission in a previous pregnancy and whether they had previously been started on a three-drug lifelong ART regimen. HIV VL testing was done by the National Health Laboratory Services using Abbott Molecular RealTime HIV-1 assay, Abbott Molecular, Illinois, USA.

7.3.3 Analysis

Analyses were performed in Stata (Stata Corporation, College Station, TX). To assess the association between travel events and VL outcomes, regardless of duration, a travel event was defined as at least one night spent outside of the City of Cape Town. At the 3-, 6-, 12-, 18- and 24-month postpartum visits, the proportion of participants who had travelled since the previous visit and the number of times each participant travelled were counted. Frequencies and proportions, means with standard deviations (SD) or medians with interquartile ranges (IQR) were used to describe characteristics at enrolment in those who did and did not travel, and based on the number of travel events. Chi squared tests, Fisher's exact tests, t-tests or rank-sum tests were used for bivariate analyses as appropriate. All statistical tests were 2-sided at $\alpha = 0.05$.

Logistic regression models using generalised estimating equations to account for repeated measures within individuals assessed predictors of travel and the association between travel and viraemia (VL $\geq$400 copies/mL) at the next study visit. This VL threshold was used as it is the value at which national guidelines recommend additional action by a clinician including a careful adherence assessment and consideration of an early repeat VL test (24). Characteristics identified *a priori* as potential confounders included age, socio-economic status, marital status, previous antiretroviral use, whether the baby lived with the mother and duration postpartum. Measures available for socio-economic status included type of housing, education and employment status. The intervention in the PACART trial was associated with a reduction in viraemia (25). We thus adjusted models assessing the association between travel and VL by PACART randomisation allocation. Results were reported as odds ratios (OR) with 95% confidence intervals. A sensitivity analysis was done to assess an alternate VL threshold (VL $\geq$50 copies/mL) as the outcome. Additional analyses were conducted to assess the association between duration of travel and VL outcomes. Travel was measured in days and was log transformed to obtain a normal distribution. Lastly, we conducted analyses stratified by randomisation allocation in the primary trial to assess for effect modification by mode of care delivery.

7.3.4 Ethics

All participants provided written informed consent prior to completing any study procedures. The study was reviewed and approved by the University of Cape Town Human Research Ethics Committee.

7.4 Results

Among the 412 women enrolled in the parent trial, one withdrew. In addition, the VL conducted at the enrolment study visit was ≥400 copies/mL in nine participants and they were excluded from further analysis (Figure 7.1). Of the remaining 402 women, mean age was 29 years (standard deviation [SD] 5.2), 384 (96%) were born in South Africa and 139 (35%) were born in the Western Cape (Table 7.1). Overall, 169 women (42%) were married or cohabiting with a partner, 214 (53%) lived in informal housing and 396 (99%) had completed at least some high school. Median duration postpartum at enrolment was 10 (IQR 6–20) days. Approximately one-quarter of enrolled women (n = 105; 26%) had a history of antiretroviral use (either antiretroviral therapy or short course prevention of vertical transmission) prior to the index pregnancy. All women had initiated ART in pregnancy and median duration on ART at enrolment was 164 (IQR 126–200) days.

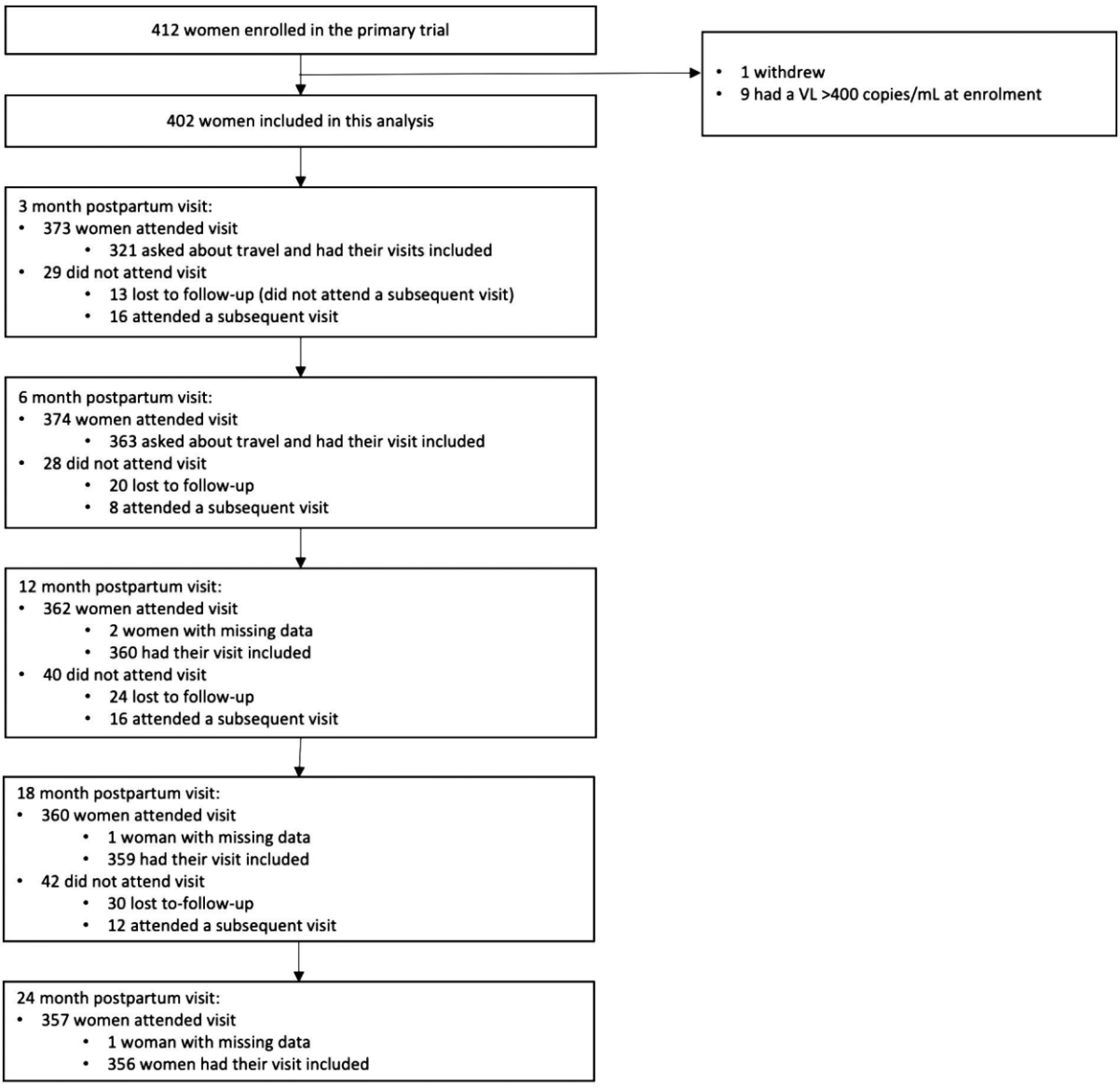

Figure 7.1 Inclusion of visits in the analysis

Table 7.1 Enrolment characteristics of women included in the analysis, overall and by travel status

Characteristics	Total (N=402)	One or more travel events over 24 months post-partum (n=279)	No travel over 24 months post-partum (n=123)	p-Value	One travel event (n=124)	Two travel events (n=77)	Three or more travel events (n=78)	p-Value
Age (years), mean (SD)	29.2 (5.2)	29.3 (5.3)	28.9 (4.9)	0.5930	29.7 (5.3)	28.9 (5.0)	29.0 (5.8)	0.5613
Born in South Africa, n (%)	384 (95.5)	269 (96.4)	115 (93.5)	0.192	121 (97.6)	76 (98.7)	72 (92.3)	0.125
Born in the Western Cape, n (%)	139 (34.6)	74 (26.5)	65 (52.9)	<0.001	40 (32.3)	21 (27.3)	13 (16.7)	0.050
Completed any high school, n (%)	396 (98.5)	277 (99.3)	119 (96.8)	0.074	122 (98.4)	77 (100.0)	78 (100.0)	0.504
Currently employed and/or studying, n (%)	127 (31.6)	86 (30.8)	41 (33.3)	0.618	45 (36.3)	21 (27.3)	20 (25.6)	0.204
Live in informal housing, n (%)	214 (53.2)	169 (60.6)	45 (36.6)	<0.001	77 (62.1)	49 (63.6)	43 (55.1)	0.499
Married or cohabiting, n (%)	169 (42.0)	131 (47.0)	38 (30.9)	0.003	59 (47.6)	37 (48.1)	35(44.9)	0.908
Primiparous, n (%)	84 (20.9)	57 (20.4)	27 (22.0)	0.743	20 (16.1)	21 (27.3)	16 (20.5)	0.172
Missing, n (%)	1 (0.3)	1 (0.4)	0		1 (0.8)	0	0	
Delivered multiples in index pregnancy, n (%)	5 (1.2)	5 (1.8)	0 (0)	0.329	4 (3.2)	0 (0.0)	1 (1.3)	0.390
Previous triple-drug ART before index pregnancy, n (%)	47 (11.7)	31 (11.1)	16 (13.0)	0.514	18 (14.5)	7 (9.1)	6 (7.7)	0.248
Missing, n (%)	6 (2.0)	3 (1.1)	5 (4.1)		2 (1.6)	0	1 (1.3)	
Previous short-course PMTCT, n (%)	80 (19.9)	59 (21.2)	21 (17.1)	0.346	29 (23.4)	14 (18.2)	16 (20.5)	0.671
Any previous ARV exposure (triple-drug ART or PMTCT), n (%)	105 (26.1)	73 (26.2)	32 (26.0)	0.975	37 (29.8)	18 (23.4)	18 (23.1)	0.458
Infant tested HIV positive at birth, n (%)	0	0	0					
Duration on ART at randomisation (days), median (IQR)	163.5 (126–200)	168 (128.5–202)	154 (120–196)	0.0654	165 (120–199)	166.5 (136–197)	176 (146–206)	0.2573
Missing, n (%)	8 (2.0)	3 (1.1)	5 (4.1)		2 (1.6)	0	1 (1.3)	

Table 1. Continued

Characteristics	Total (N=402)	One or more travel event over 24 months post-partum (n=279)	No travel over 24 months post-partum (n=123)	p-Value	One travel event (n=124)	Two travel events (n=77)	Three or more travel events (n=78)	p-Value
Regimen initiated in pregnancy, n (%)								
TDF/XTC/EFV	391 (97.3)	273 (97.9)	118 (95.9)	0.322	122 (98.4)	75 (97.4)	76 (97.4)	0.815
Other	4 (1.0)	4 (1.4)	0		1 (0.8)	2 (2.6)	1 (1.3)	
Missing	7 (1.7)	2 (0.7)	5 (4.1)		1 (0.8)	0	1 (1.3)	
Time post-partum at randomisation (days), median (IQR)	10 (6–20)	10 (6–19)	12 (6–22)	0.1194	10 (6–24)	10 (7–16)	8 (5–17)	0.2596
Missed a dose in the last 30 days, n (%)	83 (20.7)	50 (17.9)	33 (26.8)	0.042	16 (12.9)	22 (28.6)	12 (15.4)	0.015
Randomised to ACs, n (%)	203 (50.5)	150 (53.8)	53 (43.1)	0.049	69 (55.7)	40 (52.0)	41 (52.6)	0.851
VL at randomisation <50 copies/ml, n (%)	355 (88.3)	242 (86.7)	113 (91.9)	0.140	107 (86.3)	67 (87.0)	68 (87.2)	0.980

ARV, antiretroviral; PMTCT, prevention of mother-to-child transmission; XTC, emtricitabine or lamivudine.

Of the 402 women who were enrolled, 373 (93%), 374 (93%), 362 (90%), 360 (90%) and 357 (89%) attended study visits for the parent trial at 3, 6, 12, 18 and 24-months postpartum respectively. As questions regarding travel were instituted a few months into the study, 321/373 (86%) and 363/374 (97%) women who attended the 3-month and 6- month postpartum visits respectively were asked travel-related questions. Further, two, one and one women attending the 12-, 18- and 24-month visits respectively had missing data regarding travel, leaving 360/362 (99%), 359/360 (99%) and 356/357 (99%) women who attended study visits with travel-related data at these visits.

A total of 279 (69%) women reported at least one travel event over the 24 months postpartum; of these more than half (n = 155, 56%) travelled more than once. Compared to women who never travelled, a higher proportion of those who travelled one or more times lived in informal housing (61% vs 37%, p <0.001) at enrolment, were married or cohabiting (47% versus 31%, p = 0.003) and were randomised to the AC arm at enrolment (54% versus 43%, p = 0.049). A lower proportion of women who travelled were born in the Western Cape province (27% vs 53%, p <0.001).

A smaller proportion (48/321, 15%) of women reported at least one travel event between enrolment and the three-month postpartum visit compared to between 3–6 (99/363, 27%), 6–12 (114/360, 32%), 12–18 (129/359, 36%) and 18– 24 month (114/356, 32%) postpartum visits (Table 7.2). Travel was predominantly to one province, with >80% of women who reported travel at each visit travelling to the Eastern Cape province. Median duration of travel was 21 days. At all visits except for the 18-month postpartum visit, a higher proportion of participants who reported travelling did not have their baby living with them compared to those who did not report travelling. The proportion of women who attended an ART service visit at a health facility at their travel destination was 6% at 3 months postpartum and increased to 20% at 24 months postpartum. There were no clear differences in the proportions who reported a treatment interruption since the last visit or who reported missing a dose in the preceding 30 days between those who did and did not travel.

Table 7.2 Description of participants who travel and travel events by duration postpartum at which travel occurred

Characteristics	Enrolment to 2 months (n=321)			3–5 months (n=363)			6–11 months (n=360)			12–17 months (n=359)			18–24 months (n=356)		
	One or more travel events	No travel event	p-Value	One or more travel events	No travel event	p-Value	One or more travel events	No travel event	p-Value	One or more travel events	No travel event	p-Value	One or more travel events	No travel event	p-Value
Participants, n (%)	48 (15.0)	273 (85.1)		99 (27.3)	264 (72.7)		114 (31.7)	246 (68.3)		129 (35.9)	230 (64.1)		114 (32.0)	242 (68.0)	
Cumulative number who travelled	48			135			195			249			279		
Travel destination, n (%)															
Eastern Cape	41 (85.4)			83 (83.8)			101 (88.6)			112 (86.8)			105 (92.1)		
Western Cape	2 (4.2)			5 (5.1)			3 (2.6)			0			0 (0.0)		
Gauteng	2 (4.2)			4 (4.0)			5 (4.4)			6 (4.7)			1 (0.9)		
Other	3 (6.3)			7 (7.1)			5 (4.4)			11 (8.5)			9 (7.9)		
Total duration outside of Cape Town per participant (days), median (IQR)	21 (11.5–28)			21 (14–28)			21 (7–28)			21 (7–28)			21 (7–56)		
Missing, n (%)	0			1 (1.0)			0			5 (3.9)			4 (3.5)		
Infant not living with mother at start of visit interval, n (%)	4 (8.3)	2 (0.1)	0.005	13 (13.1)	11 (4.2)	0.002	20 (17.5)	15 (6.1)	0.001	20 (15.9)	36 (15.7)	0.956	34 (29.8)	34 (14.0)	<0.001
Missing, n (%)	0	2 (0.1)		0	0		2 (1.8)	1 (0.4)		3 (2.3)	0		3 (2.6)	4 (1.7)	
Attended a facility at travel destination, n (%)	3 (6.3)			13 (13.1)			11 (9.7)			17 (13.2)			23 (20.2)		
Missing, n (%)	0			0			0			1 (0.8)			0		
Treatment interruption (≥2 weeks without ART), n (%)	1 (2.1)	7 (2.6)	1.000	3 (3.0)	9 (3.4)	1.000	7 (6.1)	11 (4.5)	0.499	8 (6.2)	9 (3.9)	0.327	8 (7.0)	8 (2.9)	0.090
Missing, n (%)	0	0		0	1		0	0		0	0		0	0	
Missed dose in the last 30 d, n (%)	11 (22.9)	45 (16.5)	0.279	12 (12.1)	44 (16.7)	0.286	10 (8.8)	33 (13.4)	0.206	14 (10.9)	23 (10.0)	0.799	13 (11.4)	21 (8.7)	0.414
VL ≥50 copies/ml, n (%)	9 (18.8)	25 (9.2)	0.046	20 (20.2)	43 (16.3)	0.381	35 (30.7)	78 (31.7)	0.848	45 (34.9)	68 (29.6)	0.298	38 (33.3)	75 (31.0)	0.619
Missing, n (%)	0	0		0	0		0	0		0	0		1 (0.9)	0	
VL ≥400 copies/ml, n (%)	4 (8.3)	15 (5.5)	0.503	16 (16.2)	33 (12.5)	0.363	26 (22.8)	58 (23.6)	0.872	37 (28.7)	58 (25.2)	0.475	33 (28.9)	61 (25.2)	0.427
Missing, n (%)	0	0		0	0		0	0		0	0		1 (0.9)	0	
VL ≥1000 copies/ml, n (%)	4 (8.3)	14 (5.1)	0.324	13 (13.1)	32 (12.1)	0.795	22 (19.3)	52 (21.1)	0.688	32 (24.8)	51 (22.2)	0.570	30 (26.3)	55 (22.7)	0.432
Missing, n (%)	0	0		0	0		0	0		0	0		1 (0.9)	0	

In a univariate generalised mixed effects logistic regression model, randomisation allocation was not significantly associated with travel (OR 1.15, 95% CI 0.89–1.51; Table 7.3). In adjusted analyses predicting travel, being born outside of the Western Cape province, (adjusted odds ratio [aOR] 2.03, 95% CI 1.49–2.77) and duration postpartum (aOR 1.03, 95% CI 1.02–1.05) were associated with increased odds of a travel event. The relative odds of travel were reduced when the baby lived with the mother (aOR 0.60, 95% CI 0.38–0.93). The occurrence of a travel event since the last study visit was associated with a 92% increase in the relative odds of VL >400 copies/mL (aOR 1.92, 95% CI 1.19–3.10; Table 7.4) when adjusting for age, living in informal housing, relationship status, previous use of antiretrovirals (either ART or short-course prevention of mother-to-child transmission), randomisation allocation, duration postpartum and whether or not they lived with the baby. Using a VL $\geq$50 copies/mL as the outcome did not substantially alter the association (aOR 1.85, 95% CI 1.21–2.81; Supplementary Table 10.6.1). When including only visit intervals in which the VL at the start of the interval was <400 copies/mL, the increased relative odds of VL $\geq$400 copies/mL in those who travelled compared to those who did not persisted but was reduced (1.62, 95% CI 1.00–2.61; Supplementary table 10.6.2). There was a 24% increase in the relative odds of a VL $\geq$400 copies /mL associated with every one log increase in travel duration, but this was not statistically significant (aOR1.24, 95% CI 0.85–1.81; Supplementary table 10.6.3). In analyses stratified by randomisation allocation in the primary trial, the adjusted relative odds of a VL $\geq$400 copies/mL in those who those who travelled since the last visit compared to those who did not was higher in women randomised to the PHC clinics (aoR 2.35, 95% CI 1.12 – 4.91) versus women randomised to the adherence club intervention (aOR 1.72, 95% CI 0.91–3.25; Supplementary table 10.6.4).

Table 7.3 Results of mixed effects logistic model for relative odds of a travel event (n = 388 23)

	Unadjusted		Adjusted	
Variables	OR	95% CI	OR	95% CI
Fixed effects (at enrolment)				
Born in South Africa	0.92	0.48 to 1.76		
Born outside of the Western Cape	2.30	1.73 to 3.05	2.03	1.49 to 2.77
Age at enrolment (years)	0.99	0.96 to 1.01	0.98	0.95 to 1.01
Lives in informal housing	1.60	1.23 to 2.09	1.19	0.90 to 1.57
Any previous ARV use (triple-drug ART or short-course PMTCT)	0.90	0.66 to 1.21		
Completed any high school	4.66	0.92 to 23.6		
Working and/or studying	0.87	0.65 to 1.16		
Cohabiting or married	1.38	1.06 to 1.81	1.30	0.99 to 1.71
Randomised to AC	1.15	0.89 to 1.51		
Time-varying fixed effects (at visit prior to travel event)				
VL ≥50 copies/ml	0.99	0.73 to 1.33		
Duration post-partum (months)	1.04	1.03 to 1.06	1.03	1.02 to 1.05
Living with baby	0.40	0.26 to 0.62	0.60	0.38 to 0.93

ARV: antiretroviral; PMTCT: prevention of mother-to-child transmission.

Table 7.4 Results of mixed effects logistic model for relative odds of VL >400 copies/mL (n = 389)

	Unadjusted		Adjusted	
Variables	OR	95% CI	OR	95% CI
Fixed effects (at enrolment)				
Age (years)	0.96	0.90 to 1.01	0.91	0.83 to 1.00
Informal housing	0.60	0.32 to 1.09	0.50	0.21 to 1.21
Working and/or studying	0.59	0.30 to 1.17		
Married and/or cohabiting	0.40	0.22 to 0.75	0.31	0.12 to 0.78
Any previous ARV use (triple-drug ART or short-course PMTCT)	2.57	1.32 to 5.02	7.56	2.02 to 21.06
Duration between visits (months)	1.66	1.49 to 1.84		
Randomised to AC	0.54	0.29 to 0.99	0.46	0.20 to 1.09
Time-varying fixed effects (at visit prior to travel event)				
Travel since the last visit	2.15	1.41 to 3.26	1.92	1.19 to 3.10
Duration post-partum (months)	1.15	1.12 to 1.19	1.14	1.11 to 1.17
Living with baby	0.17	0.09 to 0.32	0.69	0.31 to 1.51

ARV: antiretroviral; PMTCT: prevention of mother-to-child transmission.

7.5 Discussion

This analysis described travel and assessed VL outcomes post-travel among women on ART enrolled within 70 days postpartum and followed up through 24 months postpartum. Almost 70% of women reported at least one travel event over the study period. Women born outside of the province and those who did not live with their child were more likely to travel. In a multivariable model, travel was associated with a 92% increase in the relative odds of elevated VL. Considering the documented number of women who travel and the

associated risk of viraemia, improving outcomes in women who travel is vital if we are to improve treatment outcomes in postpartum women.

Mobility has been associated with non-adherence and non-retention in general adults living with HIV (17-19). Types of mobility and the effects of mobility on engagement in care may differ in different contexts and populations (10,11,13). Postpartum women living with HIV are at high risk of disengagement, yet data on mobility in this group are limited. In KwaZulu-Natal in South Africa, >20% of women relocated during pregnancy and the first year postpartum (16). Also in South Africa, travel was shown to occur commonly in the immediate postpartum period but mobility beyond this period was not assessed (14). This analysis provides insight into travel up to 24 months postpartum in an urban area of South Africa with high levels of mobility and high numbers of women on ART. With the majority of women in this cohort travelling at least once over the study period, these findings emphasise the need for HIV care services that support mobile populations.

Travel was associated with viraemia regardless of duration. Research among general adults has shown that disruption of daily schedules and stigma among mobile patients who fear disclosing their HIV status by taking their medication around family or friends may lead to non-adherence (10,26,27). These factors may be relevant even to trips of short duration. The relative odds of travel increased with increasing duration postpartum and this may be because women were enrolled at a median of 10 weeks postpartum, meaning that travel events prior to this were not included. Nevertheless, travel occurred throughout the 24 months postpartum, indicating that support for women who travel is required on an ongoing basis. In contrast to a study in Johannesburg, where postpartum women were found to travel throughout South Africa immediately post-delivery, travel in our setting was primarily to one province (14). This underscores the need to assess travel patterns in different settings to understand the locations where interventions may be required. We also found that women born outside of the province and those who did not live with their child were more likely to travel, which may allow targeting of interventions. In line with previous studies, we found a strong association between previous ART use and viraemia, possibly due to development of resistance or repeated non-adherence (28). Separation of mother and child has also previously been shown to be associated with an increased risk of viraemia in postpartum women on ART (29). One explanation for this finding is that women

are motivated to take their treatment to stay healthy while with their children, but that this motivation may decrease when separated. Our results suggest that travel may also play a role in the increased risk of viraemia in women separated from their children.

Provision of chronic care services for mobile populations is an ongoing challenge (9,30). In stratified analysis, the relative odds of viraemia in women who travelled compared to those who did not travel was higher among women randomised to the PHC clinics compared to the AC intervention arm of the primary trial. Possible reasons for this include increased social support at ACs and the increased spacing between AC visits which may prevent women running out of treatment while travelling. Running out of treatment on longer trips has been cited as a reason for treatment interruption in qualitative studies (26,31). We found an increased relative odds of viraemia with duration of travel; this was not statistically significant but data on travel were collected every 3–6 months and recall bias may be present. Understanding how DSD models such as ACs may support mobile populations requiring chronic care is a potentially important avenue for further research. Patients who do run out of treatment require access to health facilities at the travel destination (26). Based on self-report, the proportion of women who travelled and attended a health facility at their destination in this analysis was low at 4% at 3 months postpartum and increased to 20% at 24 months postpartum. This could mean that women plan their trips to return before their medication runs out, that they inform their original clinics of their travel plans and obtain sufficient treatment for the duration of their trip (14), or that they run out of treatment without attending a clinic at their travel destination. Numerous barriers to attending health facilities when away from home have been described including stigma, negative interactions with health care workers and having to retell their history to health care workers (9), and transfer between health facilities has been associated with viraemia in general adults (32). Based on this, further investigation into access to care at travel destinations should be considered.

Strengths of this analysis include the 24-month duration of follow-up and the use of VL as an outcome measure which provides an objective measure of adherence. Limitations include that travel data were collected every 3–6 months and recall bias may be present and that data on engagement in care at the travel site and treatment interruptions were self-reported. In addition, we were unable to ascertain the duration between travel and VL

assessment and we did not have data on reasons for travel, which may be associated with adherence (33). While follow-up rates in the study were high, loss to follow-up (LTFU) may bias results, as mobility may be associated with LTFU status and viraemia. This may have led to an underestimation of the number of travel events and of the association between travel and viraemia.

7.6 Conclusion

In summary, approximately 70% of women travelled one or more times through 24 months postpartum and travel was independently associated with elevated VL. Interventions to support postpartum women on ART who travel are urgently required to improve treatment outcomes.

7.7 References

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Chapter 8: Experiences of transfer of care among postpartum women living with HIV attending primary health care services in South Africa

Odayar J, Myer L, Kabanda S, Knight L. Experiences of transfer of care among postpartum women living with HIV attending primary health care services in South Africa. *Manuscript under review at Glob Public Health.*

Relevance of this paper to the thesis:

In many settings including South Africa, postpartum women living with HIV must transfer from integrated antenatal/HIV care to general HIV services post-delivery. Thereafter, women in South Africa transfer frequently for reasons including geographic mobility. Women who transfer are at risk of disengagement and viraemia but the reasons for these outcomes are unclear. A better understanding of barriers to successful transfer would allow identification of areas for improvement. This paper presents the results of a qualitative analysis exploring the experiences of transfer and barriers to successful transfer among postpartum women on ART.

Contribution of the student and co-authors:

JO conceptualised the analysis with guidance from LM and LK. LM conceptualised the study from which these data arise, and was responsible for funding, study implementation and overall leadership. JO directed data collection with assistance from SK. JO conducted the analysis with guidance from LK. JO led data interpretation and drafted the manuscript. All authors reviewed the initial manuscript and provided conceptual and intellectual comment. All authors reviewed and approved the final manuscript.

8.1 Abstract

Transfers between health facilities in postpartum women living with HIV are associated with disengagement from care and viraemia. In South Africa, women must transfer from integrated antenatal/HIV care to general adult HIV services post-delivery. Thereafter, women transfer frequently e.g., due to geographic mobility. To explore barriers to transfer, we conducted in-depth interviews >2 years post-delivery in 28 participants in a trial comparing postpartum HIV care at primary health care ART facilities versus a differentiated service delivery model, the adherence clubs, which are the predominant model implemented in South Africa. Data were thematically analysed using inductive and deductive approaches. Some women at DSDs were unaware of the option to transfer. Women lacked information regarding where they could transfer to and transfer processes. Continuity mechanisms were affected when women transferred silently i.e., without informing facilities or obtaining referral letters. Silent transfers often occurred due to poor relationships with healthcare workers and were managed inconsistently. Fear of disclosure to family and community stigma led to transfers from local PHC ART facilities to facilities further away affecting accessibility. Mobility and the postpartum period presented unique challenges requiring specific attention. Information regarding long-term care options and transfer processes, ongoing counselling regarding disclosure and social support, and increased health system flexibility are required.

8.2 Introduction

The number of women on antiretroviral therapy (ART) in South Africa has increased substantially in recent years (1). However, there are concerns regarding disengagement from care in the postpartum period (2–5). Disengagement is associated with HIV disease progression, virological failure, ART drug resistance and HIV transmission including vertical transmission during breastfeeding (6–11). Understanding reasons for disengagement and developing ways to improve engagement in care in postpartum women living with HIV (WLH) are thus vital.

Transfer of care between health care facilities is a step in the continuum of care at which people living with HIV (PLH) including pregnant and postpartum women are at risk of disengagement (12–14). Transfer processes are potentially complicated, involving multiple facilities and actors. They are further complicated by the fact that they can be official or silent: official transfers are known to the health system, while silent transfers occur when patients transfer without informing the original facility or obtaining a referral letter (15,16). In settings where HIV care has been integrated into antenatal care (ANC) including South Africa and other sub-Saharan African countries, pregnant women on ART prior to pregnancy must transfer from ART facilities for general adults to integrated ANC and prevention of mother-to-child transmission of HIV services (17,18). WLH who are not on ART prior to pregnancy are initiated as part of ANC. Postpartum, all women must transfer to general adult ART facilities; however, a substantial proportion do not link to HIV care (14). Among those who do link, additional transfers between ART facilities occur frequently for reasons including geographic mobility and stigma and have been associated with viraemia (14,19,20).

Further, transfers from routine care to differentiated service delivery models may also be associated with disengagement. Differentiated service delivery models aim to simplify care and provide services based on patient needs. In South Africa, adherence clubs (ACs) are the predominant model: pre-packaged ART is provided to stable patients by community health workers (CHWs) at health facilities or community venues and postpartum women attending ACs have had good outcomes (21,22). However, 15% of both general adults and postpartum

women transferred from general adult ART PHC facilities to ACs do not attend their first AC visit (21–23).

Reasons for disengagement and viraemia among PLH who transfer are unclear. Qualitative studies suggest that current transfer services do not meet patient needs; general adult patients in South Africa who disengaged from care described the process as confusing and complicated and noted difficulties accessing care without specific documentation (24,25). Pregnant women in Malawi also described difficulty accessing care without the correct paperwork but data are limited in postpartum women and a better understanding of barriers to successful transfer is required to improve outcomes in this population (26). We used qualitative evidence to explore the experiences of transfer and possible barriers to transfer among postpartum women on ART.

8.3 Methods

8.3.1 Study setting

This study is part of the Postpartum Adherence Clubs for Antiretroviral Therapy (PACART) study, which was a randomised controlled trial of differentiated service delivery for postpartum ART delivery (NCT03200054) in Cape Town, South Africa (22,27). In this trial, postpartum women on ART were randomised to referral to the ACs (intervention) or a primary health care (PHC) ART facility (standard of care [SOC]) for ongoing HIV care. In the trial, referral to ACs was associated with reduced viraemia through 24 months postpartum compared to referral to PHC ART facilities (22). The study was conducted at a large public sector PHC facility in the City of Cape Town district. The facility serves a peri-urban community of approximately 350,000 with high levels of unemployment (28). Antenatal HIV prevalence in the district was estimated at 22% in 2019 (29). The facility includes a midwife obstetric unit (MOU) which provides antenatal, obstetric, and postnatal care, with integrated HIV care. The facility also includes a PHC ART facility separate to the MOU but on the same premises which provides HIV care to the general adult population. The PHC ART facility has an associated AC which operates off site (30).

8.3.2 Participants and description of postpartum care

Women attending the MOU post-delivery were screened for participation in the parent trial and were enrolled if they were ≥18 years, <10 weeks postpartum and had started ART in pregnancy. Additional criteria were based on eligibility criteria for referral to the ACs which require an HIV viral load (VL) <400 copies/mL in the preceding three months and no clinical conditions requiring regular clinical care.

Women randomised to the PHC ART facility arm were referred to facilities in the local community, including the PHC ART facility at the site of the MOU. Per routine care, the choice of facility was based on proximity to the woman's residence and personal preference (17). These women received a referral letter, a two-month supply of ART and were told to visit their selected PHC ART facility within two months. Women randomised to the AC arm were referred to the AC associated with the PHC ART facility on the same site as the MOU. They were accompanied to the AC office, which is at the PHC ART facility, by a CHW with their file and referral letter. At the AC office they were provided with a card with their first visit date and were given directions to the venue.

PHC ART facility visits are 1–2 monthly and include a clinical consultation by a nurse or doctor (31). The ACs operate from a community hall approximately one kilometre from the PHC ART facility. ACs are run by CHWs and comprise 25-30 patients who meet for 1-2 hours every two months, except for the end-of-year Christmas and summer holiday period in South Africa when they obtain a four-month supply of pre-packaged ART. AC participants who miss their first visit, are more than one week late for any other visit, or require clinical consultation are referred to the PHC ART facility. For the primary trial, women randomised to the AC or PHC ART facility arms could be transferred to other facilities or models of care as they would be in routine care.

8.3.3 Sampling

The parent trial followed women through 24 months postpartum. After their 24-month postpartum study visit, women were approached for participation in qualitative semi-structured in-depth interviews (IDIs). At the time of the IDIs, the parent trial staff members had had prolonged engagement with participants and had built rapport and trust over time.

Sampling was purposive to facilitate enrolment of equal numbers of participants randomised to the AC and PHC ART facility arms. Participants were contacted telephonically and informed about the interviews and invited to participate. If interested, a date was arranged for them to visit the research site for an IDI.

8.3.4 Data collection

In 2019, IDIs were conducted by a trained female research assistant who had extensive experience conducting IDIs at the research site and was from the same community as the participants. Interviews were conducted in isiXhosa or English based on participant choice. A semi-structured interview guide was developed in English and translated into isiXhosa. The interview guide included the following topic areas: the experience of transfers at ACs and PHC ART facilities, transfer processes, and reasons for transferring when applicable. Interviews were conducted in private rooms at the research site and were audio-recorded. Interviews were then translated into English if conducted in isiXhosa, and transcribed by a staff member who was not involved in the interviews. Transcriptions and translations were reviewed by the interviewer to ensure accuracy. All research procedures, any changes to procedures and interactions with participants were documented.

8.3.5 Ethics approvals

All participants provided separate written informed consent for participation in IDIs. The study was reviewed and approved by the University of Cape Town Human Research Ethics Committee.

8.3.6 Analysis

A conceptual framework to assess the quality of family planning services was adopted and adapted to guide these analyses as it maps how *programme effort* affects the *elements of the service received* which, in turn, affect programme *impacts* (32). The aim of this analysis was to identify areas for improvement of transfer services and the quality of care framework has previously been used to identify how care can be improved (33). To identify barriers to successful transfer and identify places for intervention and/or improvement, the main focus of the analysis was on the *elements in the unit of service received*. To align the framework with participant responses in relation to transfer, we adapted the elements

provided to include the following: *information provided to patients*, *interpersonal relations*, *follow-up/continuity mechanisms* and *provision of an appropriate constellation of services* (Figure 8.1) (32). In addition, to understand how policies and guidelines affect transfer services, South African guidelines related to transfers were compared to the transfer services described by participants.

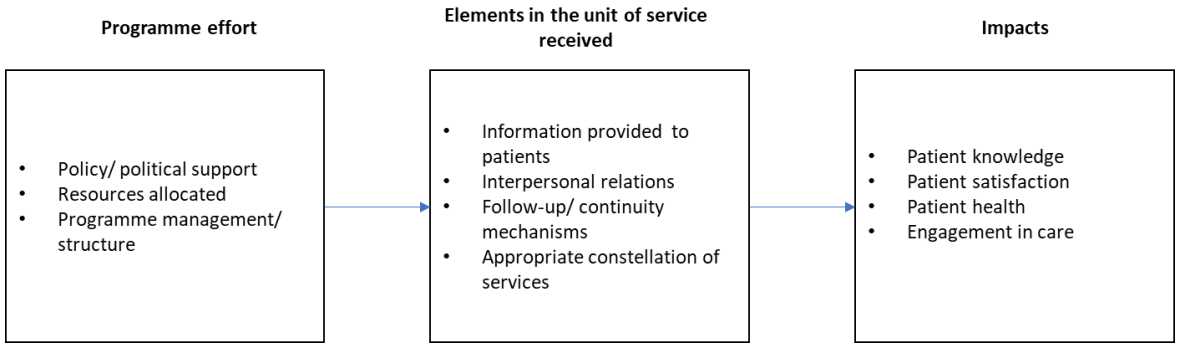

Figure 8.1 Framework assessing the quality of transfer services adapted from Bruce's framework assessing the quality of family planning services (32)

Data were analysed using thematic analysis in an iterative process (34). Interview transcripts were read for familiarisation, possible codes were identified, and these were discussed by the study team. Thereafter the transcripts were coded manually (35). Coding was both inductive, with codes informed by the adopted conceptual framework and deductive, with additional codes allowed to emerge from the data. Once coding was complete the text was organised to explore possible themes and emerging patterns with reference to the framework. In addition to identification of themes, the analysis enabled comparison between initial transfers-out from the MOU and subsequent transfers, and between participants attending ACs and PHC ART facilities. To ensure rigour, the analysis process and identified themes were discussed at regular meetings with the study team to review and compare interpretations. All decisions and changes made during analysis were documented. Development of the manuscript was guided by The Standards for Reporting Qualitative Research recommendations (36).

8.4 Results

IDIs were conducted with 28 women between July and September 2019, of whom 14 had been randomised to the AC arm and 14 to the PHC ART facility arm. At the time of the IDI, median age was 30.6 years and median duration postpartum was 26.4 months (Table 8.1). Among the 14 women randomised to the ACs, three had transferred to a PHC ART facility and one to an MOU by the time of the interview. In the 14 randomised to the PHC ART facility, five had transferred to a different PHC ART facility and four to the AC associated with the PHC ART facility they were attending.

Table 8.1 Characteristics at time of in-depth interview

	Randomised to ACs (n=14)	Randomised to PHC ART facilities (n=14)	Total (n=28)
Median age (IQR), years	30.2 (28.9–36.6)	30.2 (28.9–36.6)	30.6 (28.8–36.7)
Median duration postpartum (IQR), months	27.0 (24.2–29.2)	26.1 (24.9–29.8)	26.4 (24.7–29.2)

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range; PHC, primary health care.

The main themes were informed by the adapted quality of care framework and related to: (1) information given to patients regarding facilities to which they could transfer and what to expect at those facilities, (2) follow-up/continuity mechanisms including referral letters, (3) interpersonal and social relationships including with healthcare workers (HCWs), family and community members, and (4) appropriateness of the constellation of services provided, where we identified mobility and the postpartum period as requiring specific attention.

8.4.1 Information provided to patients

Individuals may require transfer for numerous reasons, yet a few participants who attended the ACs throughout the postpartum period were unaware that they could transfer to another facility. When asked whether she had considered requesting a transfer one participant responded:

I would not have been able to start at a new [health facility] because they don't have my information. I would have stayed here. I would have stayed here because they have my information.

(37 years, AC arm)

Participants being unaware that they could transfer did not emerge in the PHC ART facility arm.

Numerous participants randomised to both the PHC ART facility arm and the AC arm who knew that they could transfer did not know enough about facilities to which they could transfer to make an informed choice. This applied to the initial transfer-out from the MOU and to subsequent transfers. For example, a participant attending the ACs throughout the postpartum period would have considered transferring to an AC closer to home due to transport difficulties but did not know if there was one.

If there was a club in [the area closer to home], because sometimes I don't have money to travel, at least I could walk to [the area closer to home]….I don't know [if there is an AC closer], it was my first time hearing about the club here, so I don't know if there's one [there].

(37 years, AC arm)

One of the reasons for the lack of knowledge regarding options may be that many participants were initiated on ART at the MOU during ANC and did not have prior experience of PHC ART facilities. In addition, participants had no medical conditions requiring regular clinical care at enrolment and may have had limited experience of health facilities in general. A few participants who chose to attend a PHC ART facility other than the one at the MOU based their choice on prior experiences.

Yes, no one prepared me [provided her with information to make a choice]… I used to attend the [chosen PHC facility] a long time ago, besides now for my ART care, I used to go there for family planning… I knew that I would be taking my child [there], that's why I chose it.

(33 years, PHC ART facility arm)

Further, some participants indicated that they were unclear about what to expect at the facilities to which they were transferred. Participants in the PHC ART facility arm noted differences between care provided at the MOU and the PHC ART facilities. At the MOU, care is adapted to prevent delays: patients are given medication during their consultation with the nurse and do not have to queue at the pharmacy. A participant expressed surprise at PHC ART facility operations and having to wait in multiple queues.

> *I thought at [the PHC ART facility], I was going to… it's just going to enter there, produce your referral letter and then you get your medication and then you go. I didn't know that … you have to wait for your folder and stuff, see the nurses and stuff like that, and then go again to the pharmacy.*

(28 years, PHC ART facility arm)

Despite the ACs functioning differently to the MOU, participants were generally well informed about operations by staff when transferred. However, one participant was affected by the differences in operations. At the MOU, patients who attend their visits late because they still have medication are attended to, but a patient transferred to the ACs who attended her first visit late because she still had medication was considered no longer eligible for the ACs.

Once attending the ACs, participants who were transferred to the associated PHC ART facility described a lack of information regarding the process. After more than a year attending the AC, a participant missed a visit and was transferred to the associated PHC ART facility.

> *… they [AC] told me to go back to [the PHC ART facility] to look for my folder. I felt like I wasn't being given important information like 'When you leave [the club], you can go there and ask for so and so, and they will give you all of the information'. I thought that they would maybe call [the PHC ART facility] and tell them to expect a certain patient. … I didn't come to [the PHC ART facility] because I didn't know what I would say [there], this upset me… if they had told us where to go, I would ask the*

security because they are the first person you see, I would have asked them "Where in the [facility] is this side?"… but I had no other information, so I decided to go to [a different PHC ART facility].

(29 years, AC arm)

Not knowing how to navigate this transfer led her to silently transfer to a different PHC ART facility and this transfer is discussed further under the heading 'follow-up/continuity of care'.

The lack of information thus covered numerous aspects including knowledge that it is possible to transfer, where to transfer, transfer processes and care delivery at the new facility, and occurred especially when transferring from the MOU to the PHC ART facility and when transferring out of the ACs.

8.4.2 Interpersonal relationships

Interpersonal problems leading to transfers included conflict with partners and family as well as relationships with HCWs. In addition, perceived stigma from community members contributed to the decision to transfer.

8.4.2.1 Conflict with partners and family

Conflict with partners or family that led to a breakdown in personal relationships resulted in women changing their living circumstances and having to change health facilities as illustrated below:

[My mother] is in the rural areas. She said I should come back [to stay with her]… I am waiting for the child, the girl, to finish writing exams. I have already asked for a transfer letter, the nurse said when I return in November, they will give me one.

(26 years, AC arm)

This participant planned to transfer and move to her maternal home as she was in an abusive relationship which worsened after she disclosed her HIV status to her partner.

8.4.2.2 Transfers due to perceived stigma

Many who had not disclosed to family and friends did not want to attend PHC ART facilities in their communities due to the risk of disclosure if seen there by people they knew. This seemed less of a concern for those in the AC arm. A participant in the PHC ART facility arm who had not disclosed to her husband transferred to a facility further away when she saw people she knew at her first PHC ART facility visit and was still attending the facility to which she transferred two years later despite problems with transport.

> *When I started at the [PHC ART facility that] is close to my home… I would see familiar faces and think that one day when she is out of pills, she will come to my home and ask for our thing [pills]. She might find my husband at home and ask that he tells his wife to borrow her our things [pills]. When I entered [the PHC ART facility] one asked, 'You too?' and I said I was there for my cousin. When I went in to see the doctor, I asked for a transfer letter to [a PHC ART facility further from her home]. Sometimes, when I have no taxi fare, I think maybe I should go to that nearest [PHC ART facility]. But I ask myself if I am ready for it to be known before I say it. The day I disclose is the day I attend the [PHC ART facility] nearby.*
>
> (34 years, PHC ART facility arm)

A second participant also transferred after initial referral to a PHC ART facility, and she felt that this was due to her not having accepted her HIV status.

> *I just didn't feel comfortable [at the PHC ART facility in my area]... Maybe I am not okay with [my HIV status]. Maybe I still need counselling, because I still live in the area. So when I am inside [the facility in my area], I can see people I know walk by.*
>
> (24 years, PHC ART facility arm)

Women thus expressed fear of both disclosure to family and stigma from the community. At the time of the IDI, the same participant above was considering a transfer to a PHC ART facility closer to home due to difficulties with transport to the further facility.

This thing of going to [the PHC ART facility further away] is an inconvenience because sometimes I don't have money for transportation… Sometimes I have to borrow money to go for my visit. Sometimes the person I borrow money from asks questions, like why I am attending a [facility] that is far… I think that woman had mentioned that if I want to get my treatment there [a PHC ART facility close to home], I could do so. I think [the facility closer to home mentioned by the other woman] is alright… I am familiar with [it] because I used to take the older child there.

This may suggest that women who chose PHC ART facilities outside of their communities early on were willing to transfer to local PHC ART facilities at a later stage. This may have been because of disclosure as noted by a participant who disclosed to friends and family members over time and then transferred to a local PHC ART facility:

I'm past that now, I am alright now. I was still shocked then and still afraid to disclose to my family and friends, but I am fine.

(29 years, AC arm)

In contrast to the PHC ART facility where there was a risk of being seen and talked about by community members, those attending the AC described it as a space free of stigma.

What I saw is that everyone [at the AC] is open…They talk about our treatment, with no problem. It is unlike [at the PHC ART facility], where you see someone from your area and they gossip… Yes, there are people I know in the club, but they are older. No one minds your business there. It is unlike in the community.

(29 years, AC arm)

Perceived stigma and fear of disclosure therefore contributed to early transfers from the PHC ART facilities to facilities further away. In some women, internalised stigma was still affecting health behaviour more than two years postpartum.

8.4.2.3 Negative interactions with HCWs

Several participants experienced negative interactions with HCWs leading to transfers. These transfers were often silent, with participants not informing HCWs. A participant attending the AC for more than two years missed an appointment and expressed fear of attending the AC thereafter.

> *Then I made a mistake in May this year and I was already pregnant; I did not go to [the AC] and I was afraid to go back again… Then I thought I should wait until my antenatal date at the [MOU], I will the get pills from there… That is how I defaulted, I did not take the pills well since then.*
>
> (30 years, AC arm)

The fear of attending the AC after missing a visit led the participant to silently transfer to the MOU and in the process the participant was off treatment for approximately 3 months.

Another participant attending a PHC ART facility had been off treatment for a week at the time of her IDI. She had travelled and had timed her return to pick up her treatment as required without missing a dose. However, she had forgotten her treatment card at her travel destination and did not attend her visit. When asked why, she explained:

> *I don't want to go back there. Also, you can also see the way you are treated… The treatment [at the facility], you could ask a question, "Ask someone else, I don't understand your question" they will say, they will tell you to ask in the room you will be going to… So, that is why I am running away from there.*
>
> (29 years, AC arm)

Negative interactions with HCWs thus made it difficult for participants to approach staff when they had other difficulties, for example a missing treatment card. This together with dissatisfaction with the services provided led to silent transfers. Further, the participant ended up without treatment despite planning her travel around her facility visits.

8.4.3 Follow-up/continuity mechanisms

In routine care, continuity mechanisms differ for ACs and PHC ART facilities. Patients transferring between PHC ART facilities are given transfer letters. Participants transferred to the ACs are accompanied to the AC office by a CHW with their file and referral letter to facilitate continuity; no problems emerged regarding transfers to ACs. However, difficulties arose for participants transferring out of the ACs, leading to silent transfers i.e., transfers without referral letters. When participants are no longer eligible for AC attendance, e.g., those who have missed their first appointment, they are transferred to the associated PHC ART facility (23), usually with verbal instructions on where to go. As noted in the section on information provided to patients above, participants at ACs generally obtained limited information about PHC ART facility access. This led one participant transferred from the ACs to the PHC ART facility to silently transfer to a different PHC ART facility.

> *So, I thought to just come to [different facility]…. When I got [there] I told them that I am a lady who lives [in the area], I am HIV positive, I used to get my pills at [the AC] but I missed my date, so at [the AC] they told me to go back to the [PHC ART facility] … but they didn't give me any directions about what to say when I got there; I thought instead of not taking pills at all, I thought it would be better to come to the nearest place to me. She asked me if I wouldn't miss my date when I go to this [PHC ART facility], I told her that I would try my best not to miss it because it doesn't happen often and I don't like to miss my date. She said okay, then called another lady who works there who checked me and tested me first, we went to another room where she opened a new folder for me and she gave me pills for two months.*
>
> (29 years, AC arm)

Another participant in the AC arm was unable to attend her first visit as her newborn was hospitalised and she was required to stay with them. As she missed her first AC visit, she was transferred to the PHC ART facility but negative interactions with HCWs (discussed above) led her to silently transfer. She initially obtained treatment at the hospital where her baby was admitted and when the infant was discharged, she was given medication from the hospital but not a referral letter.

At [the hospital] they gave you pills… So, I think I had pills for about one to two months after being discharged at [the hospital]… I actually went to [the new PHC ART facility] while I still had pills where they told me I need to get a transfer from where I was getting my pills before, so I asked [a counsellor at the MOU] to make a transfer letter as though I had just been discharged from here.

(29 years, AC arm)

In this case, she had to take matters into her own hands and request a transfer letter from a counsellor.

Patients transferring between PHC ART facilities are given a referral letter and a date to visit the facility on their own. One participant transferred to the PHC ART facility from the MOU reported challenges because despite having a transfer letter from the MOU she was told she also needed to fetch her file from the MOU. She described navigating this experience.

…I had to wake up like early with a month-old baby, and come and sit for long hours, and then you sit for longer hours, and then you don't get the service. They tell you that 'oh we don't have your stuff', you have to go and fetch your own folders yourself. … So, it's like they were a bit rough 'We don't have your folder, so how are we supposed to know what to give you? Go and fetch your folder, you know, we don't do the work for you' and blah blah blah. I wanted to go back home, but I also wanted the medication. I just came to [the MOU] and then [the HCW at the MOU] gave me the folder. I gave [the staff at the PHC ART facility] the folder and they had to give me another date, and I had wasted transport money. They told me, 'we can't help you now, you have to come another time.' I felt like not coming back.

(28 years, PHC ART facility arm)

One participant randomised to the PHC ART facility travelled to her family home at short notice for six months due to conflict with her partner but did not know that she required a transfer letter.

I didn't know that I should ask for a letter. I just travelled there. When I got there, I saw that the pills are almost finished. I went to the well-baby clinic and I asked what I

should do. I told them I am breastfeeding, and I am on treatment. That man said… they can't give me pills but …he will do me a favour and give me one bottle and asked that I make sure that my documents have been sent by the end of the week. I asked a friend I trust to go to the MOU and ask for [a counsellor] who also worked there. They gave her that letter and she faxed it. It didn't take long. She got it immediately.

(24 years, PHC ART facility arm)

This participant obtained treatment but had to make an effort herself to obtain a letter so she could receive further treatment.

Patients who miss appointments at health facilities or the ACs should be traced telephonically or through home visits as per policy (37). However, none of the women interviewed who disengaged or silently transferred described being traced.

Overall, many patients transferred silently, especially those transferring from the ACs to the PHC ART facility. Receiving facilities managed participants who transferred silently differently, and many participants described challenges and needing to find creative ways to access documentation to obtain care.

8.4.4 Appropriate constellation of services

8.4.4.1 Mobility

South African ART guidelines state that patients should be counselled to inform HCWs of their travel plans so that they can be given extra treatment and/or a transfer letter to a facility at their destination (37). Many participants were aware of this, stating that they informed their PHC ART facility or AC when travelling and ensured that they had enough medication for the trip. Most travelled over the end of year summer holiday period in South Africa when they routinely receive 3–4 months of treatment. However, a few participants were unsure of what to do when travelling (see last participant above). A participant who had to travel at short notice to look after ill family members was unsure when she would return and discussed her lack of clarity.

As I came here, I wanted to ask a question; because I am getting my treatment from the club. I am not sure how am I supposed to do this…. My mother-in-law has been calling me saying she is not well... So, there was a possibility that I would have left this weekend, but I couldn't just go, I decided that I will wait for [tomorrow]. So, I want to ask from the sister at that club on how I am supposed to do because I have to go to [another province]… I don't think it will be easy to come back soon, when I go in December, I know that I will look at my next date and easily come back. As I have to go now because someone is sick, I don't know, I have become weak.

(37 years, AC arm)

A few participants travelling for longer durations obtained referral letters to PHC ART facilities at their travel destinations, but most preferred to obtain sufficient treatment prior to travelling and very few had attended an ART facility at the travel destination. A participant who travelled regularly was asked whether she had attended ART facilities at her travel destination:

I have never been. I usually go to home of the father of my eldest child, in [a different province]. The people that side speak [a language she does not speak], so I have not been to those [PHC ART facilities]. I don't even know how they are... In [her home town]… The [PHC ART facilities] are far, they are in town. The [PHC ART facility] in the village often runs out of medication. I rarely go there. I go and come back without going there.

(40 years, AC arm)

Another participant mentioned distance to the PHC ART facility at her travel destination as a barrier to transfer and made alternate arrangements when her medication ran out while travelling.

It is hard [to get your pills in the rural area] because you must travel and if you don't have a transfer [letter], you will not get them… It is far. You must take a taxi. [When I travelled] the pills were not enough. I asked [my husband] to collect my pills [at the AC] and give them to my uncle. My uncle is on the road a lot [bus driver]. I collected them from my uncle.

(22 years, PHC ART facility arm)

In addition, fear of community stigma if seen at facilities also affected access to care at travel destinations.

> *It is not far, its very close. But I wouldn't go because there is only this one in town so everyone I know will be there. So, I don't like to meet with them, I would rather ask for enough pills here. Otherwise I might default.*

(29 years, AC arm)

While the health system has made accommodations for WLH who are mobile, some participants were unaware of these processes. Participants mentioned numerous barriers to transferring to facilities at their travel destinations, suggesting that women who travel for long periods or at short notice may experience difficulties accessing care.

8.4.4.2 Care of postpartum/pregnant women

The experiences of a few women suggested that care was not always suited to the circumstances of postpartum women. Participants who do not attend their first AC visit are transferred to the PHC ART facilities. As mentioned above, one mother missed her first appointment because her newborn was hospitalised but the reason for the missed visit was not considered by HCWs.

> *I missed the club because I was at the hospital… When I went back to the club, they sent me to [the PHC ART facility], when I got there and was trying to explain to the Sister who I think handles these things said; 'Do you not have our phone numbers? You should have called us; I'm not getting involved with this'. I tried to explain that the phone number was on my card, which was at home. She just told me to go to reception and ask for a date to come here, mind you my child was still hospitalised, I had asked to come here for my treatment. When I explained this to her, she told me to get in the queue like everyone, I did, but I received a call telling me my child's condition was getting worse and I should get back there urgently. I was also exclusively breastfeeding so I had to go back, I went to tell her this and ask for a new*

date, she sent me to ask for a date a reception; I got there and same story, so I decided to find another way to get my pills because the care I received here was not good.

(29 years, AC arm)

The lack of consideration for her circumstances led to dissatisfaction with the care she received and led the participant to silently transfer. We also note the experience of the participant mentioned under "Follow-up and continuity of care" who spent the whole day at the PHC ART facility with her one-month-old baby without obtaining treatment and was told to return the following day. While this did not lead her to transfer or disengage, it indicates that the circumstances of postpartum women are not accommodated.

8.5 Discussion

Using an adapted quality of care framework to examine the experiences of transfer among postpartum women on ART, we identified numerous barriers to successful transfer. Differences between transfers from the MOU post-delivery versus transfers that occurred once in long-term care were revealed, as well as differences between transfers involving ACs and PHC ART facilities. We are thus able to suggest interventions based on when transfers occur, and the types of facilities involved.

Barriers to transfers included a lack of knowledge regarding transfers among participants, with some women at the ACs not knowing that they have the choice to transfer. This could lead women to continue at facilities that are inconvenient for them or where they are unhappy and contribute to disengagement. Women transferring from the MOU to the PHC ART facilities were ill-informed regarding facilities to which they could transfer and the changes in care delivery they would experience. Participants attending the ACs did not understand the process of transfer back to the PHC ART facilities. A framework to understand the effects of transfer on health behaviours emphasised the importance of preparing PLH who transfer for the changes in care delivery they will experience, and this should be applied to postpartum women (38).

Relationships with HCWs, the community and family all contributed to the occurrence of transfers. Research has shown that negative interactions and fear-based relationships with HCWs lead to disengagement, including through fear of reprimand when rules are not adhered to (39). In this analysis, we show that transfers are involved in this relationship; women who had negative interactions with HCWs silently transferred, expressing fear and/or dissatisfaction with services. Silent transfers have been associated with gaps in care and viraemia and many participants who silently transferred in this analysis experienced treatment interruptions (40,41). Further, PHC ART facilities managed silent transfers differently with some patients sent away or given short-term treatment and required to obtain a referral letter. General adults in South Africa and pregnant women in Malawi who silently transferred have described having to restart treatment or being unable to access care (24,35). Guidelines state that patients without treatment should not be refused care regardless of whether they have referral letters, but do not provide specific guidance on management and this should be addressed (42). The risk of inadvertent disclosure if seen by people they know led women to transfer, as has also been previously described among pregnant women in Malawi (26). Here, patients who transferred from the MOU to PHC ART facilities subsequently transferred to facilities further away early in the postpartum period, sometimes leading to transport difficulties. Some women were still attending these facilities at 24 months postpartum despite these difficulties. In contrast, women attending the ACs did not mention community stigma as a cause of transfer, with many finding the AC environment supportive. Relationships with partners, including the occurrence of abuse, also led to transfers. HCWs should ask about reasons for transfer and other stressors that participants may be experiencing to identify those in need of additional support.

Women who were geographically mobile experienced numerous different barriers to transfer. Some were unaware of transfer processes. Barriers to transfer at their travel destinations included fear of and lack of documentation and women preferred to take sufficient treatment with them for the duration of the trip. However, unforeseen circumstances and having to travel at short notice may affect women's ability to plan to ensure sufficient treatment and the health care system should be understanding of this.

To improve outcomes in postpartum women who transfer, women should be provided with information regarding long-term care options, particularly those being transferred from the

MOU to general adult ART care and those attending ACs. Women should be prepared for what to expect at receiving facilities, particularly those transferring from the MOU to PHC ART facilities, and transfer processes should be explained, especially when being transferred from ACs to PHC ART facilities. Considering the long-term effects of stigma on health behaviours, women may require ongoing counselling, before and after transfer, particularly around disclosure and social support, and especially those attending PHC ART facilities. In addition, the health care system needs to respond with flexibility e.g., to transfers due to mobility that occur at short notice and needs to be understanding of people's circumstances including postpartum women. Silent transfers should be prevented if possible, including by improving relationships between HCWs and patients. Strategies to improve implementation of current guidelines, including that patients should never be refused care regardless of whether they have a referral letter, should be developed and guidelines that address management of transfers comprehensively, including the management of silent transfers, are required.

This study provides insight into a population at high risk of disengagement through 24 months postpartum and provides practical suggestions for improved care delivery. Further, as far as we are aware, this is one of the first studies evaluating transfer to and from differentiated service delivery models. The fact that participants were randomised to referral to either the AC or PHC arm minimises bias when comparing transfers in the two arms; however, participation in a research study may have affected health behaviour. An additional limitation is that the study was based at one MOU and AC service and results may not be generalisable to other settings.

8.6 Conclusion

In summary, we described the experiences of transfer among postpartum women on ART and identified numerous barriers to successful transfer. Women are not provided with sufficient information regarding transfer, particularly those transferring out from the MOU and the ACs. In numerous examples, poor relationships with HCWs contributed to the occurrence of silent transfers which affect continuity of care. A lack of flexibility regarding patients' circumstances including for geographically mobile and postpartum women also

affected health care access. Information regarding long-term care options and transfer processes, ongoing counselling regarding disclosure and social support, and increased health system flexibility are required.

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Chapter 9: Discussion

9.1 Introduction

This chapter presents a discussion of findings and recommendations when viewing this thesis as a combined body of work. First, an overview of the thesis will be provided. Thereafter, discussion points from individual manuscripts will not be reiterated but themes that emerged when considering the thesis as a whole will be considered, placing these in the context of relevant publications on transfer of patients with chronic conditions, particularly in low- and middle-income countries (LMIC). Thereafter, the overall strengths and limitations of the thesis, and recommendations for policy and future research will be presented.

9.2 Discussion of key findings

9.2.1 Overview of the thesis

The process of transferring between health facilities is complex, requiring co-ordination between health care providers, health facilities and patients. Transfers are required across diseases and across populations and may be categorised along various axes, including whether they are known to the health system or not (official or silent transfers), the types or levels of facilities involved (up-referral, down-referral or lateral transfers) and the reason/s for the transfer (1–4).

Chapter 8 references a framework developed by Bruce through a review of evidence to assess the quality of care of family planning services (5). As part of the methods in Chapter 8, this framework was modified to assess the quality of care of transfer services. The modified framework (Figure 9.1) illustrates how *programme effort* affects the *elements in the unit of service received* which, in turn, affect *impacts*. *Programme effort* includes policy support and resource allocation. *Elements in the unit of the service received* include information provided to patients, interpersonal relations, follow-up/continuity mechanisms and provision of an appropriate constellation of services. The element *appropriate constellation of services*, refers to provision of services that are responsive to patient needs;

in this thesis patients who are geographically mobile or who are pregnant or postpartum were identified as having specific needs that require consideration. *Elements in the unit of service received* affect *impacts* including engagement in care. Further, the mechanisms through which *elements in the unit of service received* leads to the observed *impacts* are of interest if we are to develop strategies to improve outcomes.

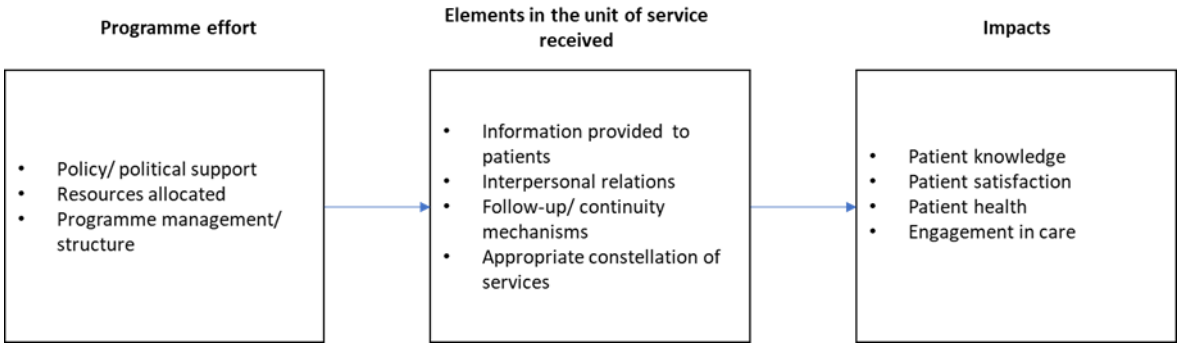

Figure 9.1 Framework assessing the quality of the transfer service experience adapted from Bruce's framework assessing quality of family planning services (5)

The aspects of transfers involving primary health care (PHC) facilities investigated in this thesis relate to *programme effort*, *elements in the unit of service received* and *impacts*. In Chapter 3, *programme effort* in the form of national policies and guidelines that address transfers of adults living with HIV were reviewed. In Chapter 4, the incidence rate of transfers, which affects resource allocation, was investigated for people living with HIV (PLH). In addition, *impacts* in the form of viral load (VL) outcomes were compared in those who did and did not transfer. However, this analysis did not differentiate between silent and official transfers. We therefore identified people transferring into a PHC facility in Cape Town from the analysis in Chapter 4 and conducted a review of their medical records to determine the proportions of patients who silently and officially transferred and compare their management, particularly follow-up and continuity mechanisms. In Chapter 6, an analysis similar to that conducted in Chapter 4 for PLH was conducted in people living with diabetes (PLD). The incidence rate of transfers and outcomes post-transfer based on change in HbA1c values, were investigated. Chapter 7 addresses two of the elements identified as requiring specific care i.e., mobility and being postpartum, by presenting the results of an analysis assessing mobility, transfers and treatment outcomes in postpartum women living

with HIV. Lastly, Chapter 8 presents the results of a qualitative analysis assessing the experiences of transfer for postpartum women living with HIV; this chapter provides insights into *programme effort*, *elements in the service received* and *impacts* and how the three inter-relate. The results of these analyses are summarised in Table 9.1.

In this process, different populations (general adults and postpartum women), different health conditions (HIV and diabetes) and different types of transfers (silent and official) were considered. Conducting these analyses in different populations and diseases and assessing different types of transfers allows comparison across these various axes and provides insights into how outcomes may occur. When viewing the results chapters as a whole, themes emerged regarding the following five areas which are explored in the ensuing sections: 1) the rate of transfers and risk of poor outcomes post-transfer, 2) the relationship between transfers and disengagement, 3) the relationship between transfers and mobility, 4) the relationship between guidelines and practice, and 5) a consolidated approach to transfers.

Table 9.1 Summary of key findings

Chapter and objective		Key findings
3	To review current guidelines for the transfer of adults living with HIV on ART attending PHC facilities in South Africa.	- Terms used to refer to transfer included referral, linkage, transfer, transition, and handover but most were not well defined, and all were used interchangeably. - Types of transfer discussed: o Linkage to care and transfers between different levels of the health system emphasised i.e., up- and down-referrals. o Patient request as an indication for transfer mentioned only in the context of mobility. o Lateral transfers, particularly between PHC facilities, received minimal attention. - Transfer processes: o Processes for linkage to care, up- and down referrals delineated, but not for transfers between PHC facilities. o Management of silent transfers and aspects of management of official transfers including clinical considerations omitted. o Recommends follow-up for official transfers only in patients linked to care or down-referred who miss appointments.
4*	To describe and characterise the transfer of adults living with HIV on ART attending PHC facilities across the Western Cape Province of South Africa and to assess and compare long-term outcomes including VL outcomes and retention in care in adults on ART who do and do not transfer.	- Transfers involving PHC facilities among people attending PHC: o 29,056/84,814 (34%) transferred at least once over 4.5 years of follow-up. o There were 44,712 transfers over 252,105 person-years of follow-up (transfer IR 12.71 per 100 person-years). - Transfers between PHC facilities: o 19,561 participants transferred between PHC facilities one or more times. o Of the 44,317 total transfers, 27,775 (63%) were between PHC facilities. o Female sex, age <30 years, and first VL >1000 copies/mL were associated with an increased rate of PHC to PHC transfers. o PHC to PHC transfers were associated with an increased odds of a VL >1000 copies/mL (aOR 1.27, 95% CI 1.20–1.35) compared to no transfer. o The relative odds of a VL >1000 copies/mL after a PHC to PHC transfer vs. no transfer were 1.27 (95% CI 1.20–1.35). - Transfers and disengagement o Including only visit intervals in which a disengagement occurred (>14 months between VLs), a VL >1000 copies/mL was more likely when PHC to PHC transfer occurred compared to no transfer (aOR 2.54, 95% CI 2.27–2.84). o Including only visit intervals without a disengagement, the effect estimate remained above one but the effect size was smaller (aOR 1.12, 95% CI 1.04–1.20).
5	To the determine the proportions of PLH on ART transferring in to a PHC facility who officially and silently transfer and to compare their management	- Of 33 transfers, 64% (n = 21) were official and 36% (n = 12) were silent. - Despite previous ART use, 4/33 (12%) patients transferred in as newly diagnosed with HIV. - 17/33 (52%) participants were not on ART, including 9/21 (43%) official transfers and 8/12 silent transfers (67%). - 4/18 (22%) official transfers had clinical concerns requiring intervention versus 6/12 (50%) who silently transferred.

6	To describe and characterise the transfer of adults living with diabetes attending PHC facilities across the Western Cape Province of South Africa and to assess and compare long-term outcomes including HbA1c outcomes in those who do and do not transfer.	- Incidence rate of transfers (all transfers involving PHC facilities) o 23,277/102,813 (23%) had at least one transfer over 27 months of follow-up. o There were 29,994 transfers over 208,030 person-years of follow-up (transfer IR rate 14.4 per 100 person-years). - Transfers between PHC facilities o Of the 29,995 total transfers, 7,884 (26%) were between PHC facilities. o The relative odds of an HbA1c >8% after a transfer between PHC facilities vs. no transfer were 1.20 (95% CI 1.05–1.37). - Transfers and disengagement o Including only visit intervals in which a disengagement occurred, the increased relative odds of an HbA1c >8% when a PHC to PHC transfer occurred versus when one did not occur persisted (aOR 1.12, 95% CI 1.03–1.21). o Including only visit intervals in which a disengagement did not occur, the effect estimate remained above one but was reduced and was not statistically significant (aOR 1.09, 95% CI 0.93–1.27).
7	To examine the relationship between travel, transfer and viraemia in postpartum women on ART.	- Description of mobility patterns o 279/402 women (69%) had at least one travel event through 24 months postpartum. o The median duration of travel was 21 days. - Engagement in care in women who travel: o The proportions attending an ART facility at their travel destination increased from 6% at 3 months postpartum to 20% at 24 months postpartum. o Travel was associated with an increased relative odds of a VL ≥400 copies/ml (aOR 1.92, 95% CI 1.19–3.10] vs no travel.
8	To explore the experience of the transfer process and identify potential barriers to successful transfer among postpartum women on ART.	The following themes were identified: - Information given to patients: Women were unclear on facilities to which they could transfer, transfer processes and care delivery at the new facility. - Follow-up or continuity mechanisms: Continuity mechanisms were affected when women silently transferred. - Interpersonal and social relationships: o Poor relationships with health care providers led to silent transfers which were managed inconsistently. o Fear of disclosure to family and community stigma led to transfers from local clinics to facilities further away. o Conflict with partners/family led women to relocate, necessitating transfers. - Appropriateness of the constellation of services provided: o Mobility and the postpartum period present specific challenges requiring consideration. o Mobile women may require transfers to facilities at the travel destination for longer trips but barriers included community stigma and poor access. o Postpartum women had difficulties attending facilities due to caring for a newborn and were unaware of routine clinic processes.

Abbreviations: aOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; HbA1c, glycosylated haemoglobin; IR, incidence rate; PHC, primary health care; PLH, people living with HIV; VL, viral load.

9.2.2 The rate of transfers involving PHC facilities

Understanding the frequency and patterns of transfers is important for health care service planning including drug forecasting and costing (2,6,7). While studies have documented the numbers of PLH who transfer, there are limited data on transfers among PLD, particularly in LMIC. In Chapter 4, the incidence rate of transfers involving PHC facilities among PLH was reported as 12.7 (95% CI 12.6–12.8) transfers per 100 person-years. In Chapter 6, the corresponding transfer incidence rate for PLD was 14.4 (95% CI 14.3–14.6) transfers per 100 person-years. The transfer incidence rate was thus slightly higher among PLD compared to PLH and indicates that transfers should not be ignored in this population.

Regarding the specific types of facilities involved in transfers, in Appendix 10.4 it was reported that most transfers among PLH (63%) were between PHC facilities. The analysis in Chapter 6 showed that, among PLD, the highest proportion of transfers were from PHC facilities to hospitals (37%), followed by hospitals to PHC facilities (34%) and PHC facilities to PHC facilities (26%). The proportion of transfers from PHC facilities to PHC facilities was thus lower among PLD compared to PLH, with relatively more PLD transferring to and from hospitals. This may indicate that PLD were less well and required more complex clinical care than PLH, or that health care providers at PHC services are less confident managing PLD than PLH. While lower than among PLH, the proportion of transfers between PHC among PLD was still substantial. These results thus show that transfers between PHC facilities occur frequently across two conditions with numerous differences including in the populations affected. While they are both chronic conditions that require lifelong care, HIV is a communicable disease, and diabetes a non-communicable disease (NCD). In South Africa, HIV incidence is highest in females aged 15–24 years (8). Among PLD, incidence is also higher in females than males, but regarding age, incidence is highest among adults aged 45–64 years (9). Geographic mobility has long been associated with HIV as a driver of transmission (10,11). Further, it is increasingly recognised as a factor affecting engagement in care among PLH and is one of the reasons that transfers between facilities may be required (12,13). Among PLD, however, there are fewer data on mobility. A study in Gauteng province in South Africa found that both internal and external migrants had a reduced relative odds of diabetes compared to non-migrants (14). Geographic mobility may be less of a factor leading to transfers among PLD compared to PLH but this requires

investigation. Data on reasons for transfers are limited among PLD. A qualitative study in Kenya indicated that health system factors play a role: people with NCDs in this setting indicated that they moved between facilities to access medications when drug stock-outs occurred at their original facilities (15). Considering the high rate of transfers documented among PLD, studies investigating the reasons for transfers are required. Overall, for both HIV and diabetes, most of the research that has been done involves transfers between levels of care i.e., hospitals to PHC facilities and PHC facilities to hospitals (16–33). The results of this thesis indicate the importance of transfers between PHC facilities in these populations. In addition, they provide a rationale for research on transfers among people with other chronic conditions including other NCDs.

As discussed further in the section on policy recommendations below, these results also demonstrate the importance of tracking the number of transfers. While many HIV care programmes monitor the number of patients transferred out as part of the HIV cascade system, patients who transfer are not tracked across facilities, meaning that a substantial proportion of patients are unaccounted for (4). A few guidelines mention that patients who are lost to follow-up should be traced including those with HIV or NCDs (34–36); this would identify silent transfers. However, tracing at facilities in South Africa has been found to be inconsistent and inefficient (37). Silent transfers who are not identified are misclassified as LTFU while in care elsewhere (2,38–45). On the other hand, patients who silently transfer may be started on ART as new patients at the facilities to which they transfer, leading to an overestimation of the numbers ever started on ART (37). For diabetes, most countries do not have systems routinely monitoring patient engagement in care, including transfers (46,47). With large proportions of PLD not in care, there have been calls for the development and implementation of monitoring systems to track individual and programme level outcomes (46,48–51). The results presented in Chapter 6 indicate the importance of including monitoring and reporting of transfers as part of any system that is implemented for PLD. From a health system perspective, numerous inadequacies have been identified in the provision of diabetes care including limited availability of equipment and medications required for monitoring and treatment (52). Transfers affect the resources required at health facilities (16,17). Any efforts to address the multiple financial, logistical and management factors affecting access to diabetes care at PHC level, including treatments and

equipment, should thus consider the volume of transfers (52). Additional research on the patterns of transfers over time including the types of facilities and locations involved are required to facilitate planning.

9.2.3 The risk of poor outcomes following transfers between PHC facilities

Data on outcomes of transfers between PHC facilities are extremely limited. Viraemia suggesting poor adherence was documented among general adult patients living with HIV requesting transfers out from one PHC facility to another but patients were not tracked to the receiving facility (53). Among PLD, we were unable to identify studies assessing outcomes of transfers between PHC facilities.

In Appendix 10.4, a transfer between PHC facilities among PLH was associated with a 27% increase in the relative odds of viraemia compared to no transfer. In Chapter 6, transfers between PHC facilities among PLD were associated with a 20% increase in the relative odds of an HbA1c >8% compared to no transfer. Considering the volume of transfers between PHC facilities among PLH and PLD documented in this thesis and the lack of data on this topic, these results are striking and require further investigation. Most previous studies assessing outcomes of transfers among both PLH and PLD involve transfers between different levels of the health system i.e., hospital to PHC facility (20,24–30,54,55) or PHC facility to hospital (19,21,32,33,56). This may be due to the assumption that patients being transferred to and from hospitals are more likely to be ill and at risk of poor outcomes. These results show that even patients transferring between PHC facilities, who are more likely to be stable than those transferring to and from hospitals, should not be ignored.

In Appendix 10.4, among PLH, the odds of viraemia were also increased after hospital to PHC facility and PHC facility to hospital transfers compared to no transfer, and these transfers require attention if we are to improve outcomes. In contrast to PLH, the odds of an HbA1c >8% were decreased after hospital to PHC facility and PHC facility to hospital transfers compared to no transfer in the primary analysis. Another type of transfer involving PHC facilities that requires consideration is between PHC facilities and differentiated service delivery models. In Appendix 10.7, 15% of general adult patients transferred from a PHC facility to an adherence club (AC), which is the predominant differentiated service delivery model implemented in South Africa (57), did not attend the

AC. This corresponds with previous research among postpartum women in which 15% of women transferred from midwife obstetric units to ACs did not attend the AC (58,59). Chapter 9 provides insight into why this may occur among postpartum women. AC rules stipulate that patients referred to the ACs must attend their first visit date or must notify the ACs that they cannot attend in advance (60). In Chapter 9, a postpartum mother was unable to attend her first AC visit as her newborn was hospitalised. This reason was not accepted, and she was referred to continue care at an PHC facility. With implementation of differentiated service delivery models being accelerated in many sub-Saharan African countries (61), understanding the reasons for non-attendance among other populations and developing ways to improve attendance is vital. Authors have previously noted that the rigidity of rules at differentiated service delivery models may affect engagement in care (62). In addition to not attending the first visit, other reasons that patients at the ACs are sent back to the PHC facility include not collecting their medication within five days of their scheduled visit (63). In a study in South Africa, 47% of patients at ACs were sent back to the PHC facility from the AC over approximately one year of follow-up; the most common reason for this was not complying with AC rules (64). Differentiated service delivery models may thus need to be more flexible and responsive to patient needs, including, the needs of pregnant women.

The results of Chapter 4, Chapter 6 and Appendix 10.4 all indicate the need for a better understanding of the mechanism of outcomes post-transfer to understand how to improve outcomes. In addition, they underscore the importance of monitoring and tracking the outcomes of patients who transfer, including patients who transfer between PHC facilities, as will be discussed further in the section on policy recommendations below.

9.2.4 The relationship between transfers and disengagement

In Chapter 4 and Appendix 10.4, the analyses show associations between the occurrence of transfers and viraemia, which is an objective marker of treatment adherence (65). Understanding the mechanism of this association is vital to developing ways to improve outcomes.

Treatment interruption and reduced adherence to ART may lead to viraemia and poor HIV treatment outcomes including HIV transmission, viral resistance, clinical deterioration, and

mortality (66–70). Bengtson et.al. previously found an association between transfers and treatment interruption – people who transferred were three times as likely to experience a treatment interruption compared to those who did not transfer (71); based on these results, it is possible that disengagement confounds the association between transfers and poor treatment outcomes and/or acts as a mediator in the association. However, this analysis did not distinguish between silent and official transfers or between transfers involving different types of facilities.

The results of this thesis provide additional insights into the relationship between transfers and disengagement. In Chapter 5, 17/33 (52%) of individuals who transferred into a PHC facility had interrupted their ART. This was made up of 9/21 (43%) official transfers and 8/12 (67%) silent transfers. While this analysis was small, it appears that treatment interruptions occur among both silent and official transfers. In Chapter 8, postpartum women, in particular those who silently transferred, described not obtaining treatment or being turned away from health facilities. This has also previously been described among general adult patients (73,73). Here, disengagement acts as a mediator: the act of transferring may lead to or lengthen disengagement, which would then lead to viraemia (Figure 9.2a). Ensuring that patients who silently transfer obtain care and are not turned away from facilities is vital to reducing viraemia. It is also possible that disengagement occurs prior to transfer (Figure 9.2b). In Chapter 8, women who missed appointments described transferring to a different facility to avoid censure from health care providers. Similar events have been described among general adults living with HIV (74,75). In this scenario, health care worker attitudes lead to silent transfers and should be addressed. In addition, this scenario illustrates the importance of ensuring rapid care for patients who silently transfer to decrease the duration of disengagement.

a) Transfer may lead to disengagement which may lead to viraemia. Transfer may also lead to viraemia independent of disengagement

b) Disengagement may lead to silent transfer. In this scenario, silent transfer may reduce viraemia if access to care is obtained. Disengagement may also independently lead to viraemia.

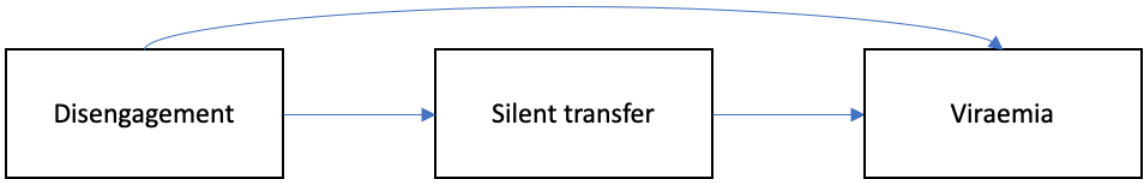

Figure 9.2 Hypothesised relationships between transfers, disengagement and viraemia

In Appendix 10.4, among PLH, the relationship between transfers and viraemia is shown to be modified by disengagement (Figure 9.3). The relative odds of viraemia after a transfer between PHC facilities compared to no transfer were higher when disengagement occurred compared to when disengagement did not occur. However, the odds ratio when disengagement did not occur was still increased and statistically significant. Based on this, minimising disengagement in PLH who transfer is vital to reducing viraemia but will not eliminate it. Viraemia may also be caused by reduced adherence. Many of the reasons that people transfer are also factors that affect adherence including stigma, mobility, and interpersonal stressors (76). Among PLH who transfer, understanding the reasons for transfer and assessing patients for other factors that may affect adherence and retention are vital.

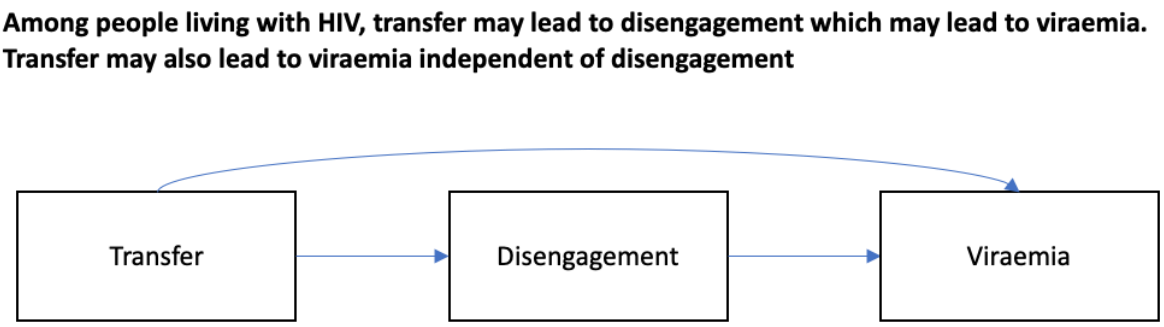

Figure 9.3 Effect modification of the relationship between transfers and viraemia by disengagement among people living with HIV

In Chapter 6, a similar analysis to assess effect modification by disengagement in the relationship between transfers and HbA1c outcomes was conducted among PLD. When including only visit intervals in which a disengagement occurred, the relative odds of an HbA1c >8% at the end of intervals in which a transfer between PHC facilities occurred was significantly increased compared to intervals in which a transfer between PHC facilities did not occur. When including only visit intervals without a disengagement, the effect estimate remained above one but was reduced and was no longer statistically significant. This reinforces the importance of preventing disengagement among PLD who transfer. A better understanding of transfer processes, reasons for transfer, and reasons for disengagement among people with diabetes who transfer is required to better understand this relationship. Overall, considering the relationship between transfers and disengagement among both PLH and PLD, efforts to prevent disengagement must take transfers into account.

9.2.5 The relationship between transfers and mobility

In Chapters 4 and 6, transfer is examined as the exposure, and the effects of transfer on VL and HbA1c respectively outcomes are assessed. However, it is possible for transfer to be conceptualised in other ways depending on the context, for example, in mobile populations. Geographic mobility is increasingly recognised as a factor affecting long term engagement in care (11,12). Mobility may lead to poor treatment adherence or treatment interruption, particularly if trips are of longer duration, and this may lead to viraemia (11,77–79). Transfers may be required to prevent treatment interruption among those travelling for longer durations or relocating.

Postpartum women are highly mobile in South Africa, and mobility is hypothesised to play a major role in the high levels of disengagement seen in this group (80–82). However, the overall relationship between mobility and treatment outcomes in PLH, and how transfer is involved in this relationship, has been unclear. In Chapter 8, among women living with HIV on ART, travel in the 24 months postpartum was associated with a 92% increase in the odds of a VL >400 copies/mL compared to no travel. This is the first study that we know of that directly compares VL outcomes in mobile and non-mobile postpartum women on ART and the results confirm that there is an increased risk of poor treatment outcomes among those who are mobile. In this cohort, the percentage of women who reported that they had travelled in the preceding 3–6 months and that they had attended an ART facility at their travel destination was 6% at 3 months postpartum, increasing to 20% at 2 years postpartum. The low proportion of transfers may be due to the relatively short duration of travel, with a median travel duration of three weeks, meaning that women may have had enough treatment to last the duration of the trip and did not need to transfer. This would suggest that poor adherence may play a large role in the association between mobility and viraemia. However, in the qualitative analysis in Chapter 8, instances in which transfer may be required among mobile postpartum women were raised. South African ART guidelines state that patients should be counselled to inform health care providers of their travel plans so that they can be provided with extra treatment and/or a transfer letter to a facility at their destination (35). However, a few women were unaware of these processes. Women sometimes had to travel at short notice, meaning that they may not have had time to visit the clinic for additional treatment if necessary and women were also sometimes unaware of how long the trip would be e.g., when travelling due to illness in the family. Women also noted numerous barriers to transfer at their travel destinations. These included potential stigma from the community if seen receiving HIV care at an ART facility and distance to the ART facility. Most women had never attended the ART facility at their travel destination and knew little about the facility. Overall, these analyses indicate that while many women in this context may not need to transfer, those who do may encounter difficulties and this requires further consideration. In addition, further research assessing the relationship between mobility and adherence to treatment in postpartum women is required as this may be a factor contributing to the occurrence of viraemia in this population.

9.2.6 The relationship between guidelines and practice

Considering the risks associated with transfers, development of appropriate management strategies is vital. However, there is a lack of clarity regarding several aspects of management of transfers of PLH between health facilities, particularly between PHC facilities, in national guidelines and this may contribute to inconsistent management and poor patient outcomes (83,84).

First, clinical assessment of patients who transfer, including history-taking, is not addressed in national guidelines. In Chapter 5, more than one-quarter of participants transferring into a PHC facility had clinical problems requiring intervention and more than half were not on ART. Patients off ART and with potential clinical complications included both official and silent transfers. Silent transfers did not have transfer letters and while official transfers had transfer letters, these sometimes included incorrect information or had information omitted. Lack of informational continuity may negatively impact clinical decision-making and could contribute to the poor outcomes post-transfer documented in Chapter 4 and Appendix 10.4 (85). Approaches to obtaining clinical information in patients who transfer should thus be developed. The Western Cape province has an integrated health information system with a unique patient identifier allowing integration of patient information into a single electronic record (86). This provides a potential source of clinical history, but it is unclear if and how this is used in patients who transfer. In Chapter 5, three participants with evidence of previous ART use transferred into a PHC facility in the Western Cape province and were registered as new patients with no history of ART, suggesting that the electronic health system was not used to access information. Development of an integrated health information system is proposed nationally, which would facilitate sharing of information between facilities and allow tracking of patient movements nationally (87). The establishment of such systems should be accompanied by clear guidance regarding its use for patients who transfer.

Second, there is a limited guidance regarding management of silent transfers in general in national guidelines. In Chapter 5, more than one-third of patients transferring into a PHC facility transferred silently; 67% of silent transfers were not on ART and 45% had clinical concerns requiring a change in management. Ensuring appropriate management of PLH

who transfer silently is thus vital. Three guidelines clearly state that patients who present to health facilities without transfer letters who have run out of ART should not be refused treatment (3,88–90). However, further management is not detailed. In addition, management of PLH who silently transfer and still have ART when seen at the new facility is unclear. In Chapter 5, after transfer-in to a PHC facility, four participants disengaged from the facility during follow-up and subsequently returned to request a transfer letter. Patients without referral letters being refused care has previously been documented and it is possible that these patients returned to the PHC facility to obtain a referral letter for this reason (72,73). In Chapter 8, the experiences of postpartum women showed that women who silently transferred were managed differently at different facilities. Management ranged from being turned away from the facility to which they silently transferred, to being retested for HIV and re-initiated on ART, to being provided with treatment but told that they needed to obtain a referral letter before obtaining further medication. The different approaches to management may partly be due to the lack of guidance in national guidelines. A clear approach to the management of silent transfers is required and research is required to inform such guidelines, as discussed further in the section on future research priorities below.

9.2.7 A consolidated approach to transfers

Transfers may be required in all diseases and all populations but are generally discussed within specific disease groups and/or populations. As discussed in Chapter 2, most research on transfers has been done in PLH. Regarding types of transfers, transfers between different levels of the health system have been researched (22,28,91–93), especially hospital discharge among the elderly with chronic conditions who have had acute episodes of illness (26,94–98). In addition, transfers involving PHC facilities have been assessed, i.e., hospital to PHC facility, PHC facility to hospital and PHC facility to PHC facility (71,99) but few studies have disaggregated transfers between PHC facilities (100,101). Research on transfers has been conducted among different populations including general adults living with HIV, postpartum women living with HIV, and adolescents (99,102–105). In general, research on transfers in specific populations does not reference research from other areas. Yet, findings from this thesis illustrate commonalities across populations. For example, the results of the qualitative analysis among postpartum women presented in Chapter 8 show

that silent transfers are often related to actions of the health system, including negative interactions with health care providers which lead women to access care elsewhere without informing the original facility. Similarly, Beeman et.al., described a reluctance among general adults who disengaged to return to the same facility due to fear of the responses from health care providers (74). A qualitative analysis in Malawi among postpartum women found that women previously on ART who silently transferred sometimes did not provide their history of previous diagnosis at the new facility and were retested for HIV (106). Similarly, in Chapter 6, general adults with a history of ART presented as newly diagnosed. Similarities thus occur across settings and populations.

Chapter 3 describes the numerous terms used to denote transfers between facilities in guideline documents; in addition to transfer, terms used included linking to care, transition, referral, and handover (3,35,89,90,107,108). These terms are ill-defined and sometimes used interchangeably and/or inconsistently and this could contribute to the fragmented nature of literature on transfers. Research has been conducted on transfers among PLD attending PHC and different terms are sometimes used compared to literature among PLH. A few articles that do directly address transfers among PLD refer to them as "switching" between health facilities (101,109). Due to the different terminology, these manuscripts were not picked up in the initial literature review but only when developing the manuscript for Chapter 6. This illustrates how researchers may be unaware of research on transfers being conducted in other contexts. For PLD, research has also been conducted relating to continuity of care, which is affected by transfers between facilities in addition to other factors. Continuity is measured in numerous ways, but commonly used measures providing an indication of the number of providers seen by a patient (110–113). Fewer measures directly indicate the number of facilities attended (114). However, while not directly addressing transfers between facilities, research among PLD to improve continuity of care by addressing care co-ordination may be relevant to improving outcomes among people who transfer. Care co-ordination involves the organisation of patient care to enable provision of health care delivery and research on improving care co-ordination include the use of care co-ordinators to facilitate communication across facilities (115). While researchers have suggested that care for NCDs could be improved by leveraging the systems

in place for HIV and tuberculosis, it may also be possible that HIV and TB systems can learn from research conducted for other chronic conditions including diabetes.

As described in Chapter 3, different aspects of transfer management for PLH are also addressed in different guideline documents. For example, the Ideal Clinic guidelines have a strong focus on down-referrals including to community-based services (108,116). Adult clinical care guidelines include indications for up-referral of acutely ill general adults living with HIV and maternity care guidelines provide indications for up-referral of pregnant women living with HIV (117,118). With management differing based on health condition, the types of referral and the indication for transfer it is sometimes unclear which guidelines are applicable to specific situations. One document that attempts to coalesce the information on transfers in one place is the South African National Referral Guideline (3). The document address transfers between facilities as a function of the health system overall and not in a disease specific manner. While it provides an overall approach to management of transfers, it focuses predominantly on transfers between levels of the health system. Lateral transfers are mentioned, but management of lateral transfers including transfers between PHC facilities are not specifically addressed. Considering the high volume of transfers between PHC facilities documented in Chapter 6 and in Appendix 10.4, as well as the complications related to management discussed in Chapters 6 and 9, this is an omission that requires urgent attention.

Investigating transfers within different populations, health conditions and in different settings is vital to assess differences related to transfers. For example, Chapters 4 and 6 illustrate differences between predictors of transfers between PHC facilities among PLD and PLH. In Chapter 7, postpartum women at a facility in Cape Town were found to travel predominantly to one province of South Africa; this differs from findings from a study in Gauteng, where women were found to travel to eight provinces in South Africa and four international countries (82). Understanding how best to manage transfers requires an understanding of these differences. However, currently, research and guidelines on transfers are disconnected. Different bodies of work may have different strengths and limitations; consolidation of research and guidelines on transfers across diseases, populations and transfer types will allow cross-pollination of ideas and will simplify management of transfers for health care providers.

9.3 Strengths and limitations

Strengths and limitations of each analysis are presented within the discussion sections of each chapter. Here, the strengths and limitations of this thesis as a whole are considered.

This thesis provides novel data on a topic which has received minimal attention from researchers up to this point, the transfer between PHC facilities of stable patients with chronic conditions. As mentioned above, work on transfers to this point has generally been done within specific silos. A strength of this work is that it involves different population groups, different diseases and differentiates different types of transfer. In this way, the thesis begins to leverage and coalesce information on patient transfers across health conditions and populations to develop a multi-faceted view of transfers. Having said this, the thesis involves two health conditions and in terms of populations, includes general adults and postpartum women and is focused on one setting; as discussed above, there are differences in relation to transfers based on these and other factors and research is required on transfers among people with other conditions, in other populations and in other locations.

The thesis makes use of province-wide routinely collected data from the National Health Laboratory Service (NHLS) for two analyses, data from a randomised controlled trial (RCT) for two analyses, and data obtained via data abstraction from medical records for one analysis. The NHLS data is from a well-maintained database with minimal missing data and allows tracking of patient movement across the province (119). However, as this is data meant for patient care and not research, available variables were limited, particularly for potential confounders. Use of data from an RCT for a quantitative and qualitative analysis, and from a review of medical records allowed more detailed analyses, although the record review is subject to what information was documented in patient files. Overall, these data sources have allowed a high-level overview of transfer patterns across the province for diabetes and HIV, and a more detailed understanding of transfers in a specific population i.e., postpartum women. In particular, the qualitative findings have allowed a better understanding of the quantitative results.

Another strength of the thesis is that it is set in a location with a high prevalence of both HIV and diabetes (120,121). However, a limitation related to the setting includes that the four analytic chapters are conducted within populations from one province in South Africa. The findings may not be directly generalisable to other settings but should be applicable to similar setting in South Africa and sub-Saharan Africa, particularly those with high levels of mobility. In addition, ideas regarding the overall approach to transfers may be applicable beyond these settings. Due to the higher volume of research on transfers among PLH compared to PLD, this thesis is able to provide more recommendations for HIV programmes than for diabetes programmes, and these results show the importance of further research regarding transfer among PLD.

An important limitation of this thesis is a lack of data on co-morbidities in PLH and PLD. PLH and PLD have high rates of multimorbidity which may complicate management (122–124). Depending on the setting, people with multimorbidity may have to see multiple health care providers. Transfers among people with multimorbidity are an important avenue for future research.

9.4 Recommendations for policy and future research

These findings provide insight into the volume of transfers among people with chronic conditions attending PHC, the associations between transfers and treatment outcomes and possible reasons for poor outcomes. Based on this evidence, this section will outline recommendations for policy and future research priorities.

9.4.1 Policy recommendations

When viewing the findings of this thesis as a whole, three main policy recommendations emerge regarding the need for: 1) Monitoring and reporting of the frequency and outcomes of transfers as part of programme outcomes, 2) Follow-up and support of patients who transfer, and 3) Improved guidance regarding transfer management.

9.4.1.1 Monitoring and reporting of the frequency and outcomes of transfers as part of programme outcomes

In many countries, HIV monitoring systems monitor and report patient outcomes using a cascade of care approach, where the numbers officially transferred out are reported but not their outcomes (125–127). In addition, the number of silent transfers is not reported. Numerous variations to the traditional cascade have been proposed. For example, the realisation that people may disengage and re-engage in care numerous times, referred to as cycling in and out of care, has led to proposed modifications to allow people to re-enter the cascade after disengaging from care (Figure 9.4) (128). Cascades by their nature present data at the level of a specific cohort e.g., at the level of a facility, district, or province; people who transfer out move into another cohort/cascade and are not followed up as part of the original cascade (125,129,130). The modified cascade in Figure 9.4 allows people to disengage and re-enter care. However, people may disengage and then re-enter care at a different facility, but the cascade does not account for these participants. Considering the relationship between transfers and disengagement discussed in section 9.2.4 above, not accounting for transfers when assessing disengagement presents an incomplete picture. For example, patients who disengaged in Figure 9.4 may have silently transferred to another facility and may subsequently re-engage in the original facility/cascade but this is not considered.

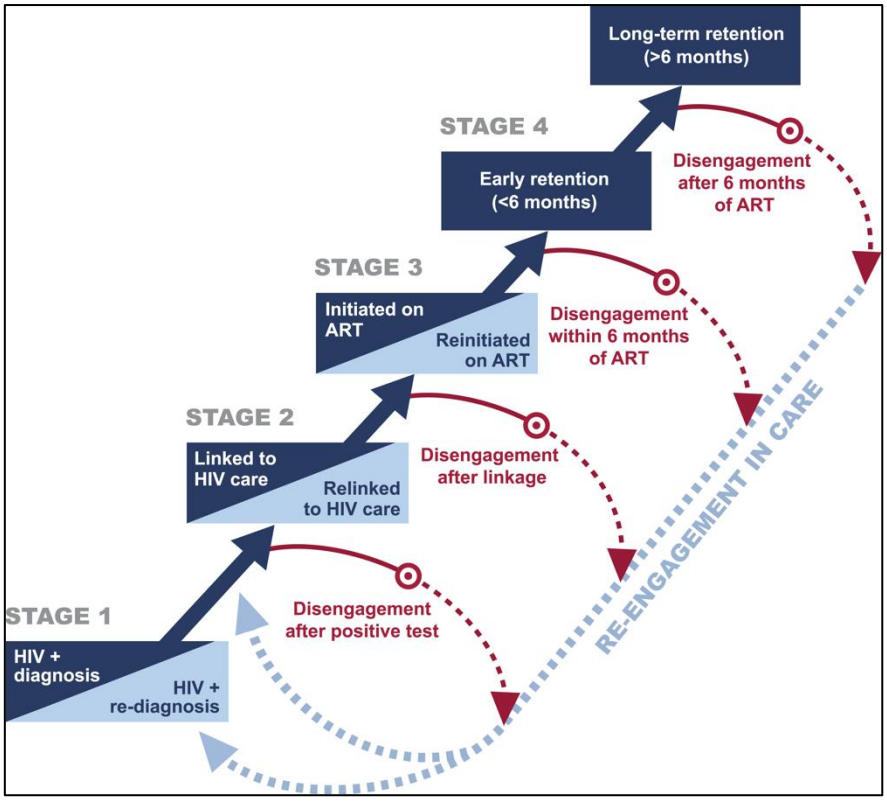

Figure 9.4 Cyclical cascade of HIV care which indicates people disengaging and re-engaging in care at the level of the cascade but does not indicate movement between facilities, from Ehrenkranz et al (128)

Reporting on outcomes of transferred patients may thus require a mechanism beyond the level of the cascade. Follow-up to determine outcomes should be easier to set up when electronic patient record systems are in use. The Western Cape has linked electronic patient information systems with unique identifiers, and clinical information from facilities across the province is consolidated into a single record for each patient (86). In such a setting, all patients captured electronically at a facility level as transferred out or lost to follow-up could be identified and their outcomes assessed. Patients who have transferred-in to another facility in the Western Cape could be identified from the electronic system. Those not found to have transferred to a different facility could have their information cross-checked with the mortality registry to identify deaths. Patients who are categorised as lost to follow-up after this process could then be flagged for more intensive follow-up. An important consideration would be who would be responsible for these tasks.

As transfers occur beyond the level of the facility, and because patients may transfer repeatedly, it may be necessary to appoint specific individuals or a specific office as responsible for this. Another factor for consideration is the level at which this process would be conducted. The percentage of patients who transfer from their province of initiation to another province ranges from 3% in the Northern Cape to 30% in Gauteng. Ultimately, the process of determining transfer outcomes would thus have to occur at a national level.

In the absence of linked electronic health data systems, determining transfer outcomes would require additional steps. In section 9.4.1.2 below, recommendations include that, to improve patient outcomes, patients who have officially transferred out or are lost to follow-up should be followed-up to assess whether they have accessed care at a different facility or require assistance doing so. This could be through telephone calls and/or home visits. Collating of the results of individual patient tracking at a facility level and reporting of these results should be considered. Again, assigning responsibility for reporting of outcomes would be important. Within TB programmes, patients transferred out from the facility at which they are registered are initially categorised as transferred out from that facility (51). The receiving facility is then responsible for following the patient up and reporting the final outcome back to the registration facility, where the patient is reclassified from transferred out to the final outcome. The initial registration facility thus remains responsible for reporting final treatment outcomes. The system of back-reporting is feasible for TB programmes as TB is treated for a limited time period and is curable, with final treatment outcomes. However, it may be possible to adapt such a system for health conditions requiring longer-term or lifelong treatment. For example, if dedicated individuals or offices were appointed to determine outcomes at a programme level, facilities could submit their lists of transfers-out and lost to follow-up patients together with the results of their tracing efforts to these appointees. Simultaneously, facilities could submit lists of patients transferring into their facilities to the same office, who could cross-reference these lists and update patient outcomes. Patients with unknown outcomes could then be identified and flagged for more intensive follow-up. This system would require reliable use of unique identifiers e.g., national identifiers.

The results of this thesis show that programme outcomes cannot be understood without considering transfer outcomes. While it would not be possible to determine outcomes for all patients, even determining outcomes to a certain extent e.g., reporting of results at facility, district or provincial levels would improve our understanding of programme outcomes.

For PLD, most countries do not have cohort monitoring systems and there are calls for these to be established (47,49). Any systems that are established should include mechanisms to monitor transfer numbers and outcomes. South Africa plans to implement a national electronic health information system with a unique patient identifier which would allow easier identification of transfer outcomes (87). It is vital that roll-out of such a system includes plans for monitoring and reporting of transfer outcomes.

9.4.1.2 Follow-up and support of patients who transfer

PLH who transfer should be followed-up to prevent or minimise disengagement and reduce the occurrence of viraemia. Patients who officially transfer should be followed-up to determine whether they attended the receiving facility and to provide support, if necessary. In national guidelines, tracing of patients who officially transfer is recommended only for patients being linked to care post-HIV testing and for patients who are down-referred who miss their visits at the receiving facility, but not for other transfers (35,90,131). Tracing should be extended to other patients who transfer including patients on ART who transfer between PHC facilities. In addition, follow-up should be considered prior to missed visits in order to prevent disengagement if possible.

National guidelines also recommend tracing of patients who have not transferred out who miss their scheduled visits (34–36,90,108,116,118). This would identify patients who silently transferred or are in the process of silently transferring. Follow-up of people who miss visits and of patients who officially transfer out should be done rapidly to reduce the time spent out of care.

PLH may also disengage due to negative interactions with health care providers and dissatisfaction with health care services, leading to silent transfers. Patients who silently transfer may then be turned away from facilities. Guidelines state that no patient without

ART should be turned away without receiving care; application of this principle to patients who do have ART should be considered. In addition, health care worker training regarding the importance of attending to patients who silently transfer is required. Further, considering the risk of poor outcomes associated with silent transfers and that silent transfers may be caused by the actions of health care workers, actions to reduce the occurrence of silent transfers for this reason are required. The results of this thesis also indicate that disengagement should be prevented among PLD transferring between PHC facilities. Further research is required to understand the reasons for disengagement among people living with diabetes who transfer to develop appropriate strategies.

To provide comprehensive care, providers should also enquire about the reasons patients transfer and other problems that may affect patient health. As documented in Chapter 9, patients may transfer for numerous reasons e.g., perceived stigma and relationship difficulties including abuse. These factors may also affect engagement in care and should be addressed.

9.4.1.3 Detailed guidance regarding management of transfers

Clearer and more detailed guidelines are required for management of transfers. Management of silent transfers is largely overlooked in South African national guidelines. Silent transfers should be avoided, if possible, particularly if caused by actions of the health system e.g., health care provider attitudes. However, as demonstrated in Chapter 8, postpartum women living with HIV sometimes experience unforeseen circumstances leading to silent transfers. Other studies have also documented unforeseen circumstances leading to silent transfers among general adults, including reasons related to their livelihoods, and a certain number of silent transfers are thus unavoidable (1,74). Guidance is required on the management of patients without referral letters who do and do not have ART. For both official and silent transfers, guidelines should include information on the important aspects of clinical history, examination and investigations that are required. In addition, methods to obtain clinical history should be addressed including use of electronic health records when available. Determining the best ways to manage transfers will require further research. However, in the meanwhile development of consensus documents by experts should be considered. Further, guidelines on transfers are currently found in separate documents, and

recommendations differ based on the type of transfer, the health condition, and the population (3,34,35,89,90,116,117). Overall, guidance for health care providers should be consolidated and simplified.

9.4.2 Future research priorities

This thesis indicates numerous important avenues for future research. Based on the results of Chapter 4 as well as prior research, it is clear that rates of transfer are high, and that transfer is associated with poor outcomes in general adults living with HIV. Further research is required to understand the reasons for poor outcomes among PLH who transfer including qualitative research to understand the experiences of transfer for both health care providers and patients and to identify barriers to successful transfer. Among postpartum women living with HIV, numerous barriers to successful transfer were identified in Chapter 9 including a lack of information on where they could transfer to and transfer processes. Among both general adults and postpartum women, development and testing of possible interventions to improve transfer outcomes are required, including strategies to reduce disengagement in those who transfer.

In Chapter 6, it was shown that transfers between PHC facilities among PLD occur frequently and are associated with poor outcomes. However, little is known regarding why PLD transfer between PHC facilities, or the reasons for poor outcomes. Research to determine reasons for transfer, and the experiences of transfer for patients and providers are required to better understand transfers among PLD. In addition, the occurrence of silent transfers has been well-documented among PLH, this has not been investigated for other conditions. Research should be done to understand transfer processes in PLD including the occurrence of silent transfers. For both PLH and PLD who transfer, disengagement appears to play a role in the development of poor outcomes and strategies to prevent or reduce disengagement should be investigated. Lastly, research on transfers among people with other common chronic conditions should be conducted.

9.5 Conclusions

This thesis investigated transfers between PHC facilities among people with chronic conditions in South Africa. The topic of transfers between PHC facilities has hitherto received minimal attention from researchers and policymakers. The data presented in this thesis contribute two results that are both novel and have implications for the health system. First, transfers between PHC facilities occur frequently and are associated with poor outcomes. Considering the volume of transfers and the associated risks outcomes, this thesis speaks to the need for the implementation of systems to monitor and report the number and outcomes of transfers. Second, transfers between PHC facilities occur at similar rates and are associated with poor outcomes for two different chronic conditions, HIV and diabetes. This suggests that research on transfers is required for other chronic conditions.

Findings from this thesis also deepen our understanding of the reasons for transfers, transfer processes and the mechanisms of poor treatment outcomes among people with chronic conditions who transfer and provide a basis for developing potential strategies to improve transfer outcomes. Disengagement likely contributes to the occurrence of poor outcomes among PLH and PLD who transfer, particularly among silent transfers and strategies to prevent or reduce disengagement are required. Silent transfers may be at increased risk of poor outcomes. It is not possible to completely prevent silent transfers as they may occur due to unforeseen circumstances. However, silent transfers may also occur due to the actions of the health system including poor relationships between patients and health care workers. Strategies to prevent silent transfers caused by the health system and to manage them appropriately when they occur are required. Transfers among postpartum women living with HIV have previously been associated with disengagement and viraemia and the results of this thesis can be used to inform numerous potential interventions to improve outcomes post-transfer in this population including provision of comprehensive information regarding transfer options and processes post-delivery and ongoing counselling and disclosure support to prevent transfers to facilities far from their residences. Current guidelines regarding transfers between PHC facilities are inadequate; this likely reflects the lack of research on management of these transfers. Studies assessing comprehensive

approaches to the management of patients transferring between PHC facilities are required. Lastly, another novel finding that warrants further attention is disengagement of stable patients transferred from PHC facilities to differentiated service delivery models. Considering the scale up of differentiated service delivery models particularly in LMIC, understanding why this occurs and how to prevent it is vital.

Ultimately, transfers between PHC facilities require attention if we are to provide chronic services that address patient needs, facilitate long-term engagement in care and improve outcomes. While transfers have previously been dealt with in a siloed fashion, this thesis advocates for a unified and consolidated approach to transfers.

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Chapter 10: Appendices

10.1 Ethical approvals

10.1.1 University of Cape Town Human Research Ethics Committee approval for this thesis: initial approval

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

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

30 October 2020

HREC REF: 503/2020

Prof L Myer
Division of Epidemiology & Biostatistics
5th Floor, Falmouth Building -FHS
Email: landon.myer@uct.ac.za
Student: jasanthaodayar@gmail.com

Dear Prof Myer

PROJECT TITLE: PATTERNS, PREDICTORS AND OUTCOMES OF PATIENT TRANSFER IN PUBLIC SECTOR CHRONIC PRIMARY CARE SERVICES-PHD CANDIDATE DR JASANTHA ODAYAR

Thank you for your response letter dated 12 October 2020, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

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

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 October 2021.

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

The HREC acknowledge that the student: - Dr Jasantha Odayar will also be involved in this study.

Please quote the HREC REF in all your correspondence.

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

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

HREC/REF:503/2020sa

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/REF:503/2020sa

10.1.2 University of Cape Town Human Research Ethics Committee approval for this thesis: current approval

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/10/2024
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	11/10/2023

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

Comments to PI from the HREC
Thank you for the further document

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	10 October 2023		
HREC REF Number	503/2020	Current Ethics Approval was granted until	30 October 2021
Protocol title	Patterns, predictors and outcomes of patient transfer in public sector chronic primary care services		
Protocol number (if applicable)	Protocol version 4.0		
Are there any sub-studies linked to this study?		☐ Yes	✓ No
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Professor Landon Myer		

HUMAN RESEARCH ETHICS COMMITTEE
11 OCT 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

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

Department / Office Internal Mail Address	Division of Epidemiology & Biostatistics, 5th Floor Falmouth Building, Faculty of Health Sciences

1.1 Does this protocol receive US Federal funding?	☐ Yes	✓ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-submission@uct.ac.za)	☐ Yes	☐ No

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Ethics Renewal Fee

Please **(tick ✓)** appropriate box for billing purposes:

Submission Type	*Description*	*New fee (Vat Incl.)*	*tick ✓*
Research funded solely from UCT departmental/ divisional/group budget	Annual evaluation of research progress report for re-certification	**R0,00**	☐
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Annual evaluation of research progress report for re-certification	**R0,00**	✓
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R7000,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Expedited review	**R3 710.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R6000.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National Grant funded research for Annual evaluation of research progress report for re-certification for Expedited review	**R1 500.00**	☐

NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from these charges.

Please provide details for Invoicing, either complete section 1 or 2 :

1. Invoice billing – Directly to Sponsor

Sponsor's name	
Billing Address of Sponsor:	
Vat Number:	

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

Contact person	
Telephone number	
Email Address	
2. **Internal Journal Billing:**	
Fund Number:	
Cost Centre Number:	
Account Holder Name:	
Division of Account Holder:	

2. List of documentation for approval

PhD Protocol Version 4.0 (March 2022)

3. Protocol status (tick ✓)

☐	Open Enrolment
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
✓	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	0
Number of participants enrolled, since last HREC Progress report (continuing review)	0
Additional number of participants still required	0

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	0

6. Cumulative summary of participants

Total number of participants who provided consent	**0**
Number of participants determined to be ineligible (i.e. after screening)	0
Number of participants currently active on the study	0
Number of participants completed study (without events leading to withdrawal)	0
Number of participants withdrawn at participants' request (i.e. changed their mind)	0
Number of participants withdrawn by PI due to toxicity or adverse events	0
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	0
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	0
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	0

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
Data analysis is complete and the manuscripts for the 5 PhD objectives have either been published submitted to journals. The final PhD thesis is being complied.

8. Protocol violations and exceptions (tick ✓ all that apply)

✓	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

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

✓	No Prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
NA

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	✓ Not applicable
If yes, please describe:		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	☐ No	✓ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	✓ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	☐ No

If yes, please explain:

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
✓	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.

13. Insurance

Please confirm that valid no fault insurance is still in place? (tick ✓)			
☐ Yes	☐ No	✓ Not Applicable – N/A	
If yes, please complete the following:			
Insurer's name:			
Policy no.		*Coverage Period:	
For UCT sponsored studies please liaise the Insurance office via fhs.sponsorship@uct.ac.za regarding the required documentation and information required obtain a renewed UCT No-fault Insurance Certificate.			

14. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	✓ No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

15. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	10.10.2023

10.1.3 University of Cape Town Human Research Ethics Committee approvals for the PACART trial: initial approval

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

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

17 April 2015

HREC REF: 194/2015

Prof L Myer
Epidemiology & Biostatistics
Public Health & Family Medicine
Falmouth Building

Dear Prof Myer

PROJECT TITLE: POSTPARTUM ADHERENCE CLUBS FOR ANTIRETROVIRAL THERAPY (PACART)

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

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

Approval is granted for one year until the 30th April 2016.

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

Please quote the HREC REF in all your correspondence.

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

Yours sincerely

pp TuBurgess

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki guidelines.

HREC 194/2015

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 194/2015

10.1.4 University of Cape Town Human Research Ethics Committee approval for the PACART study: study closure report

UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE
27 JAN 2021
HEALTH SCIENCES FACULTY

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS010: Study Closure Report

HREC office use only (FWA00001637; IRB00001938)			
Noted and filed. This serves as acknowledgement that this study is closed.			
☑ Approved	Study closure report		
☐ Not Approved	Study closure report		
Chairperson of the HREC signature/Designee		Date	30/1/24

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown

1. Principal Investigator to complete the following:

Date (when submitting this form)	21 Jan 2020
HREC REF Number	194/2015
Protocol Title	Postpartum Adherence Clubs for Antiretroviral Therapy
Protocol number (if applicable)	Protocol version 5, 01 March 2020
Principal Investigator	Professor Landon Myer
Department / Office Internal Mail Address	5th Floor Falmouth Building, Division of Epidemiology and Biostatistics, School of Public Health & Family Medicine

2. Please confirm (tick ✓)

This study is closed to enrollment	✓ Yes	☐ No
Participants have completed all research-related interventions	✓ Yes	☐ No
Participants have completed all research-related follow-up	✓ Yes	☐ No
Data analysis is complete	✓ Yes	☐ No
Your sponsored protocol is closed	✓ Yes	☐ No

If you answered 'no' to any of the above questions, you must keep your study open until all research activity is completed.

3. What is the reason for closing the study? (tick ✓)

Research completed	✓	No time	
Terminated due to toxicity/adverse event		PI left UCT or affiliated sites	
Slow accrual		Insufficient funding	
Loss of interest		Research never began	
Other. Please specify:			

4. For clinical trials, please describe the arrangements for provision of care after research, including (where applicable) post-trial access to the investigational product.

Not applicable

5. Please explain how the research findings have been disseminated to participants, communities, and/or stakeholders.

Results were presented at the Conference for Retroviruses and Opportunistic Infections 2020. A manuscript of the primary finding has been drafted and is being finalized for submission to a medical journal. Results will be presented at the next Western Cape Provincial Research Day and at the next Gugulethu community health centre health promotion event.

6. Please confirm (tick ✓)

Have you submitted a final report to the Provincial Health Research Committee?	☐ Yes	☐ No	✓ N/A
Please note: Researchers must submit final reports to the relevant research co-ordinator/research directorate at City Health Department, GSH, RXH, TBH, PGWC (for non-tertiary hospitals) within six months of completion of the study and may be required to report the findings of the study to other relevant authorities including the PHRC.			

7. Please indicate how, and for how long, the data will be stored and protected.

Research data will be stored for 5 years post-study closure. Participant files and other study documentation will be archived and stored by Metrofile with potential access restricted to the PI.

8. Please list or attach any papers, abstracts, presentations or other outputs generated from this study.

Odayar J, Malaba TR, Allerton J, Lesosky M, Myer L. Delivery of Antiretroviral Therapy to HIV-Infected Women During the Postpartum Period: The Postpartum Adherence Clubs for Adherence Clubs for Antiretroviral Therapy (PACART) Trial. *Contemporary Clinical Trials Communications*.

Odayar J, Lesosky M, Malaba TR, Kabanda S et al. Differentiated Care for Postpartum ART In South African Women Living with HIV: An RCT. In: Conference on Retroviruses and Opportunistic Infections, Boston, USA; 2020.

9. Signatures

Signature of PI		Date	25 January 2021

10.1.5 University of Cape Town Human Research Ethics Committee approval for the TRAC trial: initial approval

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

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 404 7682 • **Facsimile** [021] 406 6411
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

24 October 2016

HREC REF: 764/2016

Prof L Myer
CIDER
Public Health & Family Medicine
Falmouth Building

Dear Prof Myer

PROJECT TITLE: TIMING OF REFERRAL TO ADHERENCE CLUBS (TRAC) (MPH & PhD-candidate Dr J Allerton) sub study linked to 194-2015

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

It is a pleasure to inform you that the HREC has **formally approved** the proof of concept for phase 1 of the above-mentioned study.

Approval is granted for one year until the 30th October 2017.

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

We acknowledge that the student Dr J Allerton will be involved in this study.

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

Please quote the HREC REF in all your correspondence.

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

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 764/2016

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 764/2016

10.2 Supplementary materials for Chapter 3

Supplementary table 10.2.1 Summary of transfer recommendations (n = 38 documents)

#	Document name	Source	Date	Category	Recommendations regarding transfer process
1	2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates, Version 3 (1)	HIVCS website	June 2023	HIV testing, management and/or prevention	- States that while referral letters are helpful, patients cannot be required to leave the facility without treatment to obtain a referral letter Indications for referral provided: - In pre-ART patients o e.g. opportunistic infections needing urgent care o screen for pregnancy to allow early referral to antenatal care - In patients with virological failure, consult an expert or refer if possible - If mental health disorder suspected and further care cannot be provided, refer to a psychiatric service
2	Abacavir/Lamivudine 120mg/60mg Dispersible, Scored Tablets – Training slides (2)	HIVCS website	2021	HIV testing, management and/or prevention	Nil
3	Abacavir/lamivudine (ABC/3TC) (120mg/60mg) dispersible scored tablets (3)	HIVCS website	2021	HIV testing, management and/or prevention (Circular)	Nil
4	Access to comprehensive HIV & AIDS care including antiretroviral treatment (4)	HIVCS website	May 2005	HIV testing, management and/or prevention (Circular)	Patients should not be denied ART because they do not have a South African ID document. No recommendations regarding transfer.

5	Adherence guidelines: Education on Illness and Treatment (5)	HIVCS website		Adherence - applicable to HIV, TB and NCDs	- Emphasises patient role in retention in care:
					  - If difficult to continue treatment at their clinic (e.g. relocation), patient should inform clinic and request a transfer letter.
					  - To facilitate linkage to care, patients diagnosed with a condition should discuss with HCW which facility they should be referred to for further care. Patients should then ensure that they attend the agreed upon facility.
					
					Indication for referral: Refer people with mental health or substance abuse problems or who miss appointments for support.

6	Adherence guidelines for HIV, TB and NCDs – Policy and service delivery guidelines for linkage to care, adherence to treatment and retention in care (6)	Suggested by an NDOH official	Februa ry 2016	Adherence - applicable to HIV, TB and NCDs	Travel
					
					- Adherence counselling should include what to do if travelling
					  o Patients to inform clinic of travel plans before leaving including duration and destination and should receive a referral letter and sufficient treatment
					  o If trip unplanned and patient cannot inform their clinic before travelling, they should carry evidence of their diagnosis and treatment, and should attend the nearest facility when they arrive at their destination to ensure they can access treatment.
					
					Use of transition:
					
					- To indicate movement between steps in the treatment cascade (screening, testing, enrolment in care, treatment eligibility, treatment initiation, treatment stabilisation and regular). Linkage required to move from step 1 to 2. Transfer may be required between other steps but not mentioned.
					- Patients with chronic conditions should receive care at PHC level with transition to assisted self-management in the community.
					- Transition between childhood and adolescence.
					
					Tracing
					
					- Support for linkage, adherence and retention in care includes tracing for missed appointments:
					  o Inform patients of the tracing system and request consent for tracing
					  o Obtain address and contact number and update every visit
					- Early missed appointments for patients in HIV, TB and NCD programmes should be traced
					  o Patients who have missed appointments can be identified through the appointment book, diary or electronic system e.g. Tier.net

					○ Pre-treatment patients who have missed active referral or linkage to care by >5 days should be traced - Tracing of referrals: ○ Active referrals involve making an appointment or accompanying the patient to the appointment including for co-located services and enrolment into linkage to care ○ Provide appointment date and time that is convenient for patient ○ Record appointment date in database or logbook ○ Patients who test HIV positive should be entered into HCT appointment register ○ Provide information on patients who are scheduled to link to care with the receiving facility - Tracing of missed appointments ○ SMS/phone patient and involve CHWs to trace patient if unsuccessful - Patients who return after tracing should receive additional psychosocial support - Use of a national unique identifier should allow tracking of linkage and patient movement between facilities Linkage to care: - Increased access to testing must be accompanied by improved linkage to care. - interventions to support linkage include: ○ Enhanced post-test counselling ○ Peer support ○ Tracing ○ Monitoring of linkage Monitoring and evaluation of linkage to care - Consider reporting the number of patients eligible who linked to care within 30 days and tracking of patients who have not linked to care at district and provincial level - Linkage to care should be discussed at district management meetings
7	Adult Primary Care, Symptom-based integrated approach to the adult in primary care (7)	NDOH website	2019/2020	Clinical management of common conditions including HIV	Indications for up-referral or referral for additional support/counselling in PLH - Refer to doctor if ART regimen should be switched - If poor adherence/attendance or unsuppressed VL, refer to adherence counsellor, support group, treatment buddy, community care worker - Urgency of referral sometimes specified e.g. If Cryptococcal antigen positive and symptomatic,

					refer urgently - Sometimes says refer without specifying to whom Use of linkage: PLH who are unwilling to start ART should be linked to counselling
8	Availability of combination tablets for atazanavir/ ritonavir and darunavir/ritonavir (8)	HIVCS website	2020	HIV testing, management and/or prevention (Circular)	Nil
9	Changes in the prescription of progestin subdermal implants (Implanon) in women who are taking enzyme inducing drugs such as efavirenz for HIV, rifampicin for TB, and certain drugs used for epilepsy (carbamazepine, phenytoin, and phenobarbital) (9)	HIVCS website	Octobe r 2014	HIV testing, management and/or prevention (Circular)	Nil
10	Standard operating procedures – Minimum package of interventions to support linkage to care, adherence and retention in care (10)	NDOH website	2020	Adherence - applicable to HIV, TB and NCDs	As for row 6 (Adherence guidelines for HIV, TB and NCDs)

11	Changes in regime for HIV positive pregnant women and note on those with a psychiatric illness (11)	HIVCS website	March 2012	HIV testing, management and/or prevention (Circular)	Nil
12	District Health Management Information System (DHMIS) Policy (12)	NDOH website	2011	Health facility or health system management	Nil
13	Dolutegravir (DTG) interactions - A guide for health care workers and patients (13)	HIVCS website	2020	HIV testing, management and/or prevention	Nil
14	Guideline for the Prevention of Mother to Child Transmission of Communicable Infections (14)	HIVCS website	November 2019, Updated 2020	Care of specific patient populations, including management of HIV	- Use of transition: Mothers at postnatal clubs transition to standard clubs after 18 months - Use of referral and transfer: All women living with HIV should be referred to a CHW to support adherence, breastfeeding and retention pre- and post-delivery. Postpartum women with HIV should also be linked to a CHW, support group/club, mentor mother. - No patient on ART who reports to have run out of treatment but doesn't have a transfer letter should be turned away - Emphasises linkage to care of women and children who test HIV positive. - When discharged post-delivery, provide transfer-out letter if woman will receive ART elsewhere - Pregnant women already on ART who move to collect their ART at ANC must be recorded as transferred-out from their former clinic, and not lost-to-follow-up - Indications for referral e.g. failing second-line regimens - Indications provided for CHWs caring for women at home to refer them to the clinic

15	Ideal clinic manual, version 19 (15)	NDOH website	April 2020, Updated May 2021	Health facility or health system management	As for row 16 (Ideal community health centre manual, Version 1)
16	Ideal community health centre manual, Version 1 (16)	NDOH website	Apr 2020, Updated Apr 2022	Health facility or health system management	Use of terms - Handover used in terms of handing over patients from facility to EMS and handover between shifts. - Transfer used in terms of movement of patients between facilities via EMS. - Referral used in terms of ensuring access to full range of health professionals. - Referral system should aim to ensure continuity of care between different levels of the health service. The following should be available: o National referral policy o District SOP for the referral system ▪ Services provided onsite should be differentiated from those that require referral to other facilities. ▪ Facility SOP should describe referral paths to obtain access to services unavailable at the facility. ▪ Include names and contact details of facilities to which patients should be referred for specific services. ▪ List of referral pathways should be made and displayed. o Referral register which should record all referred patients. o Copy of referral letter in the patient record. - HCWs should be trained on how to refer patients. - Referral forms should be completed when a patient is referred. A copy should be given to the patient and a copy kept in the patient record. Ensure sufficient stock of referral forms. Checklist to ensure required items included on referral form included. - Audit of patient files should include at least one patient who was referred to another facility: a copy of the referral letter should be in the patient record. - Facilities should make referrals to and receive referrals from school health services, home- and

					community-based services and environmental health services. - Facilities should refer to social development when necessary. - Facility must have access to emergency medical services transport and referred patients should be entered on a specific register. - Defaulting patients should be referred for tracing and to adherence counsellors
17	Implementation of the universal Test and Treat strategy for HIV positive patients and differentiated care for stable patients (17)	HIVCS website		HIV testing, management and/or prevention (Circular)	Successful implementation of Universal Test and Treat requires linkage to care, adherence to treatment and retention in care.
18	Integrated clinical services management (18)	NDOH website		Health facility or health system management	- Use of transfer, refer and link: o Refer and transfer used interchangeably e.g. patients who need admission or further management should be referred/transferred to hospital o Transfer and refer also used when discussing movement from clinical care rooms to the appointment desk within a facility o CHWs serve as link between facility and community Facility reorganisation - Integrated clinical services within PHC should result in strengthened up- and down-referral and improved coordination of care between clinics and community. - Prior to implementation services provided at the facility should be differentiated from that that patients need to be referred or transferred for. - Facilities will have four streams: acute episodic care/minor ailments, chronic care, preventive/promotive care and health support services. - Patients referred from community screening to the PHC facility will enter the acute episodic care/minor ailments stream and will be referred to the hospital as needed. - Unstable patients in the chronic care stream should be referred to the doctor. If unstable/uncontrolled after 3 months, they should be referred to hospital.

					- To improve flow, transfer forms should be available in all consultation rooms Screening - Screening services should be provided at strategic points and identified patients referred appropriately - Similarly, patients identified as high-risk by integrated school health teams should be referred appropriately. Down-referral - Health service reorganisation includes down-referral of stable patients with chronic conditions to the central chronic medicine distribution and dispensing unit (CCMDD), facility-based medication collection or adherence clubs. - If there is no CCMDD, down-refer to the CHW. - Down-referred patients who do not attend their appointment should be traced. - Indications provided for referral back to the facility from CCMDD - Process of down-referral to CHW also described
19	Introduction of dolutegravir in the ARV programme (19)	HIVCS website	February 2020	HIV testing, management and/or prevention (Circular)	Transition used in terms of changing drug regimens e.g. transition of patients from an EFV-based regimen to a DTG-based regimen. No recommendations regarding transfer.
20	National Adolescent and Youth Health Policy 2017(20)	NDOH website	2017	Care of specific patient populations, including management of HIV	Referral systems - If sexual and reproductive health services are not integrated with HIV/AIDS and TB, strong referral services are required to facilitate access to these services. - Referral systems will be improved by implementation of a national unique patient identifier allowing a single patient electronic health record. Linkage and referral - Youth who are tested for HIV should be linked to prevention and care. - Interventions to address violence and substance abuse should be implemented at schools with referral when necessary. Refer for social assistance when required.

21	National Consolidated Guidelines for the Management of HIV in Adults, Adolescents, Children and Infants and Prevention of mother-to-child transmission (21)	NDOH website	Februa ry 2020	HIV testing, management and/or prevention	Linkage to care
					
					- Patients who have been tested for HIV should be actively referred and linkage should be confirmed
					  o Active linkage - provide appointment date and referral slip
					  o If test negative - actively refer/link to prevention services
					  o If test positive - actively refer/link to treatment services
					- Provide post-test counselling to facilitate linkage to care
					- If possible:
					  o those who test HIV positive during community-based testing should be linked to a CHW
					  o those who test HIV positive during facility-based testing should be accompanied to the ART initiation services and introduced to receiving facility
					- Clear communication and referral pathways should exist between testing sites and sites for follow-up care. Logbooks and appointment systems should be used, and missed appointments should be traced.
					
					Linkage to care post-HIV testing for patients diagnosed in the community or workplace:
					
					- Provide enhanced post-test counseling
					- Actively refer (appointment for specific date and time and provision of referral letter).
					- Inform regarding tracing system, request consent for tracing and obtain accurate contact details.
					- If possible, CHW or peer navigator to accompany patient to appointment.
					- List of names and appointment dates should be given to the receiving facility.
					- Logbooks should be used to monitor linkage to ART initiation services.
					- Patients who miss appointments by >5 days should be identified and traced
					- Those who attend the facility after being traced should receive additional psychosocial support.
					- For key populations and patients who previously tested but did not initiate ART, who seem reluctant to start or who tested or initiated ART in hospital consider:
					  o Peer navigation to ART initiation service.
					  o Weekly telephonic follow-up until ART initiated and home visit if needed.
					- Patients diagnosed in a health facility, should be accompanied to ART initiation services and introduced to the HCW.
					
					- HIV self-screening test kits should include information for how and where to link to care and should include a referral card.

					- If HIV self-screening test is positive and this is confirmed by a trained HCW, patient should be referred for treatment - Differentiated service delivery approaches to HIV testing should include linkage information, referral card, HIV self-screening distributor contact information, national hotline support. The following is mentioned regarding transfer: - Patients on ART who have run out of treatment and present without a transfer letter should never be turned away. Indications for up-referral provided - Pre- ART initiation e.g. symptoms of meningitis - In patients on ART e.g. immune reconstitution inflammatory syndrome - Referral for support in patients with high viral loads and/or poor adherence - For referral to third-line committee in adults on second-line ART with confirmed virological failure Prevention of mother-to-child transmission of HIV - Women testing HIV-positive at any stage should be encouraged to link to care and treatment. - All women living with HIV should be referred to a CHW for support of adherence retention and breastfeeding before and after deliver - Pregnant women on ART who collect their ART at ANC should be documented as transfer-out from their former clinic, and not lost-to-follow-up - At postnatal visit, provide transfer-out letter if woman will receive their ART at a different clinic - Post-delivery, mothers on ART should be linked to mom-connect, a CHW, a mentor mother, or a support group/club if available.
22	National Digital Health Strategy for South Africa (2019 – 2024) (22)	Suggested by an NDOH official	2019	Health facility or health system management	Digital priorities include - Development of a complete electronic health record - Development of an integrated platform for health information systems that will allow interoperability and linkage of current patient-based systems. o This will allow safe sharing of health information across services

					- A unique identifier to facilitate movement of patients within and across provinces
23	National HIV self screening guidelines (23)	HIVCS website	2018	HIV testing, management and/or prevention	- HIV self-screening should be offered with referral and linkage to treatment and prevention services. - Referral and linkage information including the need to confirm positive results should be made available to those using the test and to communities. - Patients who test HIV positive should be linked to confirmatory testing. If confirmed positive, patients should be referred for treatment. - If results non-reactive refer and link to prevention services - Linkage strategies after HIV self-screening include provision of linkage information through: o Information material including manufacturer's instructions, brochures and flyers distributed with HIV self-screening kits o A telephone hotline o SMS or smartphone applications o Community follow-up by peer and/or outreach workers o Post-screen counselling an assistance with referral by community health workers o Pharmacists to ensure that people buying self-screening kits at pharmacies have referral and linkage to care information - Monitoring and evaluation should include assessment of linkage to services
24	National HIV Testing Services: Policy (24)	NDOH website	2016	HIV testing, management and/or prevention	- HIV testing should be accompanied by linkage to HIV prevention, treatment and care services o People testing HIV positive ▪ actively link/refer to treatment and care with appointment for specific date and time ▪ counselling should include discussion of barriers to linkage to care o People testing HIV negative ▪ link to preventive services - active linkage recommended ▪ counselling should include screening for PREP eligibility and linkage to PREP initiation services if eligible - Home-based HIV testing services (HBHTS): o Availability of referral services should be considered when implementing HBHTS. o HBHTS should include follow-up on linkage to care. - Specific populations o Importance of linkage post-HIV testing emphasised for pregnant women, populations abusing alcohol and drugs, key populations and couples. o For populations abusing alcohol and other drugs, peer support improve linkage to care among people abusing alcohol and other drugs who test HIV positive. - PREP services

					○ Patients who test HIV positive before or after PREP initiation should be linked/referred to care and treatment - Monitoring of HIV testing services should include indicators of referral to appropriate services e.g. TB screening, STI treatment, ART
25	National Strategic Plan for HIV Prevention, Care and Treatment for Sex Workers (25)	HIVCS website	2013	Health facility or health system management	- Use of linkage: sex workers should be linked to sex worker organisations and other services - HIV-related services for key populations at non-clinical sites include referral. - Community-based organisations should be capacitated to provide preventive services and refer to care, support and treatment. - Referral registers are a data source for indicators used to monitor the programme
26	National Strategic Plan for HIV, TB and STIs 2023-2028 (26)	HIVCS website		Health facility or health system management	- Emphasises importance of improved community-based referral systems for HIV, TB and STIs - To achieve the 95-95-95 goals, improved linkage to care is required post-HIV testing. Interventions include: ○ Facilitated linkage - scheduling appointment or accompanying patients to visits ○ Development of linkage services using differentiated models of care for priority populations required ○ Linkage after self-testing and passive referrals should be facilitated for key populations - Minimum package of services for migrants, mobile populations and undocumented individuals outlined - Flexible service delivery options are required but does not specifically mention transfer
27	Recommendations for the rational use of abacavir 600mg/ lamivudine 300mg and zidovudine 300mg/ lamivudine 150mg dual combination formulations (27)	HIVCS website	2019	HIV testing, management and/or prevention (Circular)	- Nil
28	Referral policy for South African health services and referral implementation guidelines (28)	NDOH website	August 2020	Health facility or health system management	- Use of handover: process of handover between transport staff and emergency staff - Document focusses on referral between levels and types of facilities. ○ Patients should be referred to a higher/lower levels of care based on clinical status and clearly defined referral pathways. ○ Aim is to ensure access to comprehensive healthcare and maintain the continuum of

					care. - Indications for referral: o Up-refer for care that cannot be provided at the original facility o Patients who relocate may be referred to a facility at the same level of care, e.g. given of referral from one tertiary facility to another. - Provides referral principles to help determine the most appropriate health facility a patient should be referred to based on their condition including o Refer to nearest facility that can provide the required care regardless of location. o Two-way or open referral system should exist between the referring facility and receiving facility. o Initiating and receiving facility should record all outward and inward referrals in a referral register. o Appointments at receiving facility should be scheduled. o Standardised referral form should be completed and sent with patient (include name, age, gender, presenting complaint, examination findings, investigations conducted, diagnosis and treatment provided, medication being taken, special equipment required for patient, indication for referral, referring practitioner name, signature, stamp). There should be enough information for the receiving facility to continue care. A copy of the referral letter should be kept at the original facility. o Dispensed medication to be sent to referral facility for medication reconciliation. - Additional detail provided for emergency referrals, non-urgent referrals including from CHWs to PHC facilities, inter-provincial referrals, transfer to private intensive care units, private medical practitioners/specialist and hospitals, international transfers, non-urgent self-referrals, specialised services referrals and down-referrals but not for lateral referrals. Includes the following for non-urgent self-referrals: o Patients without a referral letter must be assessed, provided with treatment, counselled and referred to their nearest facility using the standardised referral form. o No patient should be refused treatment. Monitoring - Monitoring indicators include number of referrals per 100 patients, but do not specify lateral referrals.

29	South African Maternal, Perinatal and neonatal health policy (29)	NDOH website	June 2021	Care of specific patient populations, including management of HIV	- Use of linkage: Districts and institutions to promote linkage to care through community engagement. - Emphasises the importance of effective referral pathways between levels of care
30	South African National Guidelines for Medical Male Circumcision (30)	NDOH website	2016	Care of specific patient populations, including management of HIV	-
31	Standard treatment guidelines and essential medicines list for South Africa, Hospital level, Adults (31)	NDOH website	2019	Clinical management of common conditions including HIV	- Provides indications for referral for acute conditions e.g. patients with CMV require specialist or tertiary referral - Down-referral should be considered if there are social or economic barriers to adherence in people with chronic conditions
32	Standard Treatment Guidelines and Essential Medicines List for South Africa, Primary healthcare level (32)	NDOH website	2020	Clinical management of common conditions including HIV	- Indications for referral in PLHIV e.g. o If failing a second-line regimen, refer to a specialist - Indications provided for referral or linkage provided in people being screened for and on PREP - Down-referral should be considered if there are social or economic barriers to adherence in people with chronic conditions
33	Strategic Plan 2020/21–2024/25 (33)	NDOH website		Health facility or health system management	- Reconfiguration of the referral system required to reduce maternal mortality. - Emphasises integrated services delivered according to the referral policy, at the most appropriate level. - Sets target for presence of referral systems with care pathways in all 52 districts by 2024/2025
34	Switching patients from Tenofovir 300mg/Emtricitabine 200mg back onto Abacavir/Lamivudine	HIVCS website	March 2020	HIV testing, management and/or prevention (Circular)	- Nil

	and Zidovudine 300mg/Lamivudine 150mg dual combination formulations (34)				
35	Updated guidance for the use of Dolutegravir in pregnancy (35)	HIVCS website	2021	HIV testing, management and/or prevention (Circular)	Nil
36	Urgent FDC roll out (36)	HIVCS website	Feb 2014	HIV testing, management and/or prevention (Circular)	Nil
37	Use of fixed dose combinations for first and second line antiretroviral treatment regimens (37)	HIVCS website	2015	HIV testing, management and/or prevention (Circular)	Nil
38	Use of Fixed-dose combinations in place of lamivudine single agents (38)	HIVCS website	2016	HIV testing, management and/or prevention (Circular)	Nil

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10.3 Supplementary tables for Chapter 4

Supplementary table 10.3.1 Changes in ART eligibility criteria, first-line ART regimen and VL monitoring guidelines in South Africa over the study period

		April 2010	April 2013	April 2015
Eligibility	WHO stage	4	3 or 4	3 or 4
	CD4 count	200 cells/mm^3 (350 cells/mm^3 if TB/pregnant)	350 cells/mm^3	500 cells/mm^3
	Other	MDR/XDR TB	Sero-discordant couples; TB/pregnancy or breastfeeding	TB/pregnancy or breastfeeding or known HBV
Regimen	First-line	TDF, FTC or 3TC, EFV or NVP	TDF,FTC,EFV as a fixed-does combination	TDF,FTC,EFV as a fixed-does combination
	Second-line	TDF or AZT, 3TC or FTC, LPV/r	TDF or AZT, 3TC or FTC, LPV/r	TDF or AZT, 3TC or FTC, LPV/r
Monitoring	Viral load	6m, 12m and annual	6m, 12m, and annual	6m, 12m, annually

Abbreviations: 3TC, Lamivudine; ART, antiretroviral therapy; AZT, Zidovudine; FTC, Emtricitabine; HBV, Hepatitis B Virus; LPV/r, Lopinavir/ritonavir; MDR, Multidrug-resistant; NVP, Nevirapine; TB, Tuberculosis; TDF, Tenofovir diphosphate; VL, Viral load; WHO, World Health Organization; XDR, Extensively drug-resistant.

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Supplementary table 10.3.2 Transfer incidence rates including multiple transfers per individual by participant characteristics (n = 85,814)

	Number of transfers	Person-years	Incidence rate/100 person-years (95% CI)
Overall	44,712	351,844	12.71 (12.59–12.83)
Sex			
Female	33,129	242,358	13.67 (13.52–13.82)
Male	11,583	109,486	10.58 (10.39- 10.77)
Age categories			
≥16 to <20 years	866	4737	18.28 (17.09-19.54)
≥20 years to <30 years	16,405	10,266	15.98 (15.74–16.23)
≥30 years to <40 years	17,949	149,935	11.97 (11.80–12.15)
≥40 years to <50 years	6833	68,382	9.99 (09.76–10.23)
≥50 years to <60 years	2222	21,590	10.29 (9.87–10.73)
≥60 years	437	4535	9.64 (8.75–10.58)
VL at first visit			
VL ≤50 copies/mL	28,915	250,804	11.53 (11.40–11.66)
VL >50 copies/mL	15,797	101,040	15.63 (15.39–15.88)
VL at first visit			
VL ≤400 copies/mL	34,479	295,142	11.68 (11.56 – 11.81)
VL >400 copies/mL	10,233	56,702	18.05 (17.70–18.40)
VL at first visit			
VL ≤1000 copies/mL	35,510	301,359	11.78 (11.66–11.91)
VL >1000 copies/mL	9202	50 485	18.23 (17.86–18.60)
Location of first VL			
Urban	31,241	246,210	12.69 (12.55–12.83)
Rural	13,471	105,634	12.75 (12.54–12.97)
Year of first VL			
2011	13,745	113,787	12.08 (11.88–12.28)
2012	15,819	130,155	12.15 (11.97–12.34)
2013	15,148	107,903	14.04 (13.82–14.26)

Abbreviations: CI, confidence interval; VL, viral load.

Supplementary table 10.3.3 Results of mixed effects logistic regression modelling the relative odds of a VL >1000 copies/mL with disengagement defined as >18 months without a health facility visit

VL >1000 copies/mL	Adjusted OR	95% CI
Transfer during the visit interval		
No	Reference	
Yes	1.34	1.28–1.41
Sex		
Female	Reference	
Male	1.52	1.43–1.61
Age		
≥30 years	Reference	
<30 years	1.49	1.41–1.58
Location of first VL		
Urban	Reference	
Rural	1.84	1.73–1.95
Duration on ART (years)	0.91	0.89–0.92
Disengagement in the preceding visit interval (> 18 months between VLs)	2.30	2.18–2.43

Abbreviations: CI, confidence interval; OR, odds ratio; VL, viral load.

Supplementary table 10.3.4 Results of mixed effects logistic regression modelling the relative odds of a VL >1000 copies/mL with disengagement defined as >14 months without a health facility visit

VL >1000 copies/mL	Adjusted OR	95% CI
Transfer during the visit interval		
No	Reference	
Yes	1.37	1.31–1.43
Sex		
Female	Reference	
Male	1.52	1.43–1.62
Age		
≥30 years	Reference	
<30 years	1.50	1.42–1.59
Location of first VL		
Urban	Reference	
Rural	1.85	1.74–1.96
Duration on ART (years)	0.90	0.89–0.92
Disengagement in the preceding visit interval (> 14 months between VLs)	1.84	1.76–1.92

Abbreviations: CI, confidence interval; OR, odds ratio; VL, viral load.

Supplementary table 10.3.5 Results of logistic regression modeling the relative odds of a VL >1000 copies/mL restricted to visit intervals with initial VL ≤1000 copies/mL

VL >1000 copies/mL	Adjusted OR	95% CI
Transfer during the visit interval		
No	Reference	
Yes	1.70	1.61–1.79
Sex		
Female	Reference	
Male	1.39	1.32–1.47
Age		
≥30 years	Reference	
<30 years	1.55	1.46–1.65
Location of first VL		
Urban	Reference	
Rural	1.51	1.43–1.59
Duration on ART (years)	1.05	1.03–1.06
Disengagement in the preceding visit interval (> 24 months between VLs)	3.82	3.53–4.14

Abbreviations: CI, confidence interval; OR, odds ratio; VL, viral load.

Supplementary table 10.3.6 Results of generalised mixed effects logistic regression modelling the relative odds of VL >1000 copies/mL stratified by disengagement status. Presented as odds ratios with 95% confidence intervals.

	All visit intervals	>24 months between VLs	≤24 months between VLs	>18 months between VLs	≤18 months between VLs	>14 months between VLs	≤14 months between VLs
Transfer during the visit interval	1.49 (1.42–1.56)	1.43 (1.30–1.57)	1.35 (1.28–1.41)	2.39 (2.10–2.72)	1.28 (1.22–1.34)	2.56 (2.04–3.22)	1.23 (1.16–1.29)
Male	1.53 (1.44–1.62)	1.33 (1.21–1.47)	1.51 (1.42–1.61)	1.64 (1.44–1.85)	1.51 (1.42–1.61)	2.00 (1.57–2.54)	1.50 (1.40–1.60)
First VL in a rural district	1.88 (1.77–2.00)	0.99 (0.90–1.08)	1.93 (1.81–2.05)	1.10 (0.98–1.22)	1.99 (1.86–2.12)	0.98 (0.78–1.23)	2.00 (1.87–2.14)
<30 years	1.50 (1.42–1.58)	1.45 (1.29–1.63)	1.46 (1.37–1.54)	1.96 (1.69–2.27)	1.46 (1.37–1.55)	2.74 (2.06–3.66)	1.46 (1.37–1.55)
Duration on ART in years	0.01 (0.01–0.01)	1.05 (0.99–1.12)	0.91 (0.90–0.92)	0.99 (0.93–1.05)	0.90 (0.89–0.91)	1.03 (0.91–1.17)	0.89 (0.88–0.91)

Abbreviations: ART, antiretroviral therapy; VL, viral load.

10.4 Supplemental file for Chapter 4: Frequency and outcomes of transfers between primary health care facilities among people living with HIV on antiretroviral therapy

10.4.1 Background

Transfers between health facilities include up-referrals (e.g. primary health care [PHC] facility to hospital), down-referrals (e.g. hospital to PHC facility) and lateral transfers (e.g. PHC facility to PHC facility or hospital to hospital) (1). Each type of transfer occurs for different reasons and may thus have different outcomes. In Chapter 4 of this thesis, transfers were investigated among PLH attending at least one PHC facility over the study period. However, different types of transfers were not differentiated. Following from the analysis in Chapter 4, this chapter differentiates between transfers based on the types of facilities involved to determine their frequency and outcomes, with a focus on transfers between PHC facilities.

10.4.2 Methods

National Health Laboratory Service (NHLS) data included the names of facilities at which viral loads (VLs) were taken. Each facility was categorised as a PHC facility or hospital. Transfers were then categorised as PHC facility to PHC facility, PHC facility to hospital, hospital to PHC facility and hospital to hospital and the proportion of all transfers in each category was calculated. To assess predictors of transfers from PHC facility to PHC facility, generalized estimating equations with an unstructured working correlation with Poisson regression were used to account for repeated measures in participants. Potential confounders were determined *a priori*. Multivariable models assessing predictors of transfers from PHC facility to PHC facility were adjusted for age, sex, location of the first VL (rural vs urban) and the value of the first VL. Generalized mixed effects logistic models assessed the association between the type of transfer during the visit interval and a VL >1000 copies/mL at the end of the interval. These models were adjusted for sex, age at the start of the interval, location of the visit at the start of the visit interval (rural vs urban) and occurrence of a disengagement during the visit interval (visit interval >24 months). Lastly, we conducted stratified analyses to assess effect modification of the relationship between

type of transfer and VL outcome by the occurrence of disengagement (visit interval >14 months) in the visit interval.

10.4.3Results

Among 85,814 individuals, there were a total of 44,317 transfers in the study period. Of these, the majority were between PHC facilities (n = 27,755; 63%), followed by transfers from hospitals to PHC facilities (n = 9863; 22%), PHC facilities to hospitals (n = 6233; 14%) and between hospitals (n = 476; 1%).

Overall, 19,561/85,814 (22.8%) participants transferred between PHC facilities one or more times. Among the 19,561 participants who transferred between PHC facilities at least once, almost one-third had evidence of multiple transfers: 24% (n = 4743) transferred twice and 7% (n = 1431) transferred three or more times. Including repeat transfers, there were a total of 27,754 transfers between PHC facilities.

Of those who transferred between PHC facilities, 75% were female, compared to 68% of all participants (Supplementary table 10.3.2.1). In a multivariable GEE Poisson model, female sex (adjusted incidence rate ratio [aIRR] 1.33, 95% CI 1.29–1.36), age under 30 years (aIRR 1.39, 95% CI 1.36–1.43) and a first VL >1000 copies/mL (aIRR 1.12, 95% CI 1.08–1.15) were associated with an increased rate of transfer (Supplementary table 10.3.2.2). Those with their first VL conducted in a rural area were less likely to transfer between PHC facilities compared to those with their first VL in an urban area (aIRR 0.89, 95% CI 0.87–0.91). Compared to participants who started ART in 2011, those initiating ART in 2012 (aIRR 1.07, 95%CI 1.03–1.10) and 2013 (aIRR 1.21, 95%CI 1.17–1.24) demonstrated higher PHC facility to PHC facility transfer rates.

Supplementary table 10.4.1 Description of participants included in the analysis by whether a transfer between PHC facilities occurred

	All participants	PHC to PHC transfer
Number of participants, n (%)	85,814	29,754
Age at ART initiation (years), median (IQR)	34 (28-40)	32 (27-38)
Female, n (%)	58 724 (68.4)	14,572 (74.5)
Number of visits, median (IQR)	5 (4–6)	5 (4–6)
Duration of follow up (years), mean (SD)	4.0 (1.0)	4.2 (0.7)
First VL conducted in a rural region	26,036 (30.3)	5,620 (28.7)
First VL >50 copies/mL	25,482 (29.7)	6,095 (31.2)
First VL >400 copies/mL	14,689 (17.1)	3,744 (19.1)
First VL >1000 copies/mL	13,132 (15.3)	3,341 (17.1)
Year of ART initiation		
2011	27,701 (32.3)	6,016 (30.8)
2012	31,737 (37.0)	7,059 (36.1)
2013 (01 January–30 September)	26,376 (30.7)	6,486 (33.2)

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range; PHC, primary health care; SD, standard deviation; VL, viral load.

Supplementary table 10.4.2 GEE Poisson regression assessing predictors of PHC facility to PHC facility transfers (n = 85,814)

	Unadjusted models		Adjusted model	
	IRR	95% CI	IRR	95% CI
Female	1.43	1.40–1.47	1.33	1.29–1.36
<30 years	1.49	1.46–1.53	1.39	1.36–1.43
First VL >1000 copies/mL	1.13	1.09–1.16	1.12	1.08–1.15
First VL in a rural district	0.88	0.86–0.91	0.89	0.87–0.91
First VL in 2012 (vs 2011)	1.07	1.03–1.10	1.07	1.03–1.10
First VL in 2013 (vs 2011)	1.23	1.19–1.26	1.21	1.17–1.24

Abbreviations: CI, confidence interval; GEE, generalized estimating equations; IRR, incidence rate ratio; VL, viral load.

The median duration between visits overall was 0.80 (0.49–1.04) years. The duration between visit intervals in which a transfer between PHC facilities occurred was slightly longer at 0.91 years (interquartile range [IQR], 0.51–1.25). Of the 27,754 transfers between PHC facilities, 16% (n = 4,479) were followed by a VL >1000 copies/mL at the end of the visit interval, compared to 49,398 (15%) of all visit intervals.

In a mixed effects model adjusted for age, sex, duration on ART, whether the first VL was conducted in a rural or urban district and the occurrence of disengagement in the visit interval, the occurrence of a transfer between PHC facilities was associated with a 27% increase in the odds of VL >1000 copies/mL (adjusted odds ratio [aOR] 1.27, 95% CI 1.20–1.35) (Table 3). Compared to no transfer, the relative odds of a VL >1000 copies/mL were also increased for hospital to hospital, hospital to PHC and PHC to hospital transfers.

Supplementary table 10.4.3 Results of generalised mixed effects logistic regression modelling the odds of a VL >1000 copies/mL by type of transfer. Presented as adjusted odds ratios with 95% confidence intervals.

	VL >1000 copies/mL	VL >400 copies/mL	VL >50 copies/mL
Transfer between PHC facilities during the visit interval			
No transfer	Ref	Ref	Ref
Hospital to hospital	2.82 (2.05–3.89)	3.11 (2.26–4.29)	3.49 (2.57–4.73)
Hospital to PHC facility	1.10 (1.02–1.20)	1.11 (1.02–1.20)	1.24 (1.16–1.33)
PHC facility to hospital	2.13 (1.93–2.34)	2.23 (2.03–2.46)	2.51 (2.30–2.74)
PHC facility to PHC facility	1.27 (1.20–1.35)	1.30 (1.23–1.38)	1.34 (1.28–1.41)
Sex	1.52 (1.44–1.62)	1.51 (1.42–1.60)	1.54 (1.46–1.62)
First VL in a rural district	1.87 (1.76–1.99)	2.07 (1.95–2.19)	2.31 (2.20–2.43)
Age <30 years	1.49 (1.40–1.57)	1.46 (1.38–1.55)	1.36 (1.30–1.42)
Duration on ART (years)	0.91 (0.90–0.92)	0.94 (0.93–0.95)	1.10 (1.09–1.11)
Disengagement in the visit interval (>24 months between VL tests)	2.79 (2.59–3.02)	2.78 (2.58–3.00)	2.70 (2.53–2.88)

Abbreviations: ART, antiretroviral therapy; PHC, primary health care; VL, viral load.

In sensitivity analyses assessing alternate VL thresholds, the occurrence of a transfer between PHC facilities versus no transfer was associated with slightly higher odds of VL >400 copies/mL (aOR 1.30, 95% CI (1.23–1.38)) and VL >50 copies/mL (aOR 1.34, 95% CI (1.28–1.41) compared to VL >1000 copies/mL (Table 4). The association between transfers between PHC facilities and VL >1000 copies/mL was similar when defining disengagement as >14 and >18 months between VLs (Tables 4 and 5). The increased relative odds of a VL >1000 copies/mL was sustained when including only visit intervals in which the VL at the start of the interval was <1000 copies/mL (aOR 1.55, 95% CI 1.44–1.65; table 6).

Supplementary table 10.4.4 Results of generalised mixed effects logistic regression modelling the odds of a VL >1000 copies/mL by type of transfer defining disengagement as >14 months between VL. Presented as adjusted odds ratios with 95% confidence intervals.

VL >1000 copies/mL	Adjusted OR
Transfer between PHC facilities during the visit interval	
No transfer	Ref
Hospital to hospital	2.85 (2.06–3.94)
Hospital to PHC facility	1.10 (1.01–1.20)
PHC facility to hospital	2.15 (1.95–2.37)
PHC facility to PHC facility	1.28 (1.21–1.35)
Sex	1.52 (1.43–1.62)
First VL in a rural district	1.86 (1.75–1.89)
Age <30 years	1.50 (1.42–1.59)
Duration on ART (years)	0.90 (0.89–0.91)
Disengagement in the visit interval (>14 months between VL tests)	1.85 (1.77–1.94)

Abbreviations: ART, antiretroviral therapy; PHC, primary health care; VL, viral load.

Supplementary table 10.4.5 Results of generalised mixed effects logistic regression modelling the odds of a VL >1000 copies/mL by type of transfer defining disengagement as >18 months between VLs. Presented as adjusted odds ratios with 95% confidence intervals.

VL >1000 copies/mL	Adjusted OR
Transfer between PHC facilities during the visit interval	
No transfer	Ref
Hospital to hospital	2.84 (2.06–3.92)
Hospital to PHC facility	1.10 (1.00–1.19)
PHC facility to hospital	2.12 (1.93–2.34)
PHC facility to PHC facility	1.25 (1.18–1.32)
Sex	1.52 (1.43–1.62)
First VL in a rural district	1.85 (1.75–1.97)
Age <30 years	1.49 (1.41–1.58)
Duration on ART (years)	0.90 (0.89–0.92)
Disengagement in the visit interval (>18 months between VL tests)	2.32 (2.20–2.46)

Abbreviations: ART, antiretroviral therapy; PHC, primary health care; VL, viral load.

Supplementary table 10.4.6 Results of generalised mixed effects logistic regression modelling the odds of a VL >1000 copies/mL by type of transfer restricted to visit intervals with initial VL <1000 copies/mL. Presented as adjusted odds ratios with 95% confidence intervals.

VL >1000 copies/mL	Adjusted OR
Transfer between PHC facilities during the visit interval	
No transfer	Ref
Hospital to hospital	4.58 (2.93–7.15)
Hospital to PHC facility	1.52 (1.37–1.69)
PHC facility to hospital	2.72 (2.40–3.08)
PHC facility to PHC facility	1.54 (1.44–1.65)
Sex	1.40 (1.32–1.48)
First VL in a rural district	1.52 (1.44–1.61)
Age <30 years	1.55 (1.46–1.65)
Duration on ART (years)	1.05 (1.03–1.06)
Disengagement in the visit interval (>24 months between VL tests)	3.86 (3.56–4.18)

Abbreviations: ART, antiretroviral therapy; PHC, primary health care; VL, viral load.

In adjusted stratified analyses including only visit intervals in which a disengagement occurred (defined as >14 months between VLs), a VL >1000 copies/mL was more likely to occur at the end of a visit interval in which a transfer occurred compared to one in which a transfer did not occur (aOR 2.54, 95% CI 2.27–2.84; table 7). In comparison, when including only visit intervals in which a disengagement did not occur, the odds of a VL >1000 copies/mL were still significantly higher for intervals in which a transfer occurred compared to those in which a transfer did not occur, but the effect size was smaller (aOR 1.12, 95% CI 1.04–1.20). The difference in the odds ratios between the two strata decreased when disengagement was defined as >18 months between visits and was reversed when disengagement was defined as >24 months between visits.

Supplementary table 10.4.7 Results of generalised mixed effects logistic regression modelling the odds of a VL >1000 copies/mL by type of transfer stratified by disengagement status. Presented as adjusted odds ratios with 95% confidence intervals.

	>24 months between VLs (n = 12,475 visit intervals)	**≤24 months between VLs (n = 317,922 visit intervals)**	**>18 months between VLs (n = 25,590 visit intervals)**	**≤18 months between VLs (n = 304,808 visit intervals)**	**>14 months between VLs (n = 49,374 visit intervals)**	**≤14 months between VLs (n = 281,024 visit intervals)**
Transfer type during the visit interval						
No transfer	.	Ref	Ref	Ref	Ref	Ref
Hospital to hospital	8.31 (2.17–31.82)	2.46 (1.75–3.45)	26.24 (8.56–80.40)	2.34 (1.66–3.32)	29.90 (12.29–72.73)	2.29 (1.59–3.28)
Hospital to PHC facility	1.50 (1.17–1.93)	1.06 (0.97–1.16)	2.01 (1.62–2.48)	1.04 (0.94–1.14)	2.77 (2.32–3.30)	0.99 (0.90–1.09)
PHC facility to hospital	3.55 (1.97–6.38)	2.07 (1.86–2.29)	7.48 (5.55–10.09)	2.05 (1.84–2.28)	9.70 (7.71–12.20)	2.03 (1.82–2.28
PHC facility to PHC facility	1.19 (1.04–1.36)	1.29 (1.21–1.37)	1.88 (1.64–2.15)	1.18 (1.11–1.26)	2.54 (2.27–2.84)	1.12 (1.04–1.20)
Male	1.39 (1.17–1.66)	1.52 (1.43–1.61)	1.65 (1.46–1.86)	1.51 (1.42–1.61)	1.68 (1.53–1.84)	1.50 (1.40–1.60)
First VL in a rural district	1.00 (0.90–1.11)	1.95 (1.83–2.07)	1.12 (1.01–1.25)	2.00 (1.88–2.13)	1.41 (1.29–1.55)	2.01 (1.88–2.15)
<30 years	1.51 (1.22–1.87)	1.46 (1.37–1.54)	1.92 (1.66–2.21)	1.46 (1.37–1.55)	2.08 (1.86–2.32)	1.46 (1.37–1.55)
Duration on ART in years	1.07 (0.99–1.15)	0.91 (0.90–0.92)	0.99 (0.93–1.05)	0.90 (0.88–0.91)	0.95 (0.91–0.99)	0.89 (0.88–0.91)

References

1. South African National Department of Health. Referral Policy for South African Health Services and Referral Implementation Guidelines. Pretoria: South African National Department of Health; 2020.

10.5 Supplementary materials for Chapter 6

Supplementary table 10.5.1 Summary of diabetes clinical management guidelines

	Management of type 2 diabetes in adults at primary care level (January 2014) (1)	Symptom-based integrated approach to the adult in primary care (2016/2017) (2)	Standard treatment guidelines and essential medicines List for South Africa, Primary Health Care Level (2014) (3)
Diagnosis	• Random plasma glucose ≥11.1 mmol/L if classic symptoms of diabetes or hyperglycaemic crisis is present • Fasting plasma glucose ≥7.0 mmol/L • Two-hour plasma glucose during oral glucose tolerance test ≥11.1 mmol/L • HbA1c ≥6.5%	Management based on random glucose result • Random blood glucose 11.1–25.0 and symptoms of diabetes: diagnose diabetes • Random blood glucose 11.1–25.0, no symptoms of diabetes do finger prick glucose after 8-hour fast. If finger prick glucose ≥7.0: diagnose diabetes • Patients with random glucose >25.0 should be referred for further assessment	• Symptoms of diabetes plus a random plasma glucose ≥11.1 mmol/L • Fasting plasma glucose ≥7.0 mmol/L
Frequency of HbA1c testing	• Annually if HbA1c at target and no change in treatment • 3–6 monthly if not at target and when changing medication	6 monthly if HbA1c <7.0 % but 3 months after treatment change	• Annually if treatment goals met • 3–6 monthly if therapy has changed, until stable
HbA1c treatment targets	Individualised targets: • Majority of patients: <7% • Young/low risk/newly diagnosed/no cardiovascular disease: <6.5% • Older persons/high risk/hypoglycaemic unaware/poor short-term prognosis: <7.5%	Aim for HbA1c <7.0%	• Optimal: <7% • Acceptable: 7–8% • Additional action suggested: >8%

References

1. South African National Department of Health. Management of type 2 diabetes in adults at primary care level. Pretoria; South African National Department of Health; 2014.
2. South African National Department of Health. Adult primary care: Symptom-based integrated approach to the adult in primary care. Pretoria; South African National Department of Health; 2016.
3. South African National Department of Health. Standard treatment guidelines and essential medicines list for South Africa: Primary health care level. Pretoria: South African Department of Health; 2014.

Supplementary table 10.5.2 Description of visit intervals by whether a transfer occurred in the interval and by types of facilities involved in the transfer (n = 175,574 visit intervals in 102,924 individuals)

	All transfer events (n=30,068)	Between hospitals (n=667)	PHC facility to hospital (n=11,186)	Hospital to PHC facility (n=10,282)	Between PHC facilities (n=7,933)	No transfer (n=145,506)
Duration between HbA1c tests	275 (143–436)	119 (52–222)	240 (123–404)	256.5 (134–421)	348 (211–503)	330 (182–422)
Disengagement (>14 months between tests)	8,032 (26.7)	52 (7.8)	2,598 (23.2)	2,577 (25.1)	2,805 (35.4)	36,877 (25.3)
Disengagement (>18 months between tests)	4,351 (14.5)	13 (2.0)	1,437 (12.9)	1,380 (13.4)	1,521 (19.2)	17,265 (11.9)
Transfer across districts	2,528 (8.4)	170 (25.5)	759 (6.8)	748 (7.3)	851 (10.7)	NA
Transfer across subdistricts	12,321 (41.0)	551 (82.6)	4,627 (41.4)	4,211 (41.0)	2,932 (37.0)	NA

Supplementary table 10.5.3 Results of generalised mixed effects logistic regression modelling the relative odds of HbA1c ≥8% with disengagement defined as >7 months between HbA1cs (102,924 participants with 175,574 visit intervals). Presented as adjusted odds ratios with 95% confidence intervals.

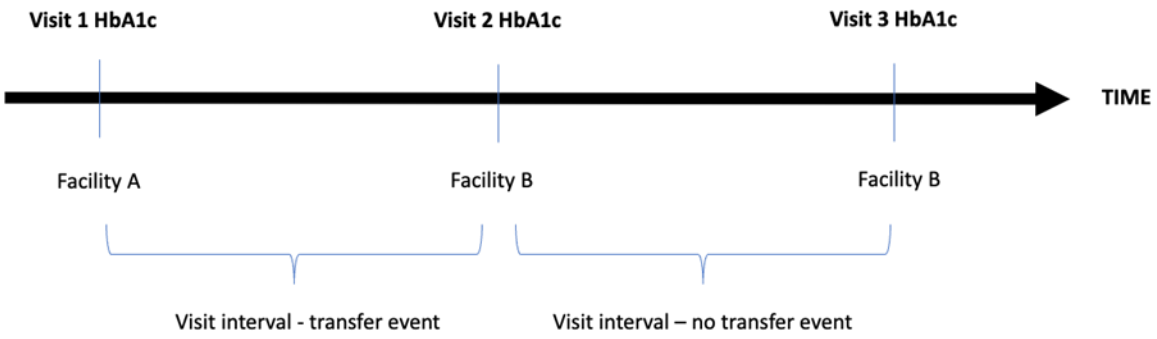
	HbA1c ≥8%
Type of transfer during the visit interval	
- **No transfer**	Ref
- **Hospital to hospital**	0.47 (0.29–0.76)
- **Hospital to PHC facility**	1.34 (1.22–1.47)
- **PHC facility to hospital**	0.91 (0.82–1.01)
- **PHC facility to PHC facility**	1.21 (1.08–1.36)
Male sex	1.05 (0.99–1.10)
HbA1c at start of visit interval done at a facility in a rural district	1.49 (1.41–1.57)
Age at start of the visit interval (years)	0.978 (0.976–0.980)
Disengagement in the visit interval (>14 months between HbA1c tests)	1.32 (1.25–1.39)

Supplementary table 10.5.4 Results of generalised mixed effects logistic regression modelling the relative odds of HbA1c >8% including only visit intervals with an HbA1c <8% at the start of the interval (52,167 participants with 73,347 visit intervals). Presented as adjusted odds ratios with 95% confidence intervals.

	HbA1c ≥8%
Type of transfer during the visit interval	
- **No transfer**	Ref
- **Hospital to hospital**	0.53 (0.38–0.73)
- **Hospital to PHC facility**	0.93 (0.84–1.03)
- **PHC facility to hospital**	1.05 (0.95–1.16)
- **PHC facility to PHC facility**	1.22 (1.07–1.39)
Male sex	0.43 (0.38–0.48)
HbA1c at start of visit interval done at a facility in a rural district	2.33 (2.09–2.59)
Age at start of the visit interval (years)	0.888 (0.885–0.891)
Disengagement in the visit interval (>18 months between HbA1c tests)	0.92 (0.82–1.03)

Supplementary table 10.5.5 Results of generalised mixed effects logistic regression modelling the relative odds of HbA1c >8% stratified by disengagement status: (a) Includes only visit intervals in which a disengagement occurs (44,909 participants with 44,909 visit intervals) and (b) includes only visit intervals in which a disengagement does not occur (72,422 participants with 130,665 visit intervals). Presented as adjusted odds ratios with 95% confidence intervals.

	(a) >14 months between HbA1cs	(b) ≤14 months between HbA1cs
Type of transfer during the visit interval		
- **No transfer**	Ref	Ref
- **Hospital to hospital**	0.76 (0.43–1.34)	0.61 (0.43–0.87)
- **Hospital to PHC facility**	0.83 (0.76–0.90)	0.93 (0.83–1.04)
- **PHC facility to hospital**	0.88 (0.81–0.95)	1.12 (1.01–1.25)
- **PHC facility to PHC facility**	1.11 (1.02–1.20)	1.10 (0.95–1.29)
Male sex	0.90 (0.86–0.94)	0.40 (0.35–0.46)
HbA1c at start of visit interval done at a facility in a rural district	1.25 (1.20 – 1.31)	1.75 (1.52–2.00)
Age at start of the visit interval (years)	0.973 (0.971–0.975)	0.902 (0.898–0.906)



Supplementary figure 10.5.1 Hypothetical timeline of health care facility visits illustrating a transfer event

10.6 Supplementary materials for Chapter 7

Supplementary table 10.6.1 Results of mixed effects logistic model for relative odds of VL≥50 copies/mL adjusted for all presented variables

	OR	95% CI
Fixed effects (at enrolment)		
Age (years)	0.94	0.87–1.01
Informal housing	0.57	0.27–1.23
Married and/or cohabiting	0.37	0.17–0.82
Any previous ART use	3.57	1.49–8.55
Randomised to AC	0.43	0.21–0.92
Time-varying fixed effects (at visit prior to travel event)		
Travel since the last visit	1.85	1.21–2.81
Duration postpartum (months)	1.11	1.09–1.14
Living with baby	0.75	0.38–1.48

Abbreviations: AC, adherence club; ART, antiretroviral therapy; CI, confidence interval; OR, odds ratio; VL, viral load.

Supplementary table 10.6.2 Results of mixed effects logistic model for relative odds of VL ≥400 copies/mL restricted to visit intervals in which the VL at the start of the interval is <400 copies/mL (n = 383 participants with 1,468 visit intervals)

	OR	95% CI
Fixed effects (at enrolment)		
Age (years)	0.93	0.88–0.98
Informal housing	0.66	0.38–1.13
Married and/or cohabiting	0.54	0.30–0.97
Any previous ARV use (triple-drug ART or short-course PMTCT)	2.99	1.59–5.62
Randomised to AC	0.58	0.34–0.97
Time-varying fixed effects (at visit prior to travel event)		
Travel since the last visit	1.62	1.00–2.61
Duration postpartum (months)	1.04	1.00–1.07
Living with baby	0.62	0.30 – 1.28

Abbreviations: AC, adherence club; ART, antiretroviral therapy; ARV, antiretroviral; CI, confidence interval; OR, odds ratio; PMTCT: prevention of mother-to-child transmission; VL, viral load.

Supplementary table 10.6.3 Results of mixed effects logistic model for relative odds of VL ≥400 copies/mL with log transformed travel duration in days

	Adjusted OR	95% CI
Fixed effects (at enrolment)		
Age (years)	0.96	0.86–1.08
Informal housing	0.88	0.26–2.98
Married and/or cohabiting	0.18	0.05–0.67
Any previous ART use	7.61	1.80–32.17
Randomised to AC	0.54	0.17–1.74
Time-varying fixed effects (at visit prior to travel event)		
Log travel duration since the last visit in days	1.24	0.85–1.81
Duration postpartum (months)	1.12	1.06–1.19
Living with baby	0.86	0.25–2.98

Abbreviations: AC, adherence club; ART, antiretroviral therapy; CI, confidence interval; OR, odds ratio; VL, viral load.

Supplementary table 10.6.4 Results of mixed effects logistic model for relative odds of VL ≥400 copies/mL stratified by randomisation allocation

	Randomised to ACs		Randomised to PHCs	
	OR	95% CI	OR	95% CI
Fixed effects (at enrolment)				
Age (years)	0.84	0.75 – 0.95	1.00	0.87 – 1.14
Informal housing	0.28	0.09 – 0.88	1.16	0.29 – 4.73
Married and/or cohabiting	0.49	0.15 – 1.62	0.16	0.04 – 0.71
Any previous ARV use (triple-drug ART or short-course PMTCT)	7.66	1.96 – 29.9	9.52	1.99 – 45.48
Time-varying fixed effects (at visit prior to travel event)				
Travel since the last visit	1.72	0.91 – 3.25	2.35	1.12 – 4.91
Duration postpartum (months)	1.13	1.09 – 1.17	1.17	1.11 – 1.22
Living with baby	0.58	0.19 – 1.77	0.84	0.27 – 2.58

Abbreviations: AC, adherence club; ART, antiretroviral therapy; ARV, antiretroviral; CI, confidence interval; OR, odds ratio; PHC: primary health care; PMTCT: prevention of mother-to-child transmission; VL, viral load.

10.7 Transfers to differentiated service delivery models

Odayar J, Malaba TR, Allerton J, Kabanda S, Huang D, Kalombo S, Lesosky M, Myer L. Virologic Outcomes After Early Referral of Stable HIV-Positive Adults Initiating ART to Community-Based Adherence Clubs in Cape Town, South Africa: A Randomised Controlled Trial. *PLoS ONE.* 2022;17(11):e0277018.

Relevance of this paper to the thesis:

This manuscript presents the results of a randomised controlled trial in which people living with HIV on ART attending a routine care antiretroviral therapy clinic were randomised to either continue care at the routine clinic or be transferred to the local differentiated service delivery model of care, the adherence club (AC) system. The paper includes data on the outcomes of transfers from the routine clinic to the AC; considering the ongoing scale up of DSDs in many countries, these results are vital to ensuring optimising DSD implementation.

Contribution of the student and co-authors:

JO conceptualised the analysis with guidance from LM. LM conceptualised the study from which these data arise, was responsible for funding and overall leadership. JA directed data collection with assistance from SK. JO conducted the analysis with guidance from ML. JO led data interpretation and drafted the manuscript. All authors reviewed the initial manuscript and provided conceptual and intellectual comment. All authors reviewed and approved the final manuscript.

10.7.1 Abstract

10.7.1.1 Background

Differentiated service delivery (DSD) models are recommended for stable people living with HIV on antiretroviral therapy (ART) but there are few rigorous evaluations of patient outcomes.

10.7.1.2 Methods

Adherence clubs (ACs) are a form of DSD run by community health workers at community venues with 2-4 monthly ART refills and annual nurse assessments). Clinic-based care involves 2-monthly ART refills and 4-monthly nurse/doctor assessments. We compared virologic outcomes in stable adults randomised to ACs at four months post-ART initiation to those randomised to primary health care (PHC) ART clinics through 12 months on ART in Cape Town, South Africa (NCT03199027). We hypothesised that adults randomised to ACs would be more likely to be virally suppressed at 12 months post-ART initiation, versus adults randomised to continued PHC care. We enrolled consecutive adults on ART for 3–5 months who met local DSD ['adherence clubs' (AC)] eligibility (clinically stable, VL<400 copies/mL). The primary outcome was VL<400 copies/mL at 12 months on ART.

10.7.1.3 Results

Between January 2017 and April 2018, 220 adults were randomised (mean age 35 years; 67% female; median ART duration 18 weeks); 85% and 94% of participants randomised to ACs and PHCs attended their first service visit on schedule respectively. By 12 months on ART, 91% and 93% randomised to ACs and PHCs had a VL<400 copies/mL, respectively. In a binomial model adjusted for age, gender, previous ART use and nadir CD4 cell count, there was no evidence of superiority of ACs compared to clinic-based care (RD, -2.42%; 95% CI, -11.23 to 6.38). Findings were consistent when examining the outcome at a threshold of VL <1000 copies/mL.

10.7.1.4 Conclusion

Stable adults referred to DSDs at 4 months post-ART initiation had comparable virologic outcomes at 12 months on ART versus PHC clinics, with no evidence of superiority. Further research on long-term outcomes is required.

10.7.2 Introduction

Globally, 21.7 million of the approximately 37 million people living with HIV were accessing antiretroviral therapy (ART) in 2016 (1). The consolidated guidelines on the use of ART released by the World Health Organization (WHO) in 2016 recommend ART initiation for all people living with HIV, regardless of clinical and immunological status, a "treat all" approach (2). Health systems thus need to expand ART access in those not on treatment while maintaining engagement in care and viral suppression in patients already on ART.

To manage this increasingly diverse patient population and support ART expansion and maintenance, the WHO recommends implementation of differentiated service delivery (DSD) models (2-4). Under this framework, patients who are clinically stable on treatment can be considered for referral to models of care which are simplified and adapted to reduce the burden on both patients and the health care system, allowing for more attention to be paid to new patients and those with complex care needs (2). A number of different DSD models have been developed which vary based on who provides the care (e.g. doctors, nurses or community health workers [CHWs]), location of care (clinic or community), frequency of visits, and services provided (e.g. ART refills, counselling) (5).

One such approach is the Adherence Club (AC) system, which was first piloted in Cape Town in 2007 and has been widely adopted since 2011 (6,7). Led by community health workers (CHWs), up to 30 adults meet 2-4 monthly for a quick clinical assessment and collection of pre-packed ART (6-9). Initially facility-based, the model has since been adapted to operate from community venues (10). Evidence from observational studies has shown high rates of viral suppression (10,11) as well as a reduced risk of loss to follow-up (LTFU) (8,12,13) in patients managed in ACs compared to clinics. However, observational studies of AC effectiveness are prone to selection bias as the decision to refer patients to ACs in routine care settings is made by clinicians, who may refer those who are more likely to adhere to treatment (4,7). A cluster randomised trial compared patients in ACs at 12 intervention sites to those eligible for ACs but managed at standard of care facilities at 12 control sites in five provinces of South Africa (14). Patients in ACs had higher retention and comparable viral suppression at one year, but referral to ACs at intervention sites was done as part of routine care and was thus at risk of similar selection bias as observational studies. In a cluster-

randomised trial in Zambia, participation in facility-based ACs was associated with a significantly reduced risk of late drug pick-up compared to clinic care, but viral load outcomes were not assessed (15). A randomised controlled trial (RCT) in South Africa comparing facility and community-based ACs raised some concern about the effectiveness of ACs: rates of loss to care were high overall and were worse in community-based compared to facility-based ACs, but virological outcomes were not assessed and there was no clinic-based care control arm (16).

Studies on effectiveness of ACs have thus provided conflicting results. Data on viral load outcomes in participants receiving care in ACs compared to clinics are limited and there are few individually randomised trials assessing AC effectiveness. To help address this gap, we compared virological outcomes in stable adults randomised to community-based ACs at four months post-ART initiation to those randomised to general primary health care (PHC) ART clinics which are the standard of care (SOC) through 12 months on ART in Cape Town, South Africa. We hypothesised that adults randomised to the ACs would be more likely to be virally suppressed at 12 months post-ART initiation, compared to adults randomised to continued PHC care.

10.7.3 Methods

10.7.3.1 Design and setting

We conducted a pragmatic randomised controlled superiority trial (Supplementary table 10.6.8.1) to compare outcomes in stable adults referred to ACs at four months post-ART initiation to those managed in general PHC ART clinics through 12 months on ART (ClinicalTrials.gov NCT03199027); registration was approved after the start of enrolment due to an administrative error. The primary outcome was HIV viral suppression at 12 months post-ART initiation.

The trial was conducted at a Community Health Centre (CHC) in an informal settlement in Cape Town, South Africa. The CHC is a large primary health care public sector facility which serves a population of approximately 400 000 who are predominantly of low-socioeconomic status [17]. The antenatal HIV prevalence is estimated at 30% (18). HIV care is provided at the CHC through an ART clinic on the premises and associated ACs which operate off-site at

a community centre approximately 1km from the clinic. The ART clinic had >5000 patients retained in care at the end of 2016, of whom approximately half were in ACs (19).

10.7.3.2 ART services

10.7.3.2.1 General adult PHC ART clinic services

General adult patients are initiated on ART at the PHC ART clinic at the CHC. All participants initiated the local first-line ART regimen of tenofovir (300 mg) + emtricitabine (200 mg) + efavirenz (600 mg) as a fixed-dose combination. Participants randomised to the PHC clinic-based care arm received continued care at the clinic, with no club referral prior to 12 months post-initiation. All clinical care and follow-up were provided by government health services and based on local public sector policies. At the PHC ART clinic, patients receive 2-6 monthly clinician review and medication refills (according to clinician discretion). Standard clinic care includes blood tests (viral load [VL] and ART safety bloods as needed) at four- and twelve-months post-ART initiation and annually thereafter. Patients attending the clinic receive a waiting room health promotion and adherence talk. Patients with clinical or psychosocial concerns may be reviewed more frequently or be referred to higher levels of care. Over the December/January holidays, patients receive three months of medication from the pharmacy (from mid-October to mid-November). Patients may send someone to collect their medication ("a buddy") on their behalf. There is no immediate follow-up for patients who default from clinic attendance, although home visits are done for those who are lost to follow-up (LTFU) every four months, depending on resources.

10.7.3.2.2 Club care

As part of routine care services, adults attending the general PHC ART clinic are eligible for referral to ACs if they have been on ART for at least six months, are virally suppressed (VL <400 copies/ml) and have no medical conditions requiring regular clinical follow-up. Participants in this trial who were randomised to the AC arm were immediately referred to ACs. All clinical care and follow-up were provided by government health services and based on public sector policies. Each AC includes 25-30 patients and meets for approximately 60 minutes every two months, except over the December/January holiday period when the appointment interval is four months. Clubs are run by CHWs who provide a group health

promotion and adherence talk. CHWs also conduct a weight check and symptom screen and dispense pre-packed ART for each club member. A nurse attends an annual visit per club to perform phlebotomy for routine VL monitoring for each patient and attends the subsequent visit to conduct a clinical assessment and check VL results. Patients who have a high VL (>400 copies/ml), are symptomatic and require further clinical assessment, or who miss a club visit and do not collect their medication within five working days of the scheduled appointment are referred back to the ART clinic. Patients in clubs may send a "buddy" (e.g. a partner, friend or relative) to attend alternate non-clinical visits to collect medication.

10.7.3.3 Participants and eligibility

HIV-positive adults ≥18 years of age attending their four-month post-ART initiation visit at the PHC ART clinic and not on treatment for tuberculosis (TB) were screened for eligibility. Those who were pregnant, had an intention to relocate out of Cape Town during the study period or had co-morbidities requiring regular clinical follow-up were ineligible for inclusion. Potentially eligible patients who were interested in the study were asked to return in a week to review results of the four-month post-ART initiation VL test and safety bloods conducted by routine services. These results were needed to screen participants as only those with a VL <400 copies/ml are eligible for referral to adherence clubs and a VL <400 copies/mL was thus an eligibility criterion for inclusion in this trial.

10.7.3.4 Sources of data

Data were collected through trial measurement visits conducted at enrolment and at four- and eight-months post-enrolment (eight- and twelve- months post-ART initiation, respectively). Trial measurement visits were conducted by trained interviewers at a dedicated research space separate from routine ART services; study visits were at the same location for all participants regardless of the location of ART service visits. At the start of each measurement visit, participants were instructed to not disclose to interviewers their initial trial allocation. Standardised questionnaires were used at study visits to collect information including demographics, past medical history, HIV disclosure and current ART use. In addition, phlebotomy for 5ml of venous blood was conducted at each visit for batched HIV RNA VL testing by the South African National Health Laboratory Services (NHLS) using the Abbott RealTime HIV-1 Assay (Abbott Laboratories, Abbott Park, Illinois, US); this

was independent from VL monitoring done as part of routine healthcare services. Participants who missed trial study visits were traced by study fieldworkers working independently of routine healthcare services. Participants found to have defaulted ART care at any time were counselled by study staff and referred for care when required.

10.7.3.5 Outcomes

The primary trial outcome was viral suppression (VL <400 copies/mL based on VL testing at trial measurement visit) at 12 months post-ART initiation. The secondary outcome was a VL <1000 copies/mL at 12 months post-ART initiation.

10.7.3.6 Sample size calculation and randomisation process

The projected minimum sample size for the trial was 214 participants. This was based on a superiority comparison using 90% power and a two-sided statistical test at α=0.05. We used 1:1 randomisation and aimed to detect an absolute difference in the primary outcome between trial arms of at least 20%, from an expected frequency of 65% in the PHC arm based on routine data, allowing for 10% loss to follow-up.

The randomisation sequence was generated by an independent statistician using STATA 14 (Stata Corporation, College Station, TX, USA). Randomisation was a 1:1 allocation using a dynamic permuted block design, with allocation via sequentially numbered opaque envelopes. These envelopes were stored in a locked and restricted access cabinet and were accessed by the study coordinator once a participant was fully consented and enrolled in the study. The allocation was then conveyed by the study coordinator to a study staff member who would ensure that the referral was made to the allocated site. The data analyst was blinded to study arm until the main trial analysis was complete.

10.7.3.7 Statistical analysis

Primary analyses used a modified intention-to-treat population that included all participants with a VL <400 copies/mL at randomisation. For participants who were LTFU, viral load results at the final study visit were imputed as unsuppressed (VL $\geq$400 copies/mL for the primary outcome and VL $\geq$1000 copies/mL for the secondary outcome). Per protocol analyses included all participants with a VL <400 copies/mL at randomisation who had at

least one visit at the intended service within four months of referral. Intervention effects were examined across *a priori* subgroups including age, gender, previous antiretroviral exposure and nadir CD4 cell count. Additive binomial regression models were used to examine the effect of trial arm on the primary outcome; results are presented as absolute risk differences (RD) with 95% confidence intervals (CI) (20). Models were adjusted for participant clinical and demographic characteristics which were thought to predict the outcome while not mediating the intervention effect. Covariates which altered the association or appeared independently associated with the outcome were included in the final model. Generalised estimating equations (GEE) under an unstructured working correlation were conducted as a sensitivity analysis to account for clustering of individuals randomised to the same AC. Analyses were conducted using STATA 14 (Stata Corporation, College Station, TX, USA) and R (R Foundation, Vienna, Austria).

10.7.3.8 Ethical approvals

Ethical approval for the study was obtained from the Human Subjects Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town (REF 764/2016). Written informed consent was obtained from all participants prior to enrolment. The authors confirm that all ongoing and related trials for this intervention are registered.

10.7.4 Results

Between January 2017 and April 2018, a total of 293 adults who were on ART for 3-5 months and not on TB treatment were screened for inclusion in the trial, of whom 220 were enrolled and randomised (Figure 10.1). The main reasons for ineligibility were patients not arriving for their follow-up screening visits (n=33, 47%), VL >400 copies/ml (n=16, 23%) and the presence of co-morbidities (n=15, 21%).

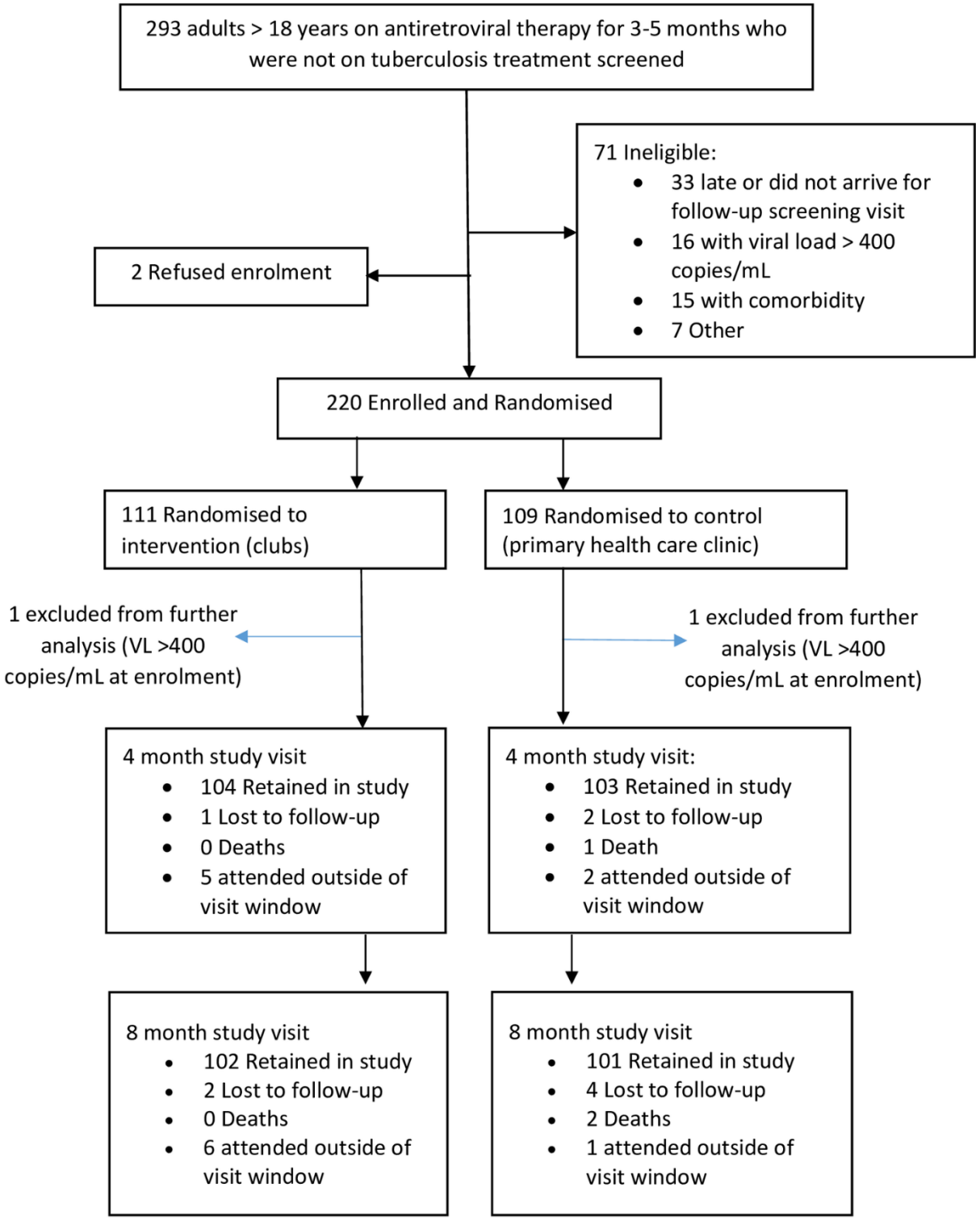


Figure 10.1 Study enrolment, randomisation and follow-up visits

Table 10.1 Enrolment characteristics of the study sample

		All (n = 218)	Randomized to PHC clinics (n = 108)	Randomized to ACs (n = 110)
Median age (IQR), years		34.7 (29.1–42.2)	34.5 (28.5–44.0)	35.0 (29.2–42.0)
Gender				
	Female	146 (67.0)	72 (66.7)	74 (67.3)
	Male	72 (33.0)	36 (33.3)	36 (32.7)
Home language: IsiXhosa		199 (91.3)	102 (94.4)	97 (88.2)
Completed secondary/any tertiary education		203 (93.1)	101 (93.5)	102 (92.7)
Currently employed and/or studying		141 (64.7)	73 (67.6)	68 (61.8)
Currently in a relationship		149 (68.4)	69 (63.9)	80 (72.7)
WHO stage				
	1	131 (60.1)	66 (61.1)	65 (59.1)
	2	45 (20.6)	22 (20.4)	23 (20.9)
	3	29 (13.3)	14 (13.0)	15 (13.6)
	4	6 (2.8)	3 (2.8)	3 (2.7)
	Unknown	4 (1.8)	2 (1.9)	2 (1.8)
	Missing	3 (1.4)	1 (0.9)	2 (1.8)
Any previous ARV use		50 (22.9)	25 (23.2)	25 (22.7)
Median time on ART (IQR), weeks		18 (17–20)	18 (17–20)	19 (17–20)
Current ART regimen				
TDF/FTC/EFV		218 (100)	108 (100)	110 (100)
Disclosed to anyone other than a health professional		205 (94.0)	102 (94.4)	103 (93.6)
Missed ART dose reported in previous 30 days		76 (34.9)	39 (36.1)	37 (33.6)
Pre-initiation CD4 count (IQR), cells/μl		364 (225–496)	318 (219–495)	379.5 (257–496)
	Missing	5 (2.3)	3 (2.8)	2 (1.8)
Viral load, copies/mL				
	<100	196 (89.9)	96 (88.9)	100 (90.9)
	100–400	22 (10.1)	12 (11.1)	10 (9.1)

AC: Adherence club, ART: Antiretroviral therapy, ARV: Antiretroviral therapy, EFV: Efavirenz, FTC: Emtricitabine, IQR: Inter-quartile range, PHC: Primary health care, TDF: Tenofovir, WHO: World Health Organization.

All participants were followed up through November 2018 with separate trial measurement visits at four months post-enrolment (eight months post-ART initiation) and at eight months post-enrolment (12 months post-ART initiation and study outcome visit). Of the 218 participants included in the analysis, 207 (95%) attended the four-month trial measurement visit, made up of 103/108 (95%) in the PHC ART clinic arm and 104/110 (95%) in the AC arm. A total of 203/218 (93%) participants attended the study outcome visit, made up of 101/108 (94%) in the PHC ART clinic arm and 102/110 (93%) in the AC arm. Among the 15 participants who did not complete the final study visit at 12 months post-ART initiation, there were two deaths, both of whom had been randomised to the PHC clinic arm. There were no substantial differences in enrolment characteristics between those who did and did not complete the final study follow-up visit (Supplementary table 10.6.8.2).

Among participants retained at the final study visit, 93% (94/101) of those randomised to the PHC arm and 92% (94/102) of those randomised to the AC arm had a VL<400 copies/mL at 12 months on ART (p = 0.816; Table 10.6.2). For the MITT analysis, VL results at 12 months on ART were imputed as unsuppressed in those not retained at the final study visit: in this analysis 87% (94/108) of those randomised to the PHC arm and 85% (94/110) of those randomised to the AC arm were categorised as having a VL<400 copies/mL at 12 months on ART (p = 0.735). In the 218 participants included in the MITT population, a binomial model adjusted for age, gender, previous ART use and nadir CD4 cell count, found no evidence of superiority of ACs compared to clinic-based care when the outcome was examined at a threshold of VL<400 copies/mL (RD, -2.42%; 95% CI, -11.23 to 6.38; Table 10.6.3) and VL<1000 copies/mL (RD, 0.55%; 95% CI, -7.80 to 8.90). In subgroup analyses, males randomised to ACs were more likely to have a VL <400 copies/mL at 12 months on ART compared to males randomised to PHC clinics, while females randomised to ACs were less likely to have a VL <400 copies/mL at 12 months on ART compared to females randomised to PHC clinics but the numbers in subgroup analyses were small and confidence intervals were wide (Table 10.6.4 and Figure 10.2). Adding an interaction term between randomisation allocation and age did not substantially alter estimates but the confidence interval for the difference in risk between those randomised to the AC arm compared to the PHC arm was wide (RD -4.43% [95% CI, -36.56 to 27.69]; Table 10.6.5). Clustering by the AC facility to which participants in the intervention arm were referred using GEE (Table10.6.6) produced similar results to the primary analysis.

Table 10.2 Comparison of VL outcomes between trial arms through 12 months post-ART initiation in those who completed the final study visit

Viral load	Total (n = 203)	Randomised to PHC arm (n = 101)	Randomised to AC arm (n = 102)	*p*-value
VL <400 copies/ml, n (%)	188 (92.6)	94 (93.1)	94 (92.2)	0.816
VL<1000 copies/ml, n (%)	191 (94.1)	94 (93.1)	97 (95.1)	0.567

AC: Adherence club, PHC: Primary health care, VL: Viral load.

Table 10.3 Results of additive binomial model examining the association between trial arms and primary outcome (VL <400 copies/mL) and secondary outcome (VL <1000 copies/mL) adjusted for demographic and clinical characteristics (n = 218)

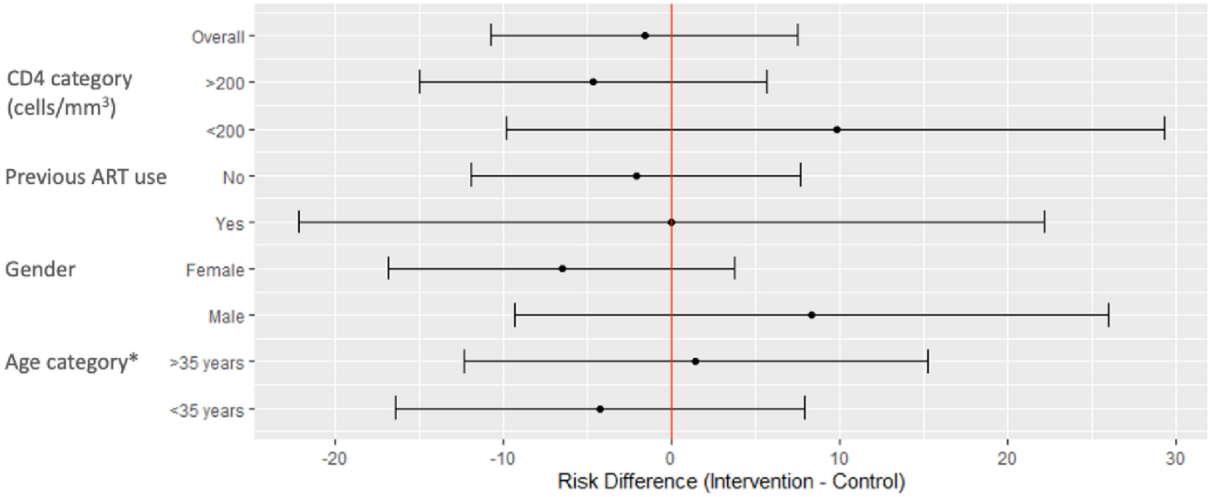
	Primary outcome (VL <400 copies/mL)		Secondary outcome (VL <1000 copies/mL)	
	Risk difference	95% CI	Risk difference	95% CI
Trial arm (intervention-control)	-2.42%	-11.23 to 6.38	0.55%	-7.80 to 8.90
Gender (male vs female)	-6.02%	-16.31 to 4.27	-3.00%	-12.47 to 6.46
Previous ART use (previous ART use vs no previous ART use)	-7.27%	-19.29 to 4.74	-9.85%	-21.90 to 2.21
Nadir CD4 cell count category (>200 vs ≤200)	-0.02%	-11.00 to 10.97	1.86%	-9.05 to 12.77
Age (years)	-0.009%	-0.44 to 0.42	0.02%	-0.38 to 0.42

ART: Antiretroviral therapy, CI: Confidence interval, VL: Viral load.

Table 10.4 Results of additive binomial models examining the association between trial arms and primary outcome (VL <400 copies/mL) in a priori subgroups of demographic and clinical characteristics (unadjusted)

	Risk difference (intervention-control)	95% CI
Gender		
Female (n = 146)	-6.53%	-16.85 to 3.79
Male (n = 72)	8.33%	-9.33 to 26.00
Previous ART use		
No (n = 168)	-2.10%	-11.88 to 7.68
Yes (n = 50)	-0.001%	-22.17 to 22.17
Nadir CD4 cell count category		
<200 (n = 46)	9.85%	-9.79 to 29.39
≥200 (n = 172)	-4.65%	-14.98 to 5.68
Age category		
<35 years (n = 113)	-4.20%	-16.38 to 7.97
≥35 years (n = 105)	1.45%	-12.33 to 15.24

ART: Antiretroviral therapy, CI: Confidence interval.



ART: antiretroviral therapy

Figure 10.2 Forest plot of primary outcome (VL <400 copies/mL at 12 months on ART) across a priori subgroups of demographic and clinical characteristics

Table 10.5 Results of additive binomial model examining the association between trial arm and primary outcome (VL <400 copies/mL) including an interaction term between the intervention and age

	Risk difference	95% CI
Trial arm (intervention-control)	-4.43%	-36.56 to 27.69
Gender (male vs female)	-6.07%	-16.37 to 4.23
Previous ART use (previous ART use vs no previous ART use)	-7.17%	-19.17 to 4.83
Nadir CD4 cell count category (>200 vs ≤200)	-0.35%	-11.28 to 10.57
Age (years)	-0.09%	-1.37 to 1.19
Interaction: Age (years)*randomisation allocation	0.06%	-0.80 to 0.92

Table 10.6 Generalised estimating equations with additive binomial regression (clustered by adherence club to which participants randomised to the intervention arm were referred) predicting future VL >400 copies/mL

	Risk difference (%)	95% CI
Trial arm (intervention-control)	-0.14%	-8.41 to 8.14
Gender (male vs female)	-6.42%	-16.70 to 3.85
Previous ART use (previous ART use vs no previous ART use)	-8.47%	-20.69 to 3.76
Nadir CD4 cell count category (>200 vs ≤200)	0.75%	-10.23 to 11.73
Age (years)	-0.007%	-0.43 to 0.41

ART: Antiretroviral therapy, CI: Confidence interval.

Among the 218 participants included in the analysis, 85% (n=94/110) of those referred to ACs and 94% (102/108) of those referred to PHC ART clinics attended the allocated service within four months of their scheduled visit and were included in the per protocol analysis. Supplementary table 10.6.8.3 compares the characteristics of those who did and did not attend the allocated site within four months of their scheduled visit. Among those randomised to ACs, median pre-initiation CD4 count was lower (247.0 cells/µl, IQR 159.5-475.5) in those who did not attend their first visit within four months compared to those who did (399.5 cells/µl, IQR 279.5-496.0). Similarly, in those randomised to the PHC arm, the median pre-initiation CD4 count was lower (209.0 cells/µl, IQR 168.0-307.0) in those who did not attend their first visit within four months compared to those who did (333.0 cells/µl, IQR 224-516). In the per protocol population, there was no significant difference in risk of viral suppression at 12 months in those randomised to the AC arm compared to those randomised to the PHC arm (RD, -2.66%; 95% CI, -11.56 to 6.24) (Supplementary table 10.6.8.4).

10.7.5 Discussion

To date there have been few randomised studies of DSD models of care for ART delivery. These novel data show no significant difference in virologic outcomes through 12 months post-ART initiation in adults randomised to referral to ACs at four months post-ART initiation versus those who received continued clinic-based care. The sample size here is limited, but the absence of evidence for the superiority of facility-based care over ACs is notable and appears consistent across subgroups of age, gender, previous ART use and CD4 cell count.

This is one of the only RCTs to compare DSD to facility-based services, but previous observational studies have shown marked benefit of ACs compared to routine care. Among 2113 patients referred to the same community-based ACs as in this trial, AC participation was associated with a 67% reduction in the risk of LTFU after 12 months compared with attendance at the PHC clinic (8). Also at a facility in Cape Town, club participation reduced loss-to-care by 57% and reduced virologic rebound in patients who were initially suppressed by 67% (13). The lack of difference between arms in this trial may be due to randomisation: in observational studies, referral of eligible patients to ACs is based on clinician discretion

and patients chosen for referral are likely to be the most adherent (16). In addition, randomisation may disrupt peer support structures by preventing patients from being referred together. A cluster randomised trial in South Africa which compared facility or community-based ACs to local clinic ART care had findings more in line with ours, with comparable levels of viral suppression found in the two groups (14). ACs have previously been found to be cost-effective (21), acceptable to patients and health care providers, and there is evidence of sustainability in the Western Cape (12,15, 21, 22); considering these factors, a finding of comparable patient outcomes between groups may be considered adequate to support referral of stable patients to ACs in this setting (14). However, follow-up in this evaluation was through 12 months post-ART initiation; considering that ART is lifelong, an assessment of longer-term outcomes is warranted.

A key finding of this trial is that 6% of those referred to the PHC ART clinic and 15% of those referred to ACs did not attend the allocated service within four months of referral. Data on attendance at facilities other than the specific PHC facility and AC to which participants were referred at randomisation were unavailable. These participants may thus have accessed care at other health facilities or may have been lost to follow-up. A study in postpartum women who initiated ART in pregnancy and were referred to community-based ACs found that 15% of women never attended the allocated service (23). Among participants randomised to ACs in our trial, those who did not attend the first visit were older and had lower CD4 cell counts than those who did attend, and a higher proportion who did not attend had missed an ART dose in the preceding 30 days. A possible reason for the lower first visit attendance in participants referred to the ACs compared to the PHC clinics is that participants randomised to the PHC clinic arm continued care at the same facility, while participants randomised to the ACs were referred to an off-site community centre. Transfer between health facilities has been identified as a high-risk period for disengagement from care among adults on ART (24). However, first visit attendance post-transfer from general adult services to DSDs has not been specifically addressed and warrants further investigation, including identification of predictors of first visit non-attendance.

Strengths of these data include the random allocation of participants to either ACs or the PHC clinics, high retention rates and use of an objective outcome measure (VL) which was

conducted separate to routine study visits. Limitations include the conduct of the study at a single set of facilities, limiting generalisability. We also did not have data on participant attendance at health care facilities other than the facilities at which the study was conducted. As part of the sample size calculation, we estimated that 65% of individuals randomised to the PHC arm would remain virally suppressed based on VL reporting from the facility at which the study was conducted. However, viral suppression rates in individuals retained in care were higher than expected. In addition, retention in care in both trial arms was high, possibly due to follow-up and tracing activities conducted as part of the trial. The figure of 65% thus proved to be an underestimate, contributing to imprecise results. We further note that subgroup analyses should be interpreted with caution due to small numbers. All participants were on TDF, FTC and EFV which was the first-line ART regimen at the time of the trial. In 2019, the first-line ART regimen in adults in South Africa was changed to TDF, FTC and dolutegravir (25). Dolutegravir may be more potent than efavirenz (26) and it is possible that the difference between arms would be smaller using the current regimen.

10.7.6 Conclusion

In summary, we found comparable virologic outcomes at 12 months on ART in stable adults referred to ACs versus those who received continued clinic-based care. Further research is required to investigate long-term outcomes. Approximately 15% of those referred to ACs did not attend an AC visit and this warrants further investigation.

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10.7.8Supplementary materials

Supplementary table 10.7.1 CONSORT diagram

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Virologic Outcomes After Early Referral of Stable HIV-Positive Adults Initiating ART to Community-Based Adherence Clubs in Cape Town, South Africa: A Randomised Controlled Trial

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Title page
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	On page called “abstract”
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Introduction, paragraphs 1-4
	2b	Specific objectives or hypotheses	Methods, section titled “Design and setting”, paragraph 1
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Methods, Design and setting, para 1 and Methods, section titled “Randomisation”
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA

Participants	4a	Eligibility criteria for participants	Methods, section titled “Participants and eligibility”
	4b	Settings and locations where the data were collected	Methods, Design and setting, paragraph 2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Methods, ART services, sections titled “General Adults PHC ART Clinic Services” and “Club Care”
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Methods, section titled “Sources of Data” and Methods, section titled “Outcomes”
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	Methods, section titled “Statistical analysis”
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Methods, section titled “Randomisation”
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Methods, section titled “Randomisation”
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Methods, section titled “Randomisation”
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Methods, section titled “Randomisation”
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Methods, section titled “Statistical analysis”

	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Methods, section titled “Statistical analysis”
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Methods, section titled “Statistical analysis”
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Results, paragraphs 1 and 5
	13b	For each group, losses and exclusions after randomisation, together with reasons	Results, paragraph 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Results, paragraphs 1 and 3
	14b	Why the trial ended or was stopped	Results, para 1
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1 in Results
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Results, paragraphs 3–5
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results, paragraphs 3–5
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Results, paragraph 3

Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Results, paragraphs 3–5
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Results, paragraphs 3 and 5
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Discussion, para 4
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Discussion, para 4
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Discussion paras 1–3
Other information			
Registration	23	Registration number and name of trial registry	Methods, Design and setting, para 1
Protocol	24	Where the full trial protocol can be accessed, if available	The protocol is available on ClinicalTrials.gov (NCT03199027)
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Section titled “Conflicts of Interest and Source of Funding”

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org

Supplementary table 10.7.2 Characteristics of participants completing the final study visit through 12 months, versus those not completing the final study visit through 12 months for any reason by randomisation allocation

	Completed final study visit (n=203)	Did not complete final study visit (n=15)	*p*-value
Median age (IQR), years	34.7 (29.1-42.2)	35.8 (24.5-45.6)	0.961
Gender, n (%)			0.552
Female	137 (67.5)	9 (60.0)	
Male	66 (32.5)	6 (40.0)	
Home language: IsiXhosa, n (%)	186 (91.6)	14 (93.3)	0.626
Completed secondary/any tertiary education, n (%)	189 (93.1)	14 (93.3)	1.000
Currently employed	124 (61.1)	7 (46.7)	0.271
Currently in a relationship	140 (69.0)	9 (60.0)	0.566
WHO stage			0.200
1	124 (62.0)	7 (46.7)	
2	42 (21.0)	3 (20.0)	
3	26 (13.0)	3 (20.0)	
4	5 (2.5)	1 (6.7)	
Unknown	3 (1.5)	1 (6.7)	
Missing: 3 (1.36)			
Any previous ARV use	46 (22.7)	4 (26.7)	0.752
Median time on ART (IQR), weeks	18.4 (17.0-20.0)	17.1 (16.7-19.9)	0.094
Current ART regimen: TDF/FTC/EFV	203 (100.0)	15 (100.00)	1.000
Disclosed to anyone other than a health professional	191 (94.1)	14 (93.3)	1.000
Missed ART dose reported in previous 30 days	69 (34.0)	7 (46.7)	0.320
Pre-initiation CD4 count (IQR), cells/µl	362 (225.0-492)	426 (225-667)	0.360
Missing	3	0	
Viral load, copies/mL			0.182
<100	184 (90.64)	12 (80.00)	
≥100	19 (9.36)	3 (20.00)	
Randomised to ACs	102 (50.2)	8 (53.3)	0.897

AC: Adherence club, ART: antiretroviral therapy, ARV: antiretroviral, EFV: efavirenz, FTC: emtricitabine, IQR: inter-quartile range, TDF: tenofovir, WHO: World Health Organization.

Supplementary table 10.7.3 Characteristics of participants who attended the allocated service within four months of randomisation versus those not attending the allocated service within four months of randomisation by randomisation allocation

	Randomized to ACs (n=110)		Randomized to PHC clinics (n=108)	
	Attended AC within 4 months of randomization (n=94)	**Did not attend AC within 4 months of randomization (n=16)**	**Attended PHC clinic within 4 months of randomization (n=102)**	**Did not attend PHC clinic within 4 months of randomization (n=6)**
Median age (IQR), years	35.1 (29.8-42.1)	33.1 (25.0-37.0)	34.5 (28.6-44.0)	36.6 (28.2-44.5)
Gender, n (%)				
Female	65 (69.15)	9 (56.25)	68 (66.67)	4 (66.67)
Male	29 (30.85)	7 (43.75)	34 (33.33)	2 (33.33)
Home language: IsiXhosa, n (%)	82 (87.23)	15 (93.75)	97 (95.10)	5 (83.33)
Completed secondary/any tertiary education, n (%)	87 (92.55)	15 (93.75)	97 (95.10)	4 (66.67)
Currently employed	60 (63.83)	8 (50.00)	68 (66.67)	5 (83.33)
Currently in a relationship	67 (71.28)	13 (81.25)	65 (63.7)	4 (66.67)
WHO stage				
1	58 (61.70)	7 (43.75)	61 (59.80)	5 (83.3)
2	16 (17.02)	7 (43.75)	21 (20.59)	1 (16.67)
3	14 (14.89)	1 (6.25)	14 (13.73)	0
4	2 (2.13)	1 (6.25)	3 (2.94)	0
Unknown	2 (2.13)	0	2 (1.96)	0
	2 (2.13)	0	1 (0.98)	0
Any previous ARV use	22 (23.40)	3 (18.75)	24 (23.53)	1 (16.67)
Median time on ART (IQR), weeks	18.4 (17.0-20.0)	19.5 (17.9-20.3)	18.1 (17.0-20.0)	18.0 (17.3-19.3)
Current ART regimen: TDF/FTC/EFV	88 (100.00)	15 (100.00)	98 (100.00)	4 (100.00)
Disclosed to anyone other than a health professional	87 (92.55)	16 (100.00)	97 (95.10)	5 (83.3)
Missed ART dose reported in previous 30 days	30 (31.91)	7 (43.75)	37 (36.27)	2 (33.33)
Pre-initiation CD4 count (IQR), cells/µl	399.5 (279.5-496)	247 (159.5-475.5)	333 (224-516)	209 (168-307)
Missing: 5	2 (2.13)	0	3 (2.94)	0
Viral load, copies/mL				
<100	85 (90.43)	15 (93.75)	91 (89.22)	5 (83.33)
≥100	9 (9.57)	1 (6.25)	11 (10.78)	1 (16.67)

AC: Adherence club, ART: antiretroviral therapy, ARV: antiretroviral, EFV: efavirenz, FTC: Emtricitabine, IQR: inter-quartile range, PHC: primary health care, TDF: tenofovir.

Supplementary table 10.7.4 Results of additive binomial model examining the association between trial arm and primary outcome (VL <400 copies/mL) in per protocol population adjusted for demographic and clinical characteristics (n = 196)

	Risk difference	95% CI
Trial arm (intervention-control)	-2.66%	-11.56 to 6.24
Sex (male vs female)	-3.26	-13.46 to 6.94
Previous ART use (previous ART use vs no previous ART use)	-10.49%	-23.30 to 2.33
CD4 category (>200 vs ≤200)	-1.23	-12.23 to 9.77
Age (years)	-0.09%	-0.52% to 0.35

ART: antiretroviral therapy, CI: confidence interval.