A mixed methods study using linked demographic surveillance and health facility data to investigate and compare loss to follow-up among women living with HIV who initiated antiretroviral therapy during pregnancy under Option B+ in Agincourt, South Africa

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Abstract

This thesis aims to investigate engagement in Option B+ (life-long antiretroviral therapy (ART) for all HIV-positive pregnant and breastfeeding women) among pregnant and postpartum women residing in Agincourt health and demographic surveillance system (HDSS) in north-east South Africa. Paper A describes outcomes for 1325 patients reported as lost to follow-up (LTFU) in routine clinic records showing that patients who were pregnant at ART initiation have differing outcomes including a lower risk of death. Paper B reports on the spatial distribution of 315 patient transfers between clinics and identifies risk factors for these transfers, showing that pregnant and postpartum women are more likely to transfer their treatment, more likely to not report their transfer to their origin clinic, and less likely to transfer to a clinic outside the study area, when compared to adults in the general population. Paper C evaluates the accuracy of mortality estimates provided through routine treatment records in TIER.Net (the national HIV database), by comparing them to data generated through the record review and patient tracing. The results suggest that TIER.Net underestimates mortality and overestimates programme attrition, with important consequences for treatment programme policy, planning, and monitoring and evaluation, and estimation of the UNAIDS 90-90-90 targets. Paper D draws on in-depth interview data with women living with HIV to explore the intersection between early infant diagnosis (EID) and maternal engagement in care, finding that continued engagement in care promotes utilisation of EID, but also that the EID result can undermine maternal engagement in care. Paper E documents the challenges faced by patient tracing programmes and the lessons learnt during the ascertainment of patient outcomes and gives recommendations for future practice.

The collective findings of this PhD research provide estimates of HIV patient outcomes after LTFU from prevention of mother-to-child transmission of HIV (PMTCT) programmes and generate new insights into some of the underlying causes. This research demonstrates the feasibility of using multiple linked data sources to improve the ascertainment of these outcomes.

Dedication

They say the fixations of our childhood become the dogged pursuits of our adulthood…

I was born in 1987, at the dawn of what most people hoped would be the beginning of peace and prosperity. Uganda was just emerging from a long protracted civil war but unbeknownst to all there was a killer among us, one whose propagation we now know was aided by the war.

What followed was a decade of social devastation and upheaval. In 1991, that devastation visited my family when my cousin Natalie not yet a year old passed away. My young mind, barely able to contemplate death, was left with many questions. Questions that the adults were ill-equipped to answer. It visited again in 1992, this time taking my aunt, her mother. Throughout my childhood, HIV was my bogeyman. Like most kids I was afraid of vampires and werewolves, but I think that deep down inside I always knew those were not real. HIV on the other hand had had a tangible effect on my life. Unfortunately, in Uganda and Africa, my story is not unique.

A decade later, we were lulled into a false sense of security as antiretroviral medication became more widely available and the devastation of yesteryear was pushed into the deep recesses of our minds, and for many, soon forgotten.

In 2011, the devastation visited again claiming the life of my remaining paternal aunt. This event was a devastating reminder of many questions that had lain dormant within my mind for many years and led to a change in my life trajectory and goals.

My attempt at facing my bogeyman and hopefully coming out on the other side with some clarity and closure has ultimately culminated in this work. It is not lost on me that my topic focuses on women and children, the most affected population in Africa, as I can personally attest. It is not very often that you can say research has been therapeutic or helped to exorcise your demons. In many ways my life has come full circle, and this feels like a natural close to an important chapter of my life.

I dedicate this work to my aunts Dorothy and Helen, and my cousins Natalie and Daniel whose lives were directly or indirectly cut short by HIV and the many people known to me who have succumbed to the virus.

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"It takes a village to raise a child", I think this sentiment holds true for the completion of a thesis and so I would like to acknowledge the village that contributed to this work.

I would firstly like to thank my supervisors Alison Wringe and Georges Reniers for their time and dedication to my research. I would like to thank them for their encouragement and guidance over this four-year journey. I am particularly grateful to Alison for the multiple Skype and WhatsApp calls throughout the lockdown period which helped to keep me focused and motivated to complete this work.

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I am grateful to the staff at the MRC/WITS Rural Public Health and Health Transitions Research Unit in Agincourt, whose assistance with implementing my fieldwork was invaluable to its timely completion. I would like to thank Nkosinathi Masilela who took time out of his busy schedule to help me to get around early on in my fieldwork. I am indebted to the fieldworkers who helped with data collection for the quantitative component (Gladstone Shabangu, Sherly Ndubane, Nobuyiselo Sibuyi, and Boldwin Mkhawanazi) and qualitative component (Ella Sihlangu, Violet Ndhlovu, Sherly Ndubane, Meriam Maritze, and Princess Makhubela). I would especially like to thank Linda and Becca whose companionship and shenanigans made life in the field a lot more enjoyable.

To the many friends I have made at LSHTM and in London at large, your companionship has made what can sometimes feel like a very solitary

endeavour a lot less so. To the many friends with whom I shared an office, who helped to break up the day-to-day mundanity with drink breaks and lunch time discussions in the common room I say thank you. To the “LSHTM crew”, Anushé Hassan, Poppy Mallinson, Judy Lieber, Shammi Luhar, and Will Rudgard, the free therapy sessions in the form of commiseration over food and drinks as well as the multitude of solutions offered, helped me keep an even keel. I cannot forget to mention the daily zoom chats at the height of lockdown which were an ever-present reminder of the community and support I had around me and a great motivation to keep working even when all I wanted to do was stay in bed all day. To the friends outside LSHTM, I consider myself lucky to have you all in my life. Thank you for reminding me of my humanity when I sometimes felt alienated by my London experiences.

Finally, I would like to thank my family who have supported me through every challenge I have undertaken in my life, even if it meant putting up with me being so far away from home for so long. To my dad I say thank you. To my mum who has made many sacrifices for us and dedicated her life to making ours better, there are no words I can say that aptly convey my gratitude. To my siblings Deborah, Diana and Alex with whom I have shared many highs and lows and who challenge me to be better, your encouragement, humour and faith in me were succour. To the newest members of the family, my nieces and nephews who showed up at different points during my PhD and remind me to look at the bigger picture, I hope you get to grow up in a better and more egalitarian world.

Table of contents

List of figures

List of tables

List of acronyms

3TC	Lamivudine
AIDS	Acquired Immune Deficiency Syndrome
ALPHA	Analysing Longitudinal Population-based HIV/AIDS data on Africa
ANC	Antenatal care
ART	Antiretroviral therapy
ARV	Antiretroviral drug
AZT	Zidovudine
CBR	Crude Birth Rate
CCMDD	Central Chronic Medicine Dispensing and Distribution
CDC	Centres for Disease Control and prevention
CHC	Community Health Centre
CHW	Community Health Worker
CICT	Client-Initiated Counselling and Testing
DNA	Deoxyribonucleic acid
DOT	Directly Observed Therapy
EFV	Efavirenz
EID	Early Infant Diagnosis
EMTCT	Elimination of Mother-to-Child Transmission of HIV
ESRC	Economic and Social Research Council
FDC	Fixed Dose Combination
FTC	Emtricitabine
GIS	Global Information System

GPS	Global Positioning System
HAART	Highly Active Antiretroviral Therapy
HBC	Home-Based Carers
HCW	Healthcare Worker
HDSS	Health and Demographic Surveillance System
HEI	HIV-Exposed Infant
HIV	Human Immunodeficiency Virus
HRSA	Health Resources and Services Administration
HTC	HIV Testing and Counselling
IDI	In-depth Interview
ICD	International Classification of Diseases
LDC	Least Developed Countries
LSHTM	London School of Hygiene and Tropical Medicine
LTFU	Loss/Lost to follow-up
MeSH	Measurement and Surveillance of HIV epidemics
MDC	Most Developed Countries
MRC	Medical Research Council
MSF	Médecins Sans Frontières
MSM	Men who have sex with men
NVP	Nevirapine
PCR	Polymerase Chain Reaction
PEPFAR	President's Emergency Plan For AIDS Relief
PHC	Primary Healthcare
PICT	Provider-Initiated Counselling and Testing
PIRL	Point-of-contact Interactive Record Linkage

PLHIV	People Living With HIV
PMTCT	Prevention of Mother-to-Child Transmission of HIV
PNC	Postnatal care
RtC	Right to Care
SAPRIN	South African Population Research Infrastructure Network
SHAPE-UTT	Strengthening Health systems for the Application of Policy to Enable Test and Treat
SSA	Sub-Saharan Africa
TAC	Treatment Action Campaign
TDF	Tenofovir
UN	The United Nations
UNAIDS	The Joint United Nations Programme on HIV/AIDS
UNGASS	United Nations General Assembly Special Session
VA	Verbal Autopsy
VL	Viral Load
WBOT	Ward-Based Outreach Team
WITS	University of the Witwatersrand
WHO	World Health Organisation
WLHIV	Women Living With HIV

1.Introduction

Advances in antiretroviral therapy (ART) have transformed the global HIV epidemic (1) and changed HIV infection from a terminal condition to a manageable chronic disease (2–4). Added to the individual benefits of ART is the reduced horizontal and vertical transmission as a result of reductions in individual and community viral load (5–7). Starting in 2001 the World Health Organisation (WHO) has recommended some form of antiretroviral drug (ARV) prophylaxis for the prevention of mother-to-child transmission of HIV (PMTCT) starting with the first recommendation of single-dose and short-course ARV prophylaxis (8). Since 2015, the WHO treatment guidelines have recommended immediate lifelong ART for all pregnant and breastfeeding women regardless of disease stage in recognition of the health and preventative benefits of ART (9). This new policy also referred to as "Option B+" recommends continued testing throughout the pregnancy, postpartum and breastfeeding period with an immediate offer of ART for any women who test HIV positive, irrespective of CD4 count (a proxy for immunological status), or WHO stage (a proxy for disease progression) (10). It is hoped that this approach will contribute to the complete elimination of mother-to-child transmission of HIV (EMTCT) worldwide (10).

However, poor engagement in care and low adherence to ART have begun to emerge as major hinderances to the achievement of PMTCT programme goals. Specifically, patients who become lost to follow-up (LTFU) are a concern and may curtail the major accomplishments to date, including increases in mothers' life expectancy and reductions in vertical transmission (11). Loss to follow-up has become a term that describes all patients who go a period without a clinic visit or are untraceable. Historically, treatment programmes were more concerned with patients who remained retained in care and patients who became LTFU were censored with the censoring assumed to be random or uninformative (12). At the advent of ART, LTFU was low and much of LTFU was attributable to mortality (13–15). However, as treatment guidelines have changed and more healthy people living with HIV (PLHIV) have become eligible for treatment, LTFU has begun to rise, and increasingly,

less of LTFU can be attributed to mortality (16). This is particularly pertinent for women in "Option B+" programmes as they are often asymptomatic and healthy in terms of immunological status and disease progression. As such, loss to follow-up amalgamates a number of possible outcomes including death, undocumented transfers, and patients who have genuinely disengaged from care. However, studies of loss to follow-up have mostly ignored women who initiate ART for PMTCT, and few studies have investigated LTFU among women in "Option B+" programmes (17–19). This group differs significantly from the general treatment population due to changes during the pregnancy and postpartum period and in terms of disease progression and symptoms at ART initiation, and as such their outcomes after LTFU might differ as well. Understanding LTFU among women in "Option B+" programmes has also become more important with the advent of "Treat all" which extends universal ART coverage to all individuals diagnosed HIV positive (10). "Option B+" women represent the first iteration of universal treatment and as such, outcomes following LTFU for this group could represent what HIV treatment programmes can expect in terms of LTFU with the move to "Treat all", and the increase in the proportion of asymptomatic patients initiating treatment.

This thesis is a study of loss to follow-up among women who initiated ART under "Option B+" in rural north-eastern South Africa where "Option B+" became the national treatment guideline in 2015. Fieldwork was conducted between August 2017 and December 2018. This research is situated within the Agincourt health and demographic surveillance system (HDSS) which has been running since 1992 (20).

As part of this research, I ascertained the outcomes for patients considered to be LTFU by conducting a comprehensive record review and tracing study. Outcomes for "Option B+" women are compared to non-pregnant women and men living with HIV who initiated ART, in order to identify any differences between these groups. Additionally, in-depth interviews (IDIs) are utilised to explore engagement in care (broadly defined as the process of accessing HIV treatment and care services and remaining actively involved with regards to guidance given by service delivery personnel) for women under "Option B+"

with the aim of understanding this process from the perspective of the participants.

In this chapter, I describe the burden of vertical transmission both globally and in South Africa, give a brief background and overview of the problem of HIV in pregnancy in sub-Saharan Africa including the problem of poor engagement in care. I give a brief overview of the change in treatment guidelines for pregnant women living with HIV including the implementation of "Option B+", an overview on definitions of engagement in care, and present the argument for utilising clinic visit logs to assess engagement in care. Finally, I formulate the rationale for conducting this PhD research, present the main aims and objectives of the study, give a brief description of the study setting, lay out the structure of the thesis and describe my role in completing this PhD research.

1.1. The global burden of vertical transmission

HIV remains a major contributor to the global burden of disease. In 2018, an estimated 37.9 million people were living with HIV, of whom 1.8 million were children (21,22). Furthermore, of an estimated 1.7 million new infections in that year, 160,000 were among children (22).

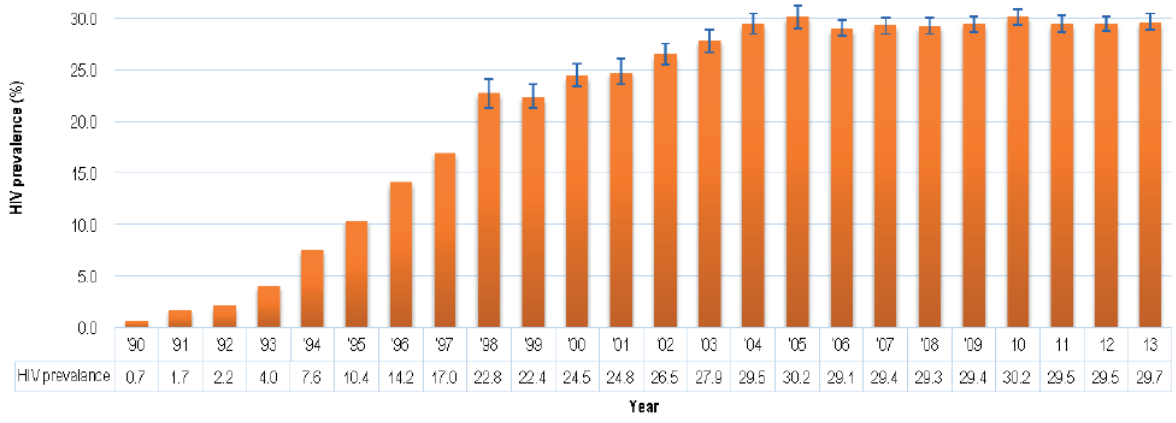
The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that about 1.5 million HIV-positive women give birth every year; a number that will only be exacerbated by the estimated 900,000 new annual infections among women of reproductive age (22). Encouragingly, 80% of HIV-positive pregnant women received ART to prevent vertical transmission globally in 2015 (21,22), representing a 60% increase since 2010. Although there was an almost threefold reduction in the mother-to-child transmission rate between 2010 and 2015, it was still estimated at 10% of all live births to HIV-infected women globally by 2015 (21). Worldwide HIV/AIDS accounted for 1.4% of all deaths among children aged 0-5 years old in 2015 (23). In sub-Saharan Africa, this proportion was estimated at 2.7%. Furthermore, among women aged 15-49 years old in this region, 11% of deaths in 2015 were attributable to HIV/AIDS (23).

In sub-Saharan Africa (SSA), women are disproportionately affected by the HIV epidemic. While 15% of the world's population lived in SSA in 2018, an

estimated 65% of 37.9 million people living with HIV worldwide, were living in SSA. This included 77% of all women living with HIV (24). In 2018, 59% of new infections in SSA occurred in women and about 90% of all pregnancies among women living with HIV occurred in this region (24). Promisingly, over 80% of pregnant women living with HIV in this region received ART for PMTCT in 2018, a figure that rises to 92% if only east and southern African countries are considered (24). However, there were still 142,000 new infections among children in SSA in 2018 (24).

In South Africa, the potential for vertical transmission is illustrated in Figure 1.1 which shows the rise of HIV prevalence in pregnant women since 1990 and its plateauing after 2005 (25). In 2013, an estimated 29.7% of women attending public sector health facilities were infected (25). In 2014, an estimated 240,000 HIV-positive women delivered in South Africa with >95% taking some form of ARV prophylaxis during their pregnancy (26). However, this was before the introduction of lifelong ART for prevention of vertical transmission (Option B+).

Figure 1.1: Prevalence of HIV infection among pregnant women in South Africa, 1990-2013*(SA NDoH (25))*



In South Africa, 9200 new-borns were perinatally infected in 2014, a 76% reduction in new infections since 2009, and 94% of HIV-exposed infants received an early infant diagnosis (EID) test by 2 months as recommended by the WHO (26,27); however, testing coverage at the end of the breastfeeding period is not as high (28). The transmission rate at 6 weeks postpartum was estimated to be 2% and increased to 4% when the breastfeeding period was included; a reduction from 15% in 2009 (26). In 2011, 70.4% of maternal

deaths and 50% of all deaths of children under five in South Africa were attributable to HIV infection (29,30).

1.2. HIV in pregnant and postpartum women

Among pregnant and postpartum women living with HIV, continued engagement in care has individual and population-level benefits (10). Firstly, ART reduces morbidity and mortality which has many benefits for these women and their immediate circle of family and friends (6). Secondly, it has the benefit of reducing the risk of vertical transmission to almost zero provided they remain virologically suppressed throughout the pregnancy and breastfeeding phase for both the current and future pregnancies (31). Finally, remaining engaged in care and virologically suppressed prevents transmission of HIV to HIV-uninfected sexual partners, a major reason underlying the change in guidance to test and treat all people who test positive for HIV (7,32,33).

Despite all the important benefits of continued engagement in care, data from PMTCT programmes and demonstration projects throughout SSA indicates that many women do not remain engaged in care and adherent to treatment (11). A systematic review in 2018 found that retention among pregnant and breastfeeding women living with HIV in Africa was as low as 42% after 12 months on ART (11). Long-term studies also had varying retention rates. For example, in Malawi, 70% of women were retained after three years on ART (34). While in Eswatini, only 53% of women were retained after two years on ART (35).

1.3. HIV treatment guidelines for pregnant and postpartum women

There has been a dramatic shift in the treatment guidelines for pregnant and postpartum women in SSA to a more holistic approach emphasising not just healthy babies but healthy mothers as well and recognising the value of HIV treatment on population health outcomes. This shift occurred concurrently with the shift in our understanding of HIV transmission and the role of ART. Global guidelines first recommended single-dose and short-course ARV prophylaxis for PMTCT in 2001 and have evolved to recommend lifelong ART

for those meeting certain criteria, to finally recommending lifelong ART for all pregnant and breastfeeding women regardless of CD4 (Figure 1.2).

Figure 1.2: Evolution of PMTCT recommendations and guidelines[1]

						
YEAR	2001	2004	2006	2010	2013	2015
PMTCT	4 weeks AZT; AZT+3TC; single dose NVP	AZT from 28 weeks + single dose NVP	AZT from 28 weeks + single dose NVP + AZT/3TC for 7 days	Option A (maternal AZT + infant NVP to the end of breastfeeding) Option B (maternal triple ARVs to the end of breastfeeding)	Option B or B+ Moving to ART for all pregnant or breastfeeding women	TREAT ALL
ART	None	CD4<200	CD4<200	CD4≤350	CD4≤500	Test and treat all

Universal lifelong ART for pregnant and breastfeeding women, also referred to as "Option B+" was first implemented in Malawi in 2011 (36). This was due to a lack of the CD4 testing capacity to use CD4 as a criterion for treatment initiation and in recognition of the substantial burden and risk of drug resistance from stopping and restarting ART during subsequent pregnancies both for the women and the health system (37,38). Since its advent, it has become the standard of care in all countries in SSA (39). As a result, antenatal care (ANC) services have become a major entry point into lifelong ART programmes for women (40,41). HIV testing during pregnancy has become the norm in most SSA countries with testing coverage among pregnant women increasing steadily (41). The elimination of CD4 count as an initiation criterion has simplified treatment guidelines, streamlined the process and minimised delays in ART initiation during pregnancy and breastfeeding with same-day initiation becoming common in SSA (31,41–43). Despite all these achievements, the success of PMTCT programmes in SSA is threatened by persistent problems with women's poor long-term engagement in care (41).

[1] AZT – Zidovudine, 3TC – Lamivudine, NVP – Nevirapine

1.4. The concepts of engagement in HIV care and loss to follow-up

Engagement in care encompasses two main concepts, retention in care and adherence to ART which have been identified as significant barriers to achieving optimum outcomes in ART programmes (44) and these have been defined and conceptualised in myriad of ways.

Most studies usually present two statistics when reporting on engagement in Option B+. The proportion of women retained in care at a specific time point following ART initiation, or the proportion of women who drop out of a treatment programme at specific points on the treatment cascade (11,35). It has been argued that the cross-sectional nature of these metrics means they do not accurately present the complicated and cyclical nature of engagement in care (45).

Other authors present different ways of conceptualising engagement in HIV care (46–48). Gardner et al describe a spectrum of engagement in care (adopted from the Health Resources and Services Administration (HRSA) continuum of engagement in ART care) according to which varies between an individual not knowing their status to being fully engaged in care, indicated by the achievement of viral suppression (46) (Figure 1.3).

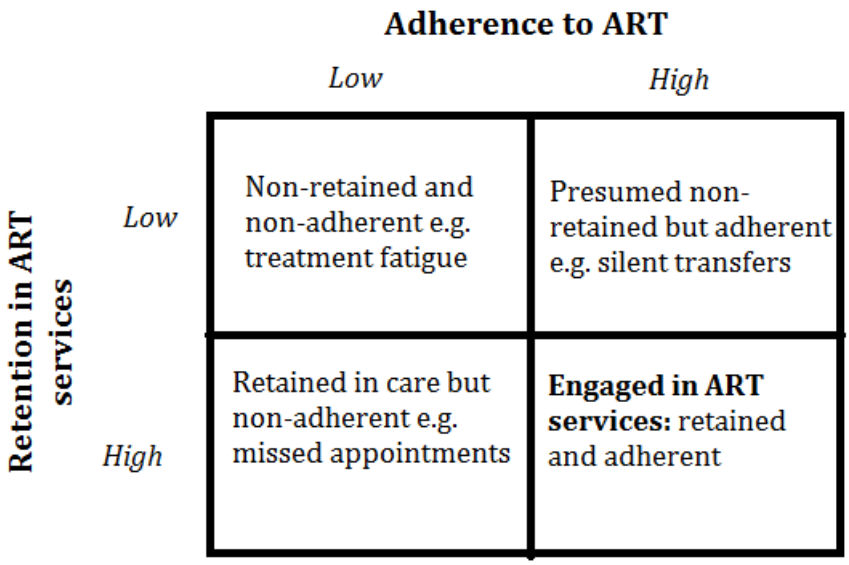
Figure 1.3: The spectrum of engagement in ART care *(The Health Resources and Services Administration (HRSA) continuum of engagement in ART care (49))*

Vrijens et al propose a framework where patients move through several stages, initiation, implementation, persistence and discontinuation. Initiation pertains to prescription of the first dose of ART, implementation to adherence

and non-adherence, and persistence to how long patients remain on treatment as prescribed without discontinuing treatment (47).

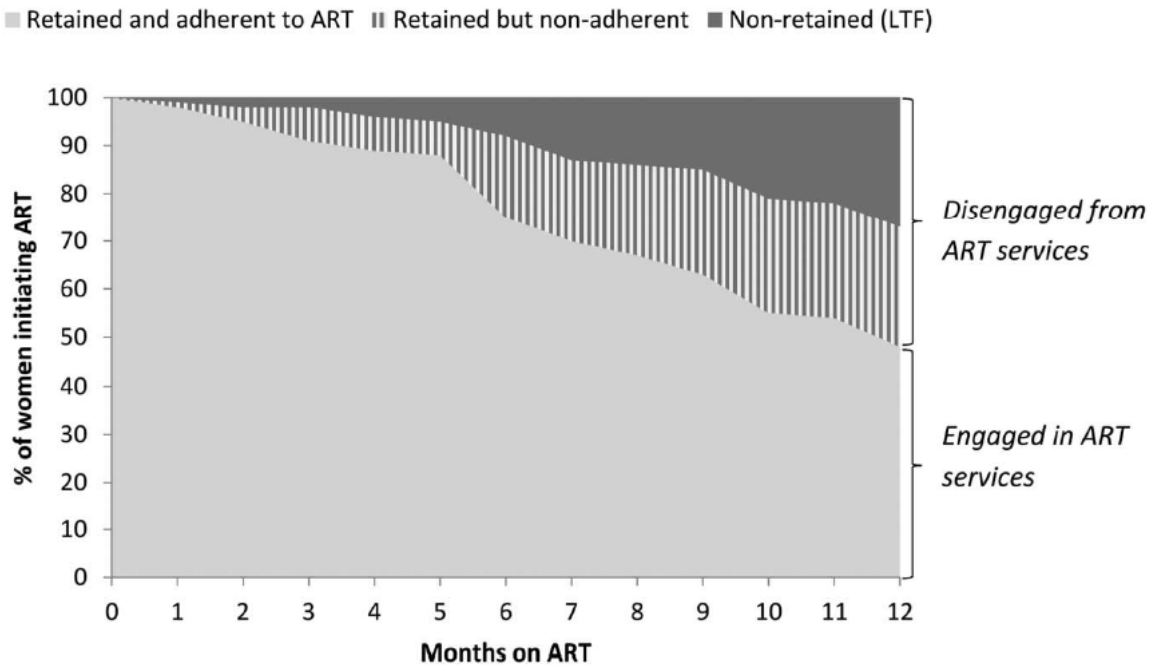
Myer et al conceptualise engagement in care using the continuum of two metrics: retention in care and adherence (48). According to Myer, an individual who remains retained in care and properly adherent is defined as engaged in care (Figure 1.4).

Figure 1.4: A framework for the relationship between ART adherence and retention in care *(Myer et al (48))*



Furthermore, Myer proposes a time dimension when thinking of engagement. As such, all women might be fully engaged in care (retained and adherent) when they initiate treatment but as time passes, some women may become disengaged from care by either being retained but non-adherent or by no longer being retained in care (48) (Figure 1.5).

Figure 1.5: Engagement in care (retention and adherence over time) (Hypothetical depiction from Myer et al (48))



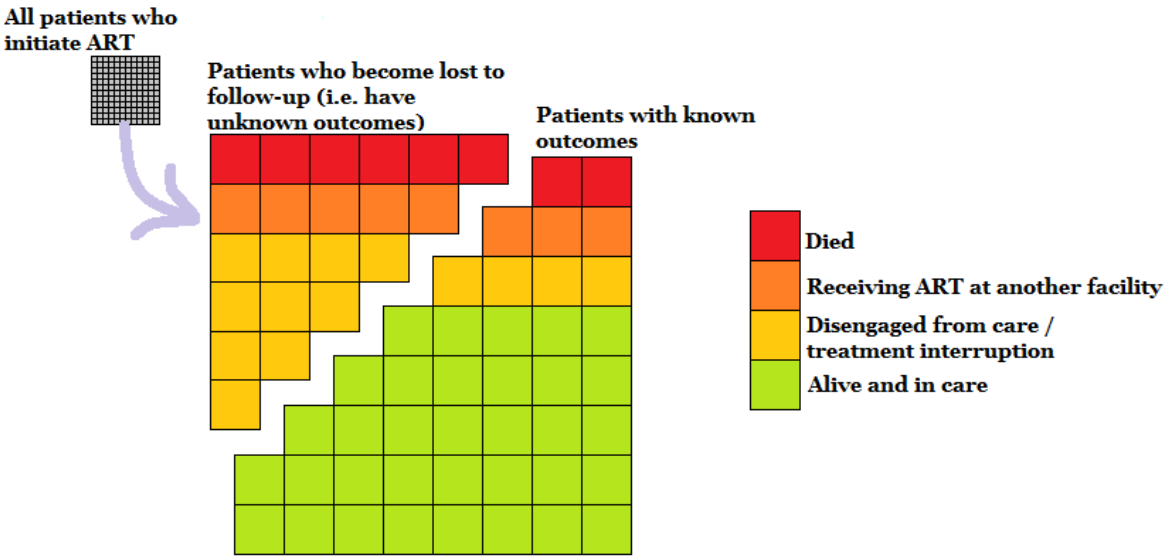
This thesis focuses on retention in care and loss to follow-up after ART initiation. These two concepts (as well as adherence) are closely related, therefore I outline the differences here.

Retention in care refers to all patients who remain active within a programme and who are routinely visiting a clinic for ART refills. Most ART programmes including those for PMTCT report a composite unfavourable outcome for patients who are no longer retained in care and who have an unknown outcome usually called loss to follow-up (Figure 1.6).

Loss to follow-up is the antithesis of retention and may be a consequence of poor engagement in care. Loss to follow-up is a general term for the unknown outcomes of patients who do not return for an ART refill appointment at a particular clinic (50–52). This variable amalgamates patients that have transferred their treatment to another clinic without proper documentation of the transfer (also referred to as unknown transfers (52), undocumented transfers (53), 'silent' transfers (54), self-transfer (15), or receiving ART at another facility) (55), patients that have had a treatment interruption or that

have stopped taking ART (also referred to as unstructured treatment interruptions (56)), patients that have died (also referred to as unreported deaths (52), and unknown death), and patients that have been misclassified either because of poor record keeping or human error.

Figure 1.6: A graphical representation of patients with known and unknown outcomes (LTFU) *(Adapted from WHO (51)).*



Loss to follow-up is commonly defined as a period without a clinic visit, a number of days late for an appointment, a missed appointment, or even a situation where a patient is untraceable. A systematic review of retention in sub-Saharan ART programmes reported eight different LTFU definitions (57). Some sources did not include a definition of LTFU. How LTFU is defined can significantly impact patient outcomes (58). For example, a short window of no visits can increase the number of patient misclassifications (59,60).

As such, how a programme defines LTFU will have an impact on estimates of retention in care. By reducing loss to follow-up, programmes improve their retention statistics. The WHO defines LTFU (a general term for non-retention) as "patients receiving ART and not seen at the clinic or pharmacy for >90 days after the date of their last missed appointment or last missed drug pick-up and who are not known to have transferred or died" (51). Importantly, the WHO recommends that a distinction should be made between patients with an

unknown outcome (LTFU) and patients who cease to engage in the continuum of care because of their own wishes, beliefs or because of barriers to continued access to care (due to transportation, stigma, resources, etc), referring to the latter as disengagement from care (51).

Adherence is a marker that measures how well a patient is taking ART as prescribed in terms of correct times and frequencies. As such, in order to be adherent, a patient should have a constant supply of ART and must therefore be retained in care (61). However, a patient can be retained in care but non-adherent for example if they attend their clinic visits regularly and collect their treatment but do not take ART as prescribed. The WHO defines ART adherence as "the extent to which a person's behaviour corresponds with the agreed recommendations from a healthcare provider" (62). Adherence can be measured in myriad ways including objective measures such as directly observed therapy (DOT) (63), drug concentrations (64,65), pill counts (66,67), pharmacy refill data (68–70), and electronic pill monitoring systems (71); and subjective measures such as self-reported adherence (72–74). Increasingly, viral load is being used as a proxy marker for adherence as adherent patients should have an undetectable viral load, provided that they do not have drug resistant HIV (75,76). By the end of 2018, 60% of low- and middle-income countries had fully implemented viral load monitoring, but multiple obstacles still exist that curtail the optimum implementation of these programmes, particularly in SSA (39,77). Viral load monitoring has its weaknesses, principle among these is that it is only taken periodically and as such might not be very informative about patterns of adherence (64). Viral load is also to a lesser extent driven by other factors such as drug resistance and comorbidities (78,79). Therefore, other measures of engagement in care remain important to monitor ART programmes and evaluate their outcomes particularly in SSA where viral load testing is not yet fully implemented (41,44). While adherence is an important measure for evaluating the benefits of ART, this thesis does not specifically address adherence and its challenges.

Epidemiological assessment of engagement in care still has its merits. Consequently, for the purpose of this thesis, engagement in care will concentrate primarily on retention in care, specifically looking at clinic visit

logs. Frequent viral load testing was not possible and viral load monitoring data was scant at the time of analysis but is being updated and provides potential future research directions. A patient was considered to be LTFU if they were >90 days late for a scheduled appointment keeping with the WHO definition. Patients that were LTFU could re-engage in care and so the Myer et al and Gardner et al definitions are also loosely considered.

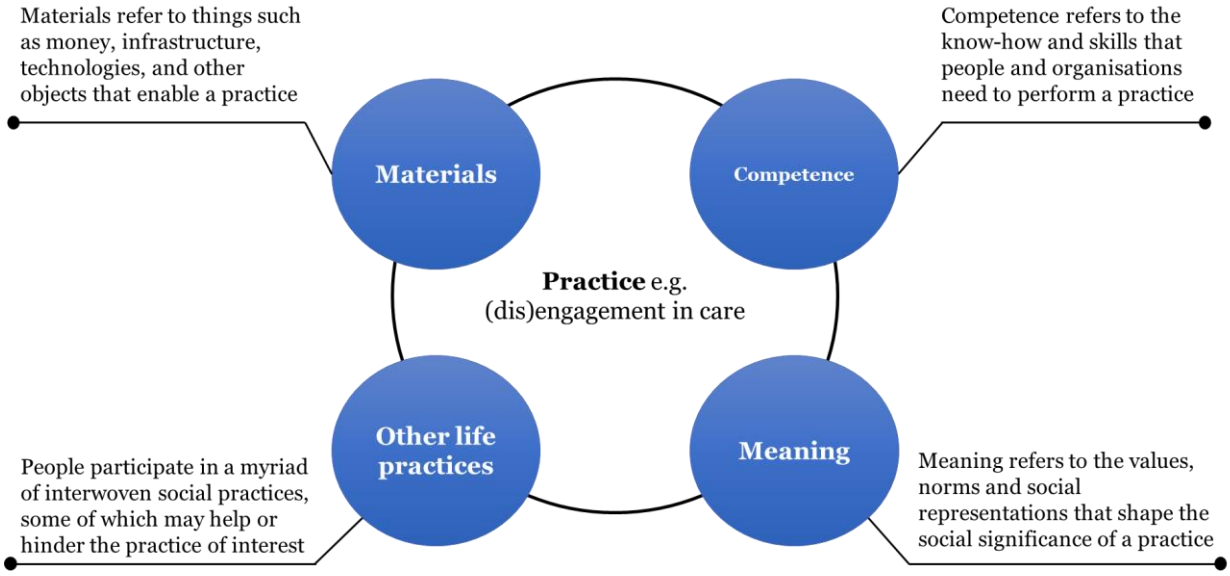
Finally, it is important to consider that some facets of engagement in care may be non-quantifiable and as such might require other methods to assess them. Engagement in care is not as neat as cascade diagrams would have us believe and therefore there are merits of a social science approach to exploring engagement (45). The concept of engagement in care as a linear, unidirectional cascade or continuum in which patients initiate treatment and remain in care until a terminal event is narrowly focused. Measures of engagement in care such as retention and adherence (usually measured through a viral load) are not a goal to be achieved per se but a state that needs to be maintained over time. While important concepts, that are essential for surveillance and a good barometer with which different treatment programmes can compare and gauge their progress, they do not shed light on the lived experience of those in care. As such, social concepts within engagement that are difficult to quantify are therefore missed in quantitative explorations of engagement. Therefore, aspects such as social and structural features of engagement in care may be better investigated and understood using qualitative methods (45).

1.4.1. Practice theory to explain engagement in care

Practice theory is increasingly being used to understand engagement in HIV care in sub-Saharan African settings (80–82). Practice theorists treat practices – "the elements that shape our perceptions, interpretations and actions" (83,84) – as their primary units of enquiry and contend that people's practices can be explained by generic 'elements' which include materials or tools required to enact a practice, symbolic meanings associated with a practice, and competence and know-how to enact a practice (Figure 1.7). Each individual has a constellation of practices that they engage in, with some of these practices interacting either harmoniously or in conflict. Consequently, the enactment of one practice is likely to affect other practices (83,85–87). As

such, the impact of all these factors is likely to be dependent on individuals' unique constellations of practices and their perceptions about HIV and its treatment (83). This theory will feature prominently in my conceptualisation and explanations of engagement in care, especially pertaining to the qualitative component of my thesis.

Figure 1.7: Summary of the practice theory framework *(Adapted from Skovdal et al (83))*



1.5. Study Rationale

The overall rationale of this thesis follows from the global push to eliminate vertical transmission of HIV. This will only be possible if pregnant women living with HIV have access to services that enable the health system to identify them in a timely manner, refer them to the appropriate HIV care, keep them retained in care for life, and follow-up on their exposed infants adequately and appropriately. Many studies in sub-Saharan Africa have reported sub-optimal rates of retention in care (11,88,89), which threaten the success of the intervention. While more recent findings suggest that Option B+ women retained in care past the first and second year of ART are lost to follow-up at a similar rate to the general HIV treatment cohort (34), work still has to be done to understand why their retention rates are lower than the general HIV treatment cohort in the first two years. Research to improve the efficacy of Option B+ will remain an important area, in order to bring vertical transmission rates around the world close to zero.

Understanding the true outcomes of women who become LTFU after initiating ART through Option B+ will help to accurately monitor and report on indicators for national ART programmes and better target tracing efforts. LTFU can lead to underestimation of retention and deaths and is likely to overestimate attrition rates (90). Accurate mortality estimates are especially important as these are used as parameters for projections in software packages such as UNAIDS spectrum package (91,92). Understanding engagement in care for HIV-positive pregnant women who are often asymptomatic will also help to understand engagement in care for patients initiated under "treat all" initiatives which provide ART to HIV-positive individuals, irrespective of their immunological or clinical status (9,10,93–96). Furthermore, with the ambitious UNAIDS targets (97,98), ascertaining HIV patients' treatment outcomes is important especially to accurately measure the proportion of people diagnosed with HIV receiving sustained ART.

Many HIV treatment programmes in sub-Saharan Africa still rely heavily on paper-based registers which suffer from several problems including incompleteness, cumbersomeness that results from increasing patient numbers and length of patient follow-up, and a lack of unique identifiers (99–101). The lack of unique identifiers in most programmes makes it impossible to link all pertinent patient data together especially for pregnant women who may attend a separate clinic for ANC and for HIV care and treatment. The lack of linkages between clinics also means that "silent transfers" (whereby patients change clinics informally, without accompanying documentation), are often missed (15,99,102). Furthermore, despite facing serious health challenges, many of these programmes lack high-quality data required to monitor and mitigate these challenges.

Long-term community cohorts (20) provide an opportunity to investigate the uptake and impact of Option B+ at a population level. These community cohorts collect demographic, behavioural and health information regularly and have unique identifiers for each individual. Agincourt Health and Demographic Surveillance System (HDSS) in South Africa, run since 1992 by the MRC/WITS Rural Public Health and Health Transitions Research Unit under the University of Witwatersrand is one of these community cohorts(20).

In 2014, Agincourt HDSS also started an innovative procedure known as Point-of-contact interactive record linkage (PIRL) linking demographic and clinical data from nearby clinics (103,104). Given that most previous Option B+ retention studies have been conducted as clinical cohorts, this linkage of multiple data sources allows for the utilisation of data not captured at the clinic level such as socioeconomic status, changes in residence and marital status. Agincourt HDSS also conducts verbal autopsies (VA) which seek to ascertain probable causes of death for HDSS residents through a structured interview conducted with people closely related to or who took care of the deceased and can report on symptoms (105,106). With the availability of VA data, causes of death for all patients found to have passed away can give an indication of predominant causes of death in mothers LTFU. Such an endeavour will allow for accurate estimation of Option B+ coverage rates, undocumented transfers between clinics, deaths, outcome misclassifications and genuine ART discontinuation. It would also allow us to understand at which specific steps in the cascade most mothers are LTFU and thereby identify interventions to mitigate these leakages.

South Africa is one of the priority countries identified by UN Global Plan towards the elimination of new HIV infections among children. In 2019 South Africa had the highest number of HIV-positive pregnant women among the 21 priority countries (an estimated 310,000) (24) and had the second highest number of children acquiring HIV through vertical transmission in 2014, an estimated 29,100 (107). Whereas UNAIDS figures indicate that >95% of HIV-positive pregnant women received ART in South Africa in 2017, studies from the country have shown that attrition rates following ART initiation vary in this setting (43,102,108,109). Compared to other SSA countries, South Africa had higher ARV prophylaxis and ART coverage rates and lower vertical transmission rates with regards to Option A, likely due to a well-resourced healthcare system (110). However, they were late in implementing Option B+. This well-resourced healthcare system offers some advantages for research into engagement with Option B+ services, most especially a well-established electronic HIV patient monitoring system called TIER.Net.

Global HIV/AIDS programmes and organisations including UNAIDS and WHO use routine data from national treatment programmes such as those produced by TIER.Net to measure progress and plan future targets. As a result, any biases in data from routine data systems have the potential to mislead national and international programmes and may lead to investment in the wrong areas. Coverage may be mis-estimated due to uncertainty in national estimates. Uncertainty arises because of (i) uncertainty around true outcomes following LTFU, (ii) human error in recording data into the system. This is discussed further in paper C. UNAIDS has called for improvements to collection and use of routine data in order to inform policy, planning and programming with the ultimate goal of improving health outcomes for HIV-positive patients including pregnant women and their infants (111). An evaluation of TIER.Net would therefore help to understand its biases and improve estimates generated from data obtained from it.

The aim of the quantitative analyses presented in this thesis is to describe HIV patient outcomes after they become lost to follow-up and to compare the outcomes of women who initiated treatment while pregnant (under Option B+) to those of the general population, more specifically non-pregnant women and men aged 18 years or older. Men in sub-Saharan Africa have been identified as a priority population, as several studies have shown them to be lagging behind women in many treatment indicators including timely ART initiation, and retention in care (112,113). As late presenters, they represent the proportion of the population that seek care later in the progression of HIV and give an indication of how effective treatment programmes may be for people who initiate treatment late. These analyses include in-depth investigations of mortality, re-engagement in care and transfers to other facilities. A second aim of the quantitative analyses is to evaluate TIER.Net in order to improve estimates generated from this system for planning and modelling purposes. Finally, qualitative methods aim to explore the intersection between EID and engagement in care further exploring factors that may influence women's decision to remain engaged in care. The mixed method approach used in this thesis will allow for a nuanced exploration of engagement in care and will help to provide recommendations for improving HIV services in this rural community, in South Africa and comparable settings.

1.6. Aims and objectives

The overall aim of this PhD research is to investigate HIV-positive women's treatment outcomes after loss to follow-up following uptake of PMTCT services and compare their outcomes to the general treatment cohort of HIV-positive patients in a rural community in north-eastern South Africa (Agincourt HDSS), in order to inform strategies to improve retention in the PMTCT programme.

The objectives are as follows:

1. To investigate loss to follow-up among patients who initiated ART under Option B+ with the following specific objectives
    a. To understand the outcomes of these patients after they become LTFU in South Africa (Agincourt HDSS)
    b. To compare their outcomes to the general HIV patient treatment cohort
    c. To explore factors associated with different outcomes following loss to follow-up
2. To critique data sources and methods typically used to investigate retention in care following uptake of PMTCT services
    a. To critique routine tracing procedures and methods used to investigate attrition from HIV treatment in primary health care in rural South Africa (Agincourt HDSS)
    b. To investigate discrepancies and biases in the official HIV-patient treatment statistics on retention rates, LTFU and mortality produced by TIER.Net, the South African HIV-patient electronic monitoring system.
3. To explore the link between maternal engagement in care and early infant diagnosis of HIV
4. To identify and recommend strategies to improve retention in PMTCT services

Table 1.1: Research objectives with methods to address each objective

RESEARCH OBJECTIVE	METHODS AND DATA SOURCES
To understand the outcomes of these patients after they become LTFU in South Africa (Agincourt)	A review of published literature A quantitative analysis of the outcomes of patients after they become LTFU using the PIRL dataset and record review and tracing data (Paper A)
To compare their outcomes to the general HIV patient treatment cohort	A spatial analysis of mobility and clinic switching after patients become LTFU using the PIRL dataset and record review and tracing data (Paper B) A quantitative analysis of the outcomes of patients after they become LTFU using the PIRL dataset and record review and tracing data (Paper A)
To explore factors associated with different outcomes following loss to follow-up	A quantitative analysis of factors associated with mortality after patients become LTFU using the PIRL dataset and record review and tracing data (Paper A) A quantitative analysis of factors associated with transfer to another facility after patients become LTFU using the PIRL dataset and record review and tracing data (Paper B)
To critique routine tracing procedures and methods used to investigate attrition from HIV treatment in South Africa (Agincourt)	A critical assessment of the challenges with tracing patients who are late for clinic appointments in rural South Africa (Paper E) Reflections, observations and informal discussions with local stake holders including healthcare workers and local researchers
To investigate discrepancies and biases in the official HIV-patient treatment statistics on retention	A quantitative analysis on misreporting of patient outcomes in the South African national treatment database, TIER.Net

rates, LTFU and mortality produced by TIER.Net the South African HIV-patient electronic monitoring system	using the PIRL dataset and record review and tracing data (Paper C)
To explore the link between maternal engagement in care and early infant diagnosis of HIV	A qualitative exploration of the intersection between women's experience of early infant diagnosis and their engagement in care using IDIs (Paper D)
To identify and recommend strategies to improve retention in PMTCT services	A review of published literature A critical assessment of the challenges with tracing patients who are late for clinic appointments in rural South Africa (Paper E) Discussions with local stakeholders

1.7. Research setting

This PhD research took place in the Agincourt HDSS, a rural north-eastern area of South Africa located in the Bushbuckridge local municipality in Mpumalanga province. The study site is run under the MRC/Wits Rural Public Health and Health Transitions Research Unit, administrated by the School of Public Health at the University of Witwatersrand (WITS) and has been tracking demographic and health events in xiTsonga or Shangaan people since 1992 being the longest running community cohort study in South Africa and one of the oldest in Africa as a whole. The Agincourt HDSS study area covers 475 km^2 and the primary healthcare system is organised into three community health centres, five clinics, and three hospitals 25-60km away from the study site. As of 2014, the population was approximately 115,000 people living in 17,000 households spread over 30 villages (20). Agincourt is part of multiple global research networks including the INDEPTH network, Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA) network and the South African Population Research Infrastructure Network (SAPRIN).

In parallel to demographic surveillance, a key element of the data infrastructure for this research consists of HIV patient visit logs collected by a study fieldworker in the health facilities that provide ART in the area. This work started in April 2014 at seven government facilities and was extended in

2015 to include one additional health facility. In addition to logging patient visits, these records are linked to the Agincourt HDSS using a procedure known as Point-of-Contact Interactive Record Linkage (PIRL) (103,104). In brief, a fieldworker conducts a short uptake interview with patients in the waiting area of the clinic. Patients who consent are asked to declare a few personal identifiers that are used to search a local copy of the Agincourt HDSS database using a probabilistic algorithm. Matches are confirmed during interactions with the patients, and the names of other household members are used as a key attribute to adjudicate between possible matches (114).

Every HIV-positive patient in the eight health facilities included in record linkage has a clinical file that is updated at each clinic visit. Following the clinical visit, information from the patient file is entered into an electronic database called TIER.Net (National HIV patients' medical records electronic database). Two non-profit organisations (Home-Based Carers (HBC) and Right-to-care (RtC)) lead tracing activities in the region. RtC has provided tracing and technical assistance in the area since 2010.

Further details of record linkage, health facilities, study population and Agincourt research activities are provided in chapter 3.

1.8. Data sources

Data for this thesis were drawn from four sources (both primary and secondary): (i) an observational cohort study of PLHIV which involved a comprehensive record review and tracing to ascertain their treatment and vital status following reported disengagement from HIV services at eight facilities located in the Agincourt HDSS, (ii) secondary data routinely collected at the eight health facilities for all patients receiving HIV care and treatment, (iii) secondary data generated through annual demographic surveillance surveys in the Agincourt HDSS, and (iv) IDIs conducted with a sample of patients who had ever received care from any of the eight facilities in the Agincourt HDSS.

1.8.1. Record review and tracing study

All HIV-positive adults (18 years or older) who had declared residence in the Agincourt HDSS during record linkage and who had enrolled in HIV care since 2014 were eligible for the study. Using the PIRL database, patients who met the criteria for LTFU (>90 days late for a scheduled appointment) were

identified. The current status of these patients was ascertained through a comprehensive record review that involved querying all available data sources in the clinics including (i) TIER.Net (the national electronic patient monitoring system) (ii) patient clinic files (iii) logbooks kept by all actors responsible for routine tracing. This was followed by a review of the PIRL database for duplicate patients (the same individual linked to multiple clinic records which probably indicated silent transfers) and a review of residency and vital status from the demographic surveillance data in the Agincourt HDSS database. A list of patients who did not have a final outcome following this process was handed over to the clinics for supplementary tracing through HBC.

These data sources are described in more detail in chapter 3.

1.9. Structure of the thesis

This thesis is presented in research paper style, including five published, in press, or submitted (and under review) publications in peer-reviewed journals (A-E), and four additional chapters including this introductory chapter.

Chapter 2 is the literature review and gives an in-depth account of the global interventions to curtail vertical transmission of HIV which culminated in the introduction of "Option B+". This chapter also collates information from published literature on the issues that have plagued the implementation of "Option B+" including poor retention in care and low uptake of early infant diagnosis. The chapter concludes by synthesising published knowledge on loss to follow-up, providing data on patient outcomes like mortality. This chapter serves as the launching pad for the investigation of engagement in care, loss to follow-up, and early infant diagnosis that follow in the results chapters.

Chapter 3 is the methodology chapter and provides details of the study setting, including local health facilities, as well as Agincourt HDSS activities. It also presents the methods used for quantitative analyses, including fieldwork undertaken to prepare databases and detailed statistical analysis methods used to analyse the data generated. The chapter concludes with an overview of the qualitative research methods and also provides full details of the qualitative fieldwork and all the analyses conducted on the data generated through this route.

Chapters 4, 5 and 6 present the results of quantitative analyses using linked demographic surveillance and clinic datasets. Chapter 4 is the first research paper (paper A), published in the Journal of Acquired Immune Deficiency Syndrome (JAIDS), describing the true outcomes for patients who had been reported as LTFU from eight health facilities in the Agincourt HDSS. The paper compares outcomes for "Option B+" women to the general HIV patient treatment population in order to identify any differences. The paper also identifies factors associated with mortality following loss to follow-up. Chapter 5 is a research paper (Paper B) submitted to the Journal of AIDS Care and currently under review. This paper describes health facility transfers and mobility for patients reported as LTFU at the facility at which they initiated ART. Chapter 6 is a research paper (Paper C) published in Frontiers in Public Health, assessing the discrepancies and biases that would arise from relying solely on patient outcomes reported in TIER.Net compared to utilising outcomes ascertained through multiple data sources from the record review and supplementary tracing process.

Chapter 7 is a research paper (Paper D) presenting the findings from the exploration of the data generated through the qualitative fieldwork. This paper published in the Journal of Global Public Health, explores the relationship between pregnant and postpartum women's engagement in care and their experiences of early infant diagnosis of HIV and how these processes interact to either undermine or support each other.

Chapter 8 is a research paper (Paper E) published in Global Health Action (GHA), describing the challenges observed with routine tracing in the health facilities that serve the Agincourt HDSS.

The thesis concludes with a discussion (chapter 9) of overall findings drawing from each of the results papers, recommendations and areas of future research, as well as the strengths and limitations of the PhD research.

The appendix includes all the study tools, and other disseminated work, including posters and slides presented at international conferences.

Table 1.2: List of papers with their objectives and data sources

	PAPER TITLE	SPECIFIC OBJECTIVES OF THE PAPER	Routine Agincourt cohort data (demographic surveillance)	Routine health facility data from eight facilities in Agincourt	Data collected through the tracing study	Qualitative (IDIs and observations)
A	Outcomes after being lost to follow-up differ for pregnant and postpartum women when compared to the general HIV treatment population in rural South Africa (115).	To describe and measure outcomes for pregnant and postpartum women following loss to follow-up and compare these outcomes to the general HIV treatment population.	✓	✓	✓	
B	Getting on with their lives: Understanding clinic transfers among HIV patients considered lost to follow-up in rural South Africa.	To investigate and describe health facility mobility of residents of the HDSS who initiated ART and who were recorded as LTFU.	✓	✓	✓	
C	Misreporting of patient outcomes in the South African national HIV treatment database: Consequences for programme planning, monitoring, and evaluation (116).	To assess misreporting in TIER.Net and potential biases in the national programme statistics reported from the TIER.Net database.	✓	✓	✓	
D	"If the results are negative, they motivate us." Experiences of early infant diagnosis of HIV and engagement in Option B+ (117).	To explore the nature of engagement in care for "Option B+" women and its relationship with experiences of early infant diagnosis of HIV.				✓
E	Challenges with tracing patients on antiretroviral therapy who are late for clinic appointments in rural South Africa and recommendations for future practice (118).	To elicit challenges in the implementation of HIV patient tracing as described in the national policy by comparing it with actual implementation.		✓	✓	

1.10. Role of the candidate

1.10.1. Overall design and planning

I led the overall conceptualisation of this research. As this research was not part of an existing study, I submitted a funding application for my proposed topic to the Economic and Social Research Council (ESRC). This included writing the research protocol for the funding application. I was also responsible for framing of the objectives and research questions and the design of the record review and tracing study, which is the primary source of data used in this research. I received academic support and feedback during this process from my supervisors Alison Wringe (AW) and Georges Reniers (GR). Technical support in the field and advice on the local setting was given by Francesc Xavier Gomez-Olive (FXGO) and Chodziwadziwa Kabudula (CK). I also designed the qualitative research component of my research with input from AW and Jenny Renju (JR). I prepared all ethics applications associated with my research project.

1.10.2. Quantitative data collection and analysis

My quantitative work in this thesis utilises secondary data generated through annual demographic surveillance surveys in Agincourt HDSS. I was not responsible for the design or management of these surveys.

For the comprehensive record review process of my fieldwork, I selected fieldworkers in collaboration with the human resources manager in Agincourt. I trained the chosen fieldworkers and designed the data entry tool in Microsoft Access (Appendix 11.3.1) to capture the data from the clinics. Data collected in this process included routine clinic data in patient files, data on TIER.Net and data captured in tracing logbooks kept by RtC and HBC. I spent a total of six months in Agincourt supervising fieldworkers and collecting some of this data myself.

I worked in collaboration with one fieldworker, FXGO, HBC and clinical staff to conduct the supplementary tracing for patients who did not have a final outcome following record review. Further details on this and the record review are discussed in chapter 3.

I merged, cleaned and prepared the final database for analysis. I designed and carried out all the analyses with guidance from my supervisors, my advisory committee and other collaborators on my papers.

1.10.3. Qualitative data collection and analysis

For the qualitative component of this PhD, I designed the data collection tools, wrote the study protocols and constructed the sampling frame using secondary datasets. I worked closely with AW and FXGO in this process. I selected fieldworkers in collaboration with the human resources manager in Agincourt. I spent one month in Agincourt on the qualitative component. During this time, I trained the fieldworkers with remote assistance from JR and AW. I drove the fieldworkers to their interviews, supervised fieldwork activities and held debriefing discussions.

I conceived the idea for the qualitative paper presented in this thesis and performed the analyses. JR double-coded a portion of transcripts and AW and Shona Horter (SH) gave guidance on qualitative analysis methods.

1.10.4. Post-graduate diploma

As part of the four-year ESRC studentship, I was expected to complete the equivalent of 120 credit hours within my registered department. I took the following modules offered at the London School of Hygiene and Tropical Medicine (LSHTM): Demographic Methods, Population Studies, Population Dynamics and Projections, Analysing Survey and Population Data, Analysis of Hierarchical and other Dependent Data, Principals of Social Research, Generalised Linear Models, Modelling and Dynamics of infectious diseases, and Advanced Statistical Modelling.

1.10.5. Dissemination

I wrote all the papers and additional chapters which are presented in this PhD, incorporating feedback from co-authors and peer-reviewers for the published collaborative papers. I attended international conferences for poster and oral presentations of findings from my research and will also disseminate the findings locally (conference posters are included in Appendix 11.1 and dissemination efforts are discussed further in chapter 9).

1.11. Ethical clearance

Ethical approval for the research in this thesis was granted by the London School of Hygiene and Tropical Medicine (Ref: 14296, Appendix 11.2.2), the University of Witwatersrand human research ethics committee (Clearance certificate number M170850, Appendix 11.2.2) and the Mpumalanga Department of health research committee (Ref: MP_MP_201709_12, Appendix 11.2.2). Informed written consent to record, analyse and disseminate information from interviews was obtained from each participant (Appendix 11.3.2 and Appendix 11.3.3).

1.12. Funding

I was awarded a four year Economic and Social Research Council (ESRC) studentship that covered all my research degree fees. The studentship was supplemented by an Advanced Quantitative Methods (AQM) stipend to encourage further training in AQM to be used in this research and beyond. The studentship also provided an annual stipend and covered all expenses for travel, accommodation, and sustenance at conferences through the Research Training Support Grant. The ESRC studentship also granted a one-time fieldwork travel grant through its Overseas Fieldwork grant which covered my first field visit. The majority of my fieldwork costs were covered by a Bill and Melinda Gates foundation grant to the Measurement and Surveillance of HIV Epidemics (MeSH) consortium (grant number: OPP1120138). Other costs were covered by a Medical Research Council (MRC) grant to the Strengthening Health systems for the Application of Policy to Enable Universal Test and Treat (SHAPE-UTT) study (grant number: MR/P014313/1) and a UNAIDS/BMF grant to the ALPHA network (grant number: OPP1164897). The ongoing Agincourt HDSS activities are supported by University of Witwatersrand, South African Medical Research Council (SAMRC), and Wellcome Trust grants (grant numbers: 058893/Z/99/A; 069683/Z/02/Z; 085477/Z/08/Z; 085477/B/08/Z).

2. Literature review

2.1. Overview

This literature review starts with a brief history of vertical transmission of HIV and its prevention both worldwide and specifically in sub-Saharan Africa, showing the great strides that have been made in the PMTCT and identifying paradigm shifts that helped to make this possible.

The review then summarises the published literature on engagement in HIV care for pregnant and post-partum women on ART, giving an overview of the evidence on maternal engagement, proposing key frameworks to consider when investigating maternal engagement in care, identifying barriers and facilitators of engagement, and reporting on outcomes among patients who are lost to follow-up.

This chapter also considers the multiple data sources and methods that have been used to measure engagement in care in Option B+ programmes, looking specifically at measures of adherence and retention in sub-Saharan African settings.

2.1.1. Search strategy

This review was undertaken by searching PubMed for literature on PMTCT, adherence or retention under Option B+ in sub-Saharan Africa, and outcomes after becoming lost to follow-up. It is not intended to be an exhaustive or systematic review but rather to present key aspects of published literature that are important to understand engagement in care under Option B+.

Nine key concepts were identified as important to the literature review and key terms for each concept were identified (Table 2.1).

Table 2.1: Key concepts and key terms used for the literature

Key concept	Key terms
HIV/AIDS	Human immunodeficiency virus, Acquired Immune Deficiency Syndrome, Opportunistic infection*, WHO stage, Viral*, OIs, Disease*, HIV*, AIDS*, Virus*
Prevention	Prevent*, Treat*, Medic*, Control*, Eliminat*, Treatment as prevention, Tasp
Transmission	Transmiss*, Infect*, vertic*
ART	Antiretroviral*, ARV*, Highly active*, ART, HAART, AZT, Zidovudine, Nevirapine, Retrovir*, NVP
Infants	Child*, Baby, Birth*, New-born, Fetal*, Perinatal*, Premature*, Infant*, Early infant diagnosis, EID, DNA*, PCR, Polymerase chain reaction, Replacement fe*, Mixed fe*, Paediatric*, Pediatric*
Mothers	Maternal*, Wom*, Parent*, Female*, Patient*, Pregnancy*, Prenatal*, Antenatal*, ANC*, Adult*, Mother*, Breast*
Mortality	Mortalit*, LTFU, Loss*, Dea*, Fatal*, Retention*, Retain*, RIC*, default*, engage*, disengage*
PMTCT	Option*, PMTCT*, B+
Limited resource settings	Poor, Sub-Saharan*, Africa*, Developing*, Constrain*, Resource*, Limit*

The search was first conducted in November 2016 using different query combinations (Table 2.2). The inclusion of the limited resource setting concept produced no results and so this was removed from all the queries.

Table 2.2: Key term combinations used in the literature review

Number	Key concept combinations
1	HIV AND Prevention AND ART AND infant AND mother AND PMTCT
2	HIV AND Prevention AND Transmission AND ART AND infant AND mother AND PMTCT
3	HIV AND Prevention AND Transmission AND Mortality AND ART AND infant AND mother AND PMTCT
4	HIV AND [Prevention OR Transmission OR Mortality] AND ART AND [infant OR mother] AND PMTCT
5	[HIV OR ART] AND [Prevention OR Transmission OR Mortality] AND [infant OR mother] AND PMTCT
6	HIV AND [Prevention OR Transmission OR Mortality] AND [infant OR mother] AND [PMTCT OR ART]

Using combinations 1, 2, and 4, I identified 353 articles that warranted further investigation. Each article's abstract was individually reviewed with 85 articles chosen for full review. The reference lists of these 85 articles were also searched for any other pertinent publications.

Additionally, I set up three Google scholar alerts with the following search terms:

[[pregnancy]OR[infants]OR[neonat*]OR[child]]AND[[HIV]OR[AIDS]OR[ART]OR["antiretroviral therapy"]]

[[LTFU]OR ["loss to follow up"]OR["loss to follow-up"]OR["lost from treatment"]]AND[[HIV]OR[AIDS]OR[ART]]

["prevention of mother to child transmission" OR [PMTCT]]

These alerts were reviewed until November 2019 with pertinent papers reviewed and their reference lists checked for any further publications of

interest. This exercise identified a further 435 articles for review with 105 identified as relevant to this literature review.

Finally, I conducted a PubMed search in July 2020 using the following key terms and restricted to articles published within the last two and a half years.

(((((((Human immunodeficiency virus OR Acquired immune deficiency Syndrome OR Opportunistic infection OR WHO stage OR Viral* OR OI* OR Disease* OR HIV* OR AIDS* OR Virus*)) AND ((Prevent* OR Treat* OR Medic* OR Control* OR Eliminat* OR Treatment as prevention OR Tasp))) AND ((Antiretroviral* OR ARV* OR Highly active* OR ART OR HAART OR AZT OR Zidovudine OR Nevirapine OR Retrovir* OR NVP))) AND ((Child* OR Baby OR Birth* OR New born OR Fetal* OR Foetal* OR Perinatal* OR Premature* OR Infant* Early infant diagnosis OR EID OR DNA* OR PCR OR Polymerase chain reaction OR Replacement f* OR Mixed f*))) AND ((Maternal* OR Wom* OR Parent* OR Female* OR Patient* OR Pregnancy* OR Prenatal* OR Antenatal* OR ANC* OR Adult* OR Mother* OR Breast*))) AND ((Option* OR PMTCT* OR B+ OR B plus))) AND ((Mortalit* OR LTFU OR Loss* OR Dea* OR Fatal* Retention* OR Retain* OR RIC* OR engage* OR dis-engage* OR default*))*

This search yielded 250 further manuscripts to review with 79 ultimately chosen as pertinent to this literature review. The titles of these 79 articles were reviewed and 16 were chosen for perusal with their reference lists also checked.

2.2. Prevention of mother-to-child transmission of HIV

2.2.1. A brief history of PMTCT efforts worldwide

Following the identification of the etiologic agent of Acquired Immune Deficiency Syndrome (AIDS) in 1983, many researchers proposed the possibility of perinatal transmission, as had been seen with other sexually transmitted infections (STIs). In 1984, Scott et al described AIDS in infants, finding that only one of fourteen infants had received a blood transfusion before development of clinical symptoms (119). As early as 1985, the Centres for Disease Control and Prevention (CDC) published their recommendations for assisting in the prevention of perinatal transmission of human T-lymphotropic virus type III (HTLV-III)/lymphadenopathy-associated virus (LAV) – both early names of what would come to be known as human

immunodeficiency virus (HIV) – in their morbidity and mortality weekly report (120). They reported that 76% of cases of AIDS in children under 13 years of age reported as of 1 December, 1985 in the United States (US) had as the only risk factor a mother from a high-risk group – defined as intravenous drug users, female sex workers, women born in countries with high rates of heterosexual transmission, and sexual partners of men in high-risk groups which also included men who have sex with men (MSM). Even at this early stage, it was known that perinatal transmission was not automatic and was estimated at anywhere between 0–65% (120). There was concern over the increased risk of progression to full-blown AIDS from this transmission route (120).

The CDC's recommendations included: targeted counselling and testing for antibodies to HIV for pregnant women or those who may become pregnant who already had evidence of HIV infection, or who were intravenous drug users, women born in countries where there is a high rate of heterosexual transmission of HIV, female sex workers, or the sexual partners of men in high-risk groups (120). They suggested that such counselling and testing be made available through the settings that women at increased risk frequented, including drug abuse treatment programmes and clinics for sexually transmitted diseases. Other recommendations were (i) that infected women be advised to delay pregnancy until more was known about the perinatal transmission of HIV, (ii) pregnant infected women be closely monitored for the development of opportunistic infections as well as psychosocial difficulties, and (iii) that men who were infected with HIV also be counselled about risks of perinatal transmission (120). Programmes for the prevention of mother-to-child transmission of HIV evolved from these recommendations.

In 1986, Ando et al published findings that suggested that transmission of HTLV-I – a related virus with similar transmission dynamics – through breastmilk, could be mitigated by a freeze-thawing process (121). With the recognition that women and children were the fastest growing demographic of AIDS cases and new HIV infections (122,123), there was a growing need for acceleration of PMTCT endeavours. Most early interventions were concentrated on behaviour change (122), directed towards limiting pregnancy

among women living with HIV (WLHIV) and the prevention of infection of women of childbearing age (124).

In 1985, scientists found that Zidovudine (Azidothymidine) (AZT) had potent efficacy against HIV in vitro (125), and following human clinical trials, received US Food and Drug Administration (FDA) approval for use against HIV and AIDS on March 20, 1987 (126). It took 25 months between the first demonstration that AZT was active against HIV in the laboratory and its approval, the shortest period of drug development, at the time (127). AZT was subsequently approved for use in infant and child treatment in 1990 (126,127). In 1994, CDC published preliminary findings from a randomized, multicentre, double-blinded clinical trial of AZT to prevent HIV transmission from mothers to their infants (AIDS Clinical Trials Group [ACTG] protocol 076), the first trial of its kind and the first proof of pre-exposure prophylaxis (128,129). With the rapidly changing antiretroviral drug (ARV) landscape, other PMTCT trials soon followed. The ACTG established nine Nevirapine (NVP) sites (ACTG 250) in the US and Puerto Rico in 1995 (130). Following the introduction of highly active antiretroviral therapy (HAART) in 1996 after seminal work presented at the 11th International Conference on AIDS in Vancouver, British Columbia (131–133), there was an exponential growth in number of ARV trials and subsequently the number of available ARVs effective against HIV.

Over the past decade, significant progress has been made in PMTCT in sub-Saharan Africa. The first attempts to prevent vertical transmission in sub-Saharan Africa were randomised control trials to determine the effect of perinatal vaginal lavage on HIV transmission (134), shown to be an ineffective public health measure (134–136). These were followed by trials on vitamin supplements for prevention of vertical transmission (137,138) and presumptive treatment of STIs during pregnancy (139) which also proved futile. There were also multiple randomised control trials of antiretroviral drugs in the prevention of mother-to-child transmission of HIV-1 in breastfeeding mothers in Africa with a myriad of intervention arms (140–147). These showed some promise with long term efficacy ranging from 7% to 66%.

In 2001, the WHO published its first recommendations on the use of ART for PMTCT (8) and it has since been promoted as a method of curtailing the HIV

epidemic. The first recommendations concluded that all regimens that had been shown to be effective in controlled clinical trials be recommended for use in these settings. These regimens include AZT alone, AZT plus lamivudine (3TC), and NVP alone. It was agreed that there was no longer any justification to limit these measures to research and pilot project settings (8).

In 2001, the United Nations General Assembly Special Session (UNGASS) on HIV/AIDS identified PMTCT as a priority need (148). One of the specific goals set for programmes was a 20% reduction in the proportion of infants infected with HIV by 2005 and a 50% reduction by 2010 (148). This gave many HIV/AIDS prevention programmes the impetus they needed to advocate for better PMTCT services. For example, in 2002, the South African high court ordered the government to make NVP available for PMTCT following legal action by the Treatment Action Campaign (TAC) (149). Whereas all the trials showed encouraging results, a major concern with the use of ARVs for PMTCT was the development of viral resistance (8,150) and loss of future ART regimens (151,152), with most of the ARV drugs used early on, particularly NVP, having a very low genetic barrier (153,154). Following mounting evidence on viral resistance for single drug prophylaxis (155,156) use of ARV drug combinations for PMTCT became commonplace (157,158). Dabis later proposed that the role of HAART in PMTCT be scientifically assessed (157) as NVP and AZT had little effect in prevention of transmission from mothers with advanced HIV infection (145,147).

Whereas many of the most developed countries (MDCs) had virtually eliminated perinatal HIV transmission by 2010, or were well on their way to its elimination (159), the least developed countries (LDCs) were lagging behind due to a number of factors including inequity in access to ART (160). From very early on in the HIV epidemic, sub-Saharan Africa had the fastest growing epidemic (161–163). Transmission by blood transfusions, contaminated injections and from mother to child was occurring more frequently than in Europe (164). Piot suggested that AIDS would probably have a profound impact on health care programmes and economic development in the continent – something that has since come to pass – and that its control should be a public health priority (164). Some aid agencies like

Médecins Sans Frontières (MSF) had implemented pilot ART programmes, providing free treatment since 2001 (165,166). In 2003, several countries in SSA established national ART programmes (166), drawing impetus from the WHO/UNAIDS "3 by 5" initiative launched on World AIDS Day in 2003 to provide three million people living with HIV/AIDS in low- and middle-income countries with life-prolonging ART by the end of 2005 (167). This was principally due to the global AIDS advocacy movement and following the establishment of ambitious programmes funded by newly established donors such as the Global Fund to fight AIDS, Tuberculosis and Malaria (166) and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). It is also noteworthy that the FDA played an important role in making ART affordable to LDCs by implementing a number of policies to enable distribution of ARVs to developing countries at low costs, even if there was still patent or market exclusivity protection for the ARVs in the USA (127).

These endeavours rapidly reduced AIDS-related mortality (2,168–174). The early impact of ART in sub-Saharan Africa was primarily because patients with more advanced disease, and most likely to die, were given priority in accessing treatment. This experience also showed that very sick patients could derive benefit from ART, even in the absence of advanced health care systems that were available in MDCs (127).

In 2004, the WHO published its first recommendations for PMTCT in resource constrained settings (175). Starting with Option A in 2006 (176), the guidelines were updated to recommend Option B in 2010 (177). In 2012, WHO released an update which while not an official guideline was considered an endorsement of Option B+ (178,179) and since 2015, have officially advocated for Option B+ (9) where all pregnant or breastfeeding WLHIV initiate ART for life (180) (Figure 2.1).

Figure 2.1: Recommended WHO PMTCT guidelines for maternal and infant treatment and prophylaxis (2010)

	Woman receives:		
	Treatment (for CD4 count ≤350 cells/mm³)	**Prophylaxis (for CD4 count >350 cells/mm³)**	**Infant receives:**
Option A	Triple ART starting as soon as diagnosed, continued for life	**Antepartum:** AZT starting as early as 14 weeks gestation **Intrapartum:** at onset of labour, sdNVP and first dose of AZT/3TC **Postpartum:** daily AZT/3TC through 7 days postpartum	Daily NVP from birth through 1 week beyond complete cessation of breastfeeding or, if not breastfeeding or if mother is on treatment, through age 4-6 weeks
Option B	Same initial ARVs for both:		Daily NVP or AZT from birth through age 4-6 weeks regardless of infant feeding method
	Triple ART starting as soon as diagnosed, continued for life	Triple ART starting as early as 14 weeks gestation and continued intrapartum and through childbirth if not breastfeeding or until 1 week after cessation of all breastfeeding	
Option B+	Same for treatment and prophylaxis:		Daily NVP or AZT from birth through age 4-6 weeks regardless of infant feeding method
	Regardless of CD4 count, triple ART starting as soon as diagnosed, continued for life		

2.2.2. The advent of Option B+ in sub-Saharan Africa

In 2010, the Malawian government developed Option B+ because the prevailing WHO guidelines for PMTCT were not feasible in this setting. The WHO guidelines were reliant on availability of a CD4 count to determine ART eligibility and this was not practical in Malawi as CD4 machines were not available in most rural areas. The programme was rolled out in July 2011 following extensive training of health staff and quickly became the gold standard for PMTCT efforts globally (180–182). Also in 2011, UNAIDS launched a "Global plan" to reduce the number of vertical infections of HIV by 90% (183). The plan identified 22 priority countries – 21 of which are in sub-Saharan Africa – with the highest estimated numbers of pregnant WLHIV (183). These initiatives represented a paradigm shift away from just preventing vertical transmission, towards a more holistic goal of an HIV free infant and a healthy, living mother. In resource-limited settings, Option B+ represented an important change in messaging to patients, transitioning from advice to wait until they got sick or their CD4 counts were low to start treatment for their own health, to an immediate initiation of ART. This called for a massive sensitization and education campaign to help the population

understand this shift. This was an enormous undertaking that was not feasible in most settings, presenting another potential problem for Option B+ programmes (184).

This new approach also represented a shift away from PMTCT goals being to eliminate vertical transmission to a strategy that was concerned with maternal health and survival (183,185,186), as well as prevention of transmission to uninfected partners (7,31,187,188) and PMTCT in subsequent pregnancies (7,36,180). It also simplified PMTCT guidelines, potentially improving access, feasibility, and acceptability (measured by uptake and retention) and generated excitement as the most promising approach to EMTCT. The implementation of Option B+ called for enhanced adherence support, increased funding, decentralisation of services as well as adoption of innovative service provision strategies like task-shifting of specific processes on the PMTCT continuum because of increased numbers of patients needing initiation into the programme (180,189), perhaps to a degree greater than current health systems could absorb (179).

Option B+ was initially met with resistance by some national programmes owing to perceived increased programme costs as well as a reluctance to task-shift ART initiation away from doctors, a prerequisite for a successful Option B+ programme (40,179,190). Option B+ was also met with reluctance by some public health practitioners because of the limited evidence on the effects of long-term exposure to ART in utero (31). Development of surveillance systems for birth defects and toxicity from ART exposure was proposed as a critical element of early Option B+ demonstration projects (31,178). In addition, questions were raised on the ethics of prioritization of healthy patients for early ART when there were many severely immunosuppressed patients, at high risk of death and in urgent need of treatment (179). The move to an ART eligibility threshold of a CD4 less than 500 copies/mL (177) meant that most pregnant women met the criteria to initiate ART. As such, PMTCT programmes would be expending considerable effort to find a minority of patients who would qualify for prophylaxis rather than ART (31), making Option B+ the obvious choice from an implementation perspective. Finally, the ethics of preferentially providing early ART to pregnant women rapidly lost

its relevance once the eligibility criteria were expanded to include all patients, following recommendations from WHO for "Treat All" which were released in 2015 (9).

Kenya was the next African country to implement Option B+, starting in 2011, although they chose a phased or piloting implementation strategy where specific sites employed Option B+ to determine the feasibility of this approach in their setting (191). It was argued that phased implementation could lead to mothers potentially hearing mixed messages regarding ART eligibility as other strategies would still exist in parallel if there was not sufficient geographic distance between Option B+ implementation sites and those following the national standard of care (184). By January 2013, 11 countries had endorsed Option B+ for their national PMTCT programmes with six others actively costing and developing operational plans to switch over (31,191).

Option B+ was estimated to cost 2-2.5 times Option A or B over ten years in Malawi (192). However, it has also been shown to potentially increase maternal life expectancy by 1.12 years compared to Option B (31,193) and in general, health outcomes are much better with early treatment for individuals (194,195) and with Option B+ for mothers (31,192). As cost effectiveness analysis showed Option B+ to be a favourable policy option (192), and following WHO recommendation of Option B+ in its guidelines in 2015 (9) all sub-Saharan African countries had switched to Option B+ at the end of 2016 (196). With the widespread adoption of "Treat All" (39), as of 2018, 74% of HIV positive women of childbearing age in sub-Saharan Africa were receiving ART further improving PMTCT (24).

The early optimism and enthusiasm regarding Option B+ was tempered owing to a myriad of issues that were identified during demonstration projects and through routine programme data in sub-Saharan Africa (179). Principal among these is that several studies from sub-Saharan Africa showed that pregnant and postpartum women have poorer engagement in care than men and non-pregnant women (11,34,68,89). This forced PMTCT programmes to come to terms with how much financial and human resource investment would be needed to make this new endeavour viable and effective. Furthermore, much is still unknown about what happens after pregnant and

postpartum women's treatment attrition and regarding the underlying mechanisms that drive this attrition (197). Although Option B+ is still recognised as the best method to achieve EMTCT, there are many programmatic gaps that still need to be addressed including low rates of repeat testing during the third trimester or during delivery for mothers who tested negative during the first trimester, low EID completion rates, and how to achieve optimum engagement in care for each patient (48,198).

2.3. Engagement in care under Option B+

As mentioned previously, engagement in Option B+ has been reported as lower than engagement for other adults on ART (11,199). Several hypotheses have been postulated for this lower engagement. This section looks at the Option B+ cascade of care identifying periods when women may be at higher risk of disengagement from care, summarising retention rates and identifying factors that influence engagement in Option B+ using a framework proposed by Myer et al (48) to summarise these factors.

2.3.1. Retention in care following ART initiation

Most studies on retention in care in Option B+ programmes in African settings have reported outcomes up to 12 months on ART (11,34,35,200–203). While the definition of retention varied widely between these studies, they reported retention rates 12 months after ART initiation ranging from 42% in Mozambique (204) to 97% in Malawi (70). In Malawi, more encouraging was the fact that excluding women who transferred their care to other facilities (9.7%), the 12-month retention in care rate was 77% similar to the rate for adults in the national ART programme (36). A 2018 meta-analysis reported a pooled retention estimate of 76% at 12 months (11). In comparison, this rate was slightly lower than the 81% reported for adults 12 months after ART initiation in Africa prior to the roll-out of universal ART (199). Some longer-term studies have more recently been published describing retention in care three to five years after ART initiation in the pregnancy and breastfeeding periods (34,35,202). With regards to long-term retention rates, these ranged from 41% in Malawi (200,201) to 77% in Ethiopia (203) after 24 months on ART. One study in Malawi showed that 70% of women remained retained in care after 3 years following ART initiation, which was similar to the adult treatment cohort, however, adequate adherence was below 30% (34). In

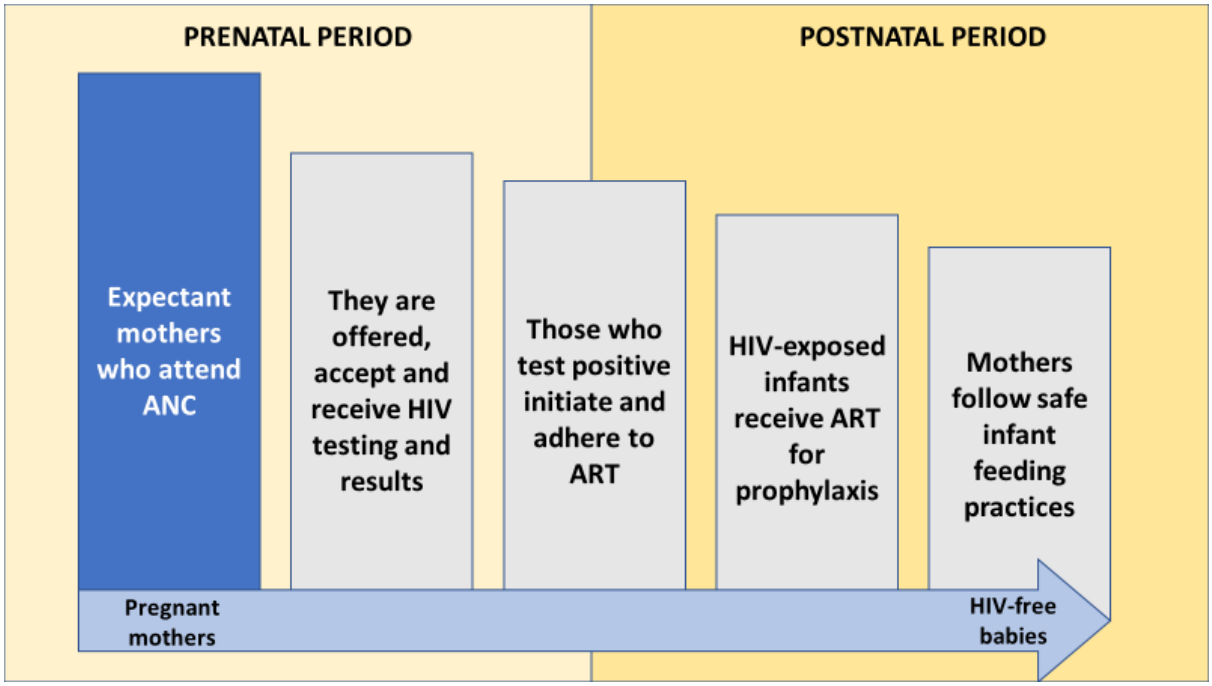
Uganda, it was estimated that 68% of women were retained in care 4 years after ART initiation (202) (Table2.3). Most study estimates were well below the UNAIDS second 90 target of 90% of patients who know their status being on ART (97). As such, questions still remain regarding the factors driving long-term retention in care given that mothers are initiating ART while still asymptomatic and often times before they have had time to digest the news of their HIV diagnosis.

2.3.2. The Option B+ treatment cascade and points of high risk of disengagement

The HIV treatment cascade was first depicted in early PMTCT studies to describe the various steps in preventing vertical transmission (205–207) and has since been expanded to include other facets of HIV treatment most notably the challenge of loss to follow-up from treatment programmes (208–213) and the uptake of viral load testing (76). The cascade is usually used to depict the proportion of patients lost or not reached at each step, giving an easily understandable summary of the magnitude of attrition at each step and potentially where interventions are needed to improve engagement. For an Option B+ programme, understanding the levels of attrition at each stage of the cascade is particularly pertinent as mothers not on treatment are more likely to transmit HIV to their infants if this attrition happens at any point before breastfeeding cessation (214).

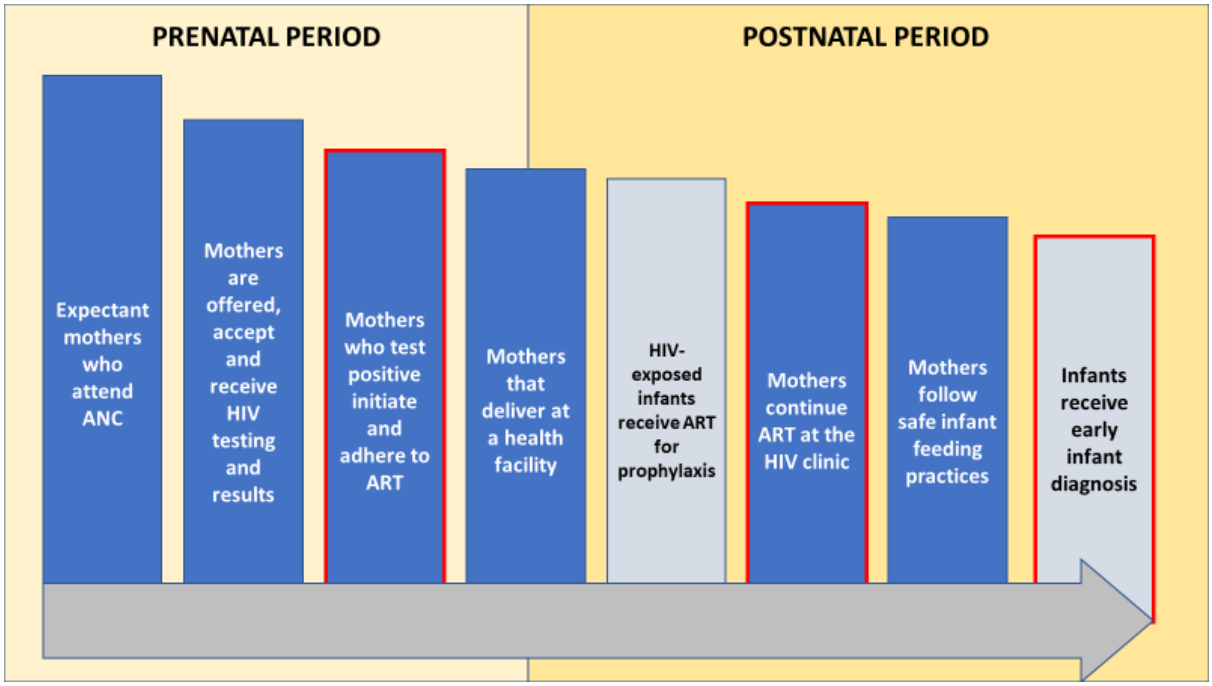
The stages of the cascade vary with different studies. However, the Option B+ cascade is often depicted as having five steps: at least one antenatal care visit; offer, acceptance, and reception of HIV testing and results; maternal antiretroviral therapy (ART) initiation and adherence; infant ART initiation for prophylaxis; and mothers following safe infant feeding practices (Figure 2.2).

Figure 2.2: The Option B+ treatment cascade



Certain steps in the cascade can be expanded or contracted and increasingly, more steps are being added to the cascade that deal with infants and their outcomes. For the purpose of this review, I will use a slightly altered cascade to better illustrate which parts of the cascade this review concentrates on (Figure 2.3).

Figure 2.3: The cascade for this thesis



The pregnancy and postpartum periods are times of change regardless of HIV-status, especially for first-time mothers. The transition through pregnancy and into motherhood comes with multiple personal milestones and unique pressures which may be exacerbated by an HIV diagnosis. Women must navigate maternal and child health clinics in addition to HIV clinics as well as the economic, social, psychological, and physiological changes that women undergo during the pre- and postnatal period (215–217).

The prenatal period

HIV testing

The circumstances under which most pregnant women discover their HIV status differs from the general population. Pregnant women are encouraged to attend ANC clinics, the entry point into most PMTCT programmes and the first step in the PMTCT cascade. It is important to note that utilisation of ANC services is still an issue in multiple settings for many reasons including socioeconomic factors, lack of autonomy and agency, and long distance to health facilities (218–221). As part of ANC services, women are encouraged to test for HIV, something they may not have planned to do. Testing all pregnant women for HIV proved initially challenging for PMTCT programmes in sub-Saharan Africa with 51% pregnant women being tested in 2013, showing heterogeneity across the continent ranging from 35% in west and central Africa to 74% in east and southern Africa (222). However, most of these programmes are now testing more than 95% of pregnant women who attend ANC (26).

During pregnancy, women may be at higher risk for HIV seroconversion especially in areas with high population HIV prevalence (223). As such, for those pregnant women that test negative, repeat testing throughout the vertical transmission risk period is of paramount importance to identify any new seroconversions. To do this, repeat testing for HIV-negative pregnant women is recommended in the third trimester and again in the postpartum period in high prevalence settings (224). However, this has been implemented to varying degrees of success, with some countries doing better than others (225). The major barriers to achieving optimal levels of repeat testing include

client-level barriers such as late presentation for ANC or low completion of recommended ANC visits. Provider-level barriers include heavy workloads, time limitations, and forgetting to check retest eligibility at every facility visit. Facility-level barriers include inconsistent volume of clients and lack of dedicated space for confidential HIV testing. Finally, health system barriers include test kit supply chain ruptures and the design of ANC patient registers (226). Repeat testing has been an issue for PMTCT programmes since their inception, but it has become more pronounced with the move to Option B+.

ART initiation

Once pregnant women have tested positive for HIV, current WHO recommendations suggest prompt initiation of ART and achievement of adherence to ensure virologic suppression by the time of delivery. In Malawi by 2012, a year into implementation of Option B+, quarterly ART initiations for pregnant and breastfeeding women jumped up by 748% (36). These high rates of uptake also reported by the Ministry of Health (227) were likely due to excellent sensitisation and mobilisation campaigns (184). Since then, several clinical cohorts of pregnant women who have tested positive for HIV have been followed with varying levels of ART initiation reported (11,228,229). These varying levels of initiation were likely due to health system barriers such as poor integration of ART and ANC services (230), and slow patient treatment preparation procedures (231,232), coupled with delayed presentation to ANC services (233), as well as psychosocial barriers including denial of HIV status and fear of disclosure (234).

Women diagnosed during pregnancy face a triple burden of the transition into pregnancy, acceptance of an HIV diagnosis and the requirement to initiate lifelong ART as soon as possible (232). Rapid ART initiation is one reason why messaging often focuses on protection of the unborn child as the principle reason for initiating ART, which potentially introduces ART adherence problems postpartum (235). The need to initiate ART quickly has led to most PMTCT programmes advocating for same-day ART initiation provided that the patient seems ready to start (and do not have tuberculosis or cryptococcal meningitis) which is also a WHO recommendation (236).

The first part of the Option B+ treatment cascade i.e. the proportion of expectant mothers who attend ANC, consent to HIV testing and receive their results and are subsequently offered and initiate ART varies for different Option B+ programmes in sub-Saharan Africa. For example, while >95% of pregnant WLHIV receive ART for PMTCT in South Africa this proportion was estimated at 25% in Chad (26).

Early data from PMTCT programmes suggests that the major obstacle to achieving optimal PMTCT goals is not about convincing women to start but rather keeping them on treatment for life (36). Even with the need to protect their unborn child being a major motivating factor (237–240), ART initiation rates in PMTCT programmes vary in different settings (36,241). A first leakage in the PMTCT cascade is the small proportion of women who refuse treatment outright and women who accept treatment but never return for subsequent visits (11).

ART adherence

Following ART initiation, several studies have shown that the risk of disengagement from care is highest just after initiation and then reduces steadily the longer women remain in care (11,42). The biggest losses have been observed immediately after initiation with no further clinic visits following the ART initiation visit , with up to 46% of women never returning for another clinic visit following their initial ART initiation visit (11,42). In spite of several barriers including coming to terms with the reality of lifelong ART, many studies have reported higher levels of ART adherence and viral suppression during pregnancy compared to the postpartum period (68,242–244). This might be due to several reasons, for example, the expectation of regular attendance of a health facility makes it easier to explain monthly clinic visits for ART refills and the need to take daily medication (245).

Delivery

Women living with HIV are encouraged to deliver their child at a health facility as this allows for interventions to reduce the risk of transmission at birth (246). New-borns are also tested for HIV and can be initiated on ART at this point if necessary (224). Furthermore, for infants who test negative, mothers

are provided with prophylaxis to further reduce the risk of transmission (9,177). While beyond the scope of this review, facility delivery is still a major hurdle in multiple settings with only 22% of deliveries occurring in a health facility in 29 sub-Saharan African countries with heterogeneity by region and socioeconomic status (247,248).

The postnatal period

ART adherence

Some studies have reported high risk of disengagement from care in the first year on ART often following delivery or breastfeeding cessation (203,249–251). In the postpartum period, changes in motivation to continue treatment following delivery and weaning possibly contribute to women's disengagement (245,251,252).

The success of Option B+ in the antenatal period has meant that mother-to-child transmission of HIV is increasingly occurring through breastfeeding in the postpartum period (253). Provided that mothers remain adherent to ART, the risk of transmission through breastfeeding is negligible and is far outweighed by the benefits accrued from breastfeeding (253). In resource limited settings formula-feeding is less feasible owing to the economic burden this entails. Formula feeding also presents an increased risk of diarrhoeal diseases due to contamination (especially due to a lack of clean water sources). Given that diarrhoea and malnutrition are common causes of child mortality in these settings, the World Health Organisation (WHO) now recommends breastfeeding up to 24 months in low-income settings (254).

In the postpartum period, new mothers must navigate several activities or practices. In addition to remaining adherent to their own treatment, mothers must also administer antiretroviral prophylaxis to their infant and adhere to infant feeding recommendations, which can be a burden (197). If the risk of transmission through breastfeeding is understood by the mothers, then their motivation to stay in care for the health of their infant might still be high (252,255). However, relief at a negative HIV test result for the infant may be a barrier to their own continued engagement in care (252,255).

The first 24 months of child-rearing still involve routine visits to the clinics for immunisation as well as early infant diagnosis. Women are assumed to have integrated into the adult ART population. Retention rates and reasons for treatment discontinuation during the period following breastfeeding cessation have not been well described, with most research focusing on the periods of pregnancy and breastfeeding. However, following delivery and breastfeeding cessation, women disengage from care at higher rates than the rest of the adult ART population (11,197). Whereas some PMTCT programmes provide integrated care throughout the breastfeeding period, in some settings, women are expected to transfer their care to an adult ART clinic (256,257) and this transfer may also undermine their continued engagement in care. This transition presents a new set of challenges. Women must find reasons other than the health of their infant to motivate themselves to continue adhering to treatment. This sometimes proves difficult given that most of them were asymptomatic when they initiated ART (258,259).

In regions with high fertility, women may move between pregnancy, breastfeeding, and post-breastfeeding periods throughout their reproductive years. It is important to integrate HIV services into these periods in order to improve maternal health and reduce the risk of mother-to-child transmission both for incident and subsequent pregnancies.

Early infant diagnosis

The major goal of PMTCT programmes is to reduce vertical transmission, and the global scale-up of ART has been the primary contributor to reduction in vertical transmission. Therefore, EID results are an important metric for assessing whether PMTCT efforts are being effective. As such, it is impossible to evaluate this goal without first achieving high EID testing coverage throughout the vertical transmission risk period. Serological assays used for adult testing are not reliable for infants given that maternal HIV antibodies can persist in infants up to 18 months. Therefore, EID seeks to establish the presence of HIV infection in children less than 18 months old through DNA polymerase chain reaction (PCR) testing, and is critical to reduce infant morbidity and mortality through timely ART initiation for those infants that test positive (260–262).

Early on, when ART was not provided to all women for life, research found that infants of mothers on ART were more likely to complete EID (263), it was therefore hoped that universal ART would translate to higher completion rates of EID but this has not materialised (198). It is imperative that there be high coverage of EID testing up to the end of the breastfeeding period for HIV-exposed infants (HEI), however, testing rates remain low in the countries with the highest HIV-burden (198).

Most studies documenting uptake across the PMTCT cascade have been undertaken as cohort studies (11,228,229) of mothers without links to exposed infants. Many studies are implemented drawing on paper-based registers in which data are not consistently entered and which often lack unique identifiers meaning that not all available data can be utilised. Lack of links between mother-baby pairs also means that identifying exposed infants in child registers is impossible (99).

Ninety percent of HEI should be tested by eight weeks according to the World Health Organisation global targets, but EID uptake in many sub-Saharan African countries is suboptimal, with only half of HEI in 21 priority countries reported to have been tested in 2015 (26,110,198,227,264). Based on national data, only 35.1% of infected mothers intended to access EID services in South Africa (110). In Malawi, only 43% of exposed infants were enrolled in follow up before 2 months (227).

Retention of HEI in the postpartum period and ascertainment of HIV status at the end of their risk period remains a major gap for reasons including health system barriers that result in fragmented services for mother-baby pairs and a lack of focus on critical healthcare needs for HEI (265,266). Some authors point to concentration on the birth or 6-week EID test to the detriment of the rest of the risk period up to the end of breastfeeding (6-month and 18-month test which are just as important) as a major reason for this gap (28,264). Lack of knowledge regarding EID and infant ART, lack of psychosocial support, fear of disclosure of own and/or child's HIV status, the perception of health care workers as authority figures, and intent to shorten the life of the child have also emerged as reasons for low EID testing rates (267). One study found that counterintuitively longer distance from the clinic improved EID uptake but

might be explained by the tendency of patients to seek care further away from home in order to avoid being recognised at clinics in their own neighbourhoods and the decreased fear of social stigma by seeking care outside of one's community (268). Another factor is emotional intimate partner violence which reduces the likelihood of EID completion (269). Maternal postpartum ART adherence continues to be a facilitator of high EID testing completion rates (268,269).

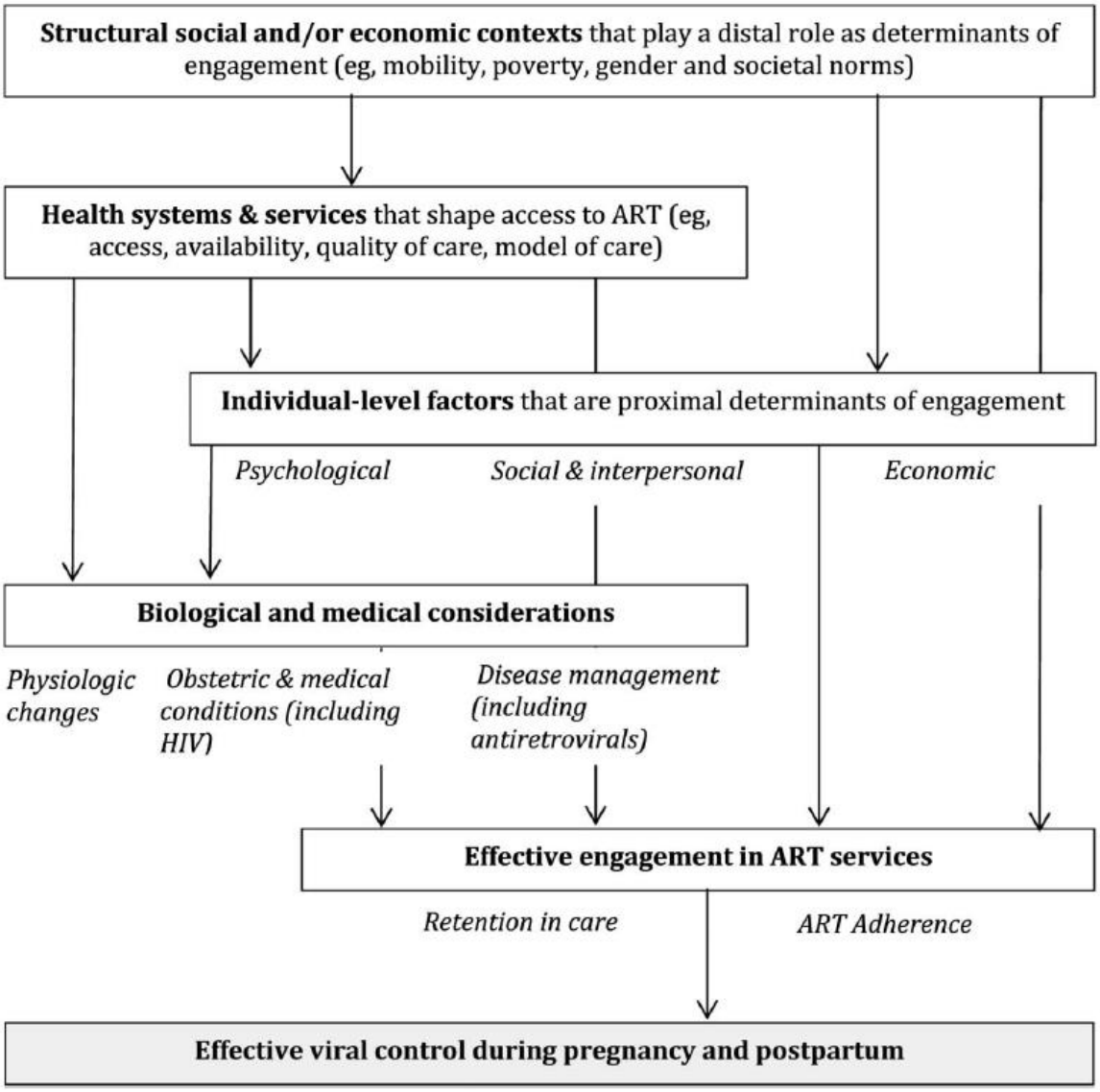
Innovations like point-of-care EID tests (270) and use of mobile technology interventions like the HITSystem (271,272) have significantly improved EID uptake and encouragingly, data from Zambia shows that EID completion rates have improved steadily between 2006 and 2016 probably due to increased attention and funding (273).

However, with more than 50% of infant HIV infections happening in the postpartum period (198), this reflects the relatively high coverage of interventions in the antenatal period and the need for greater attention to postpartum women and their exposed infants. Especially as HIV-exposed uninfected infants experience a myriad of challenges including higher mortality (274–276).

2.3.3. Influences on engagement in care under Option B+

Several authors have suggested ways to conceptualise adherence and engagement in care for pregnant and postpartum women (48,62). The WHO considers five dimensions that can help conceptualise the multiple factors at play for patient adherence, health system factors, socioeconomic factors, therapy-related factors, patient-related factors, and condition-related factors (62). Myer et al (48) suggest a framework for conceptualising pregnant and postpartum women's engagement in care which considers structural factors, social and economic conditions, health systems and services, individual-level factors and biological and medication conditions (Figure 2.4). I use this framework to collate the various influences on engagement in care for pregnant and postpartum women that have been reported in the published literature.

Figure 2.4: Conceptual model for the determinants of engagement in care for pregnant and postpartum women *(Myer et al (48))*



Structural, social, and/or economic contexts

These are factors that play a distal role as determinants of engagement and include factors such as mobility, poverty, gender, and societal norms. Male partner involvement in all the levels of the PMTCT cascade (especially ANC visits, HIV testing and treatment) has been identified as a potential barrier to women's long-term retention in care. This is particularly pertinent in patriarchal societies where women are heavily reliant on their partners for approval or financial support in order to attend health services (277–279).

More broadly, family and community have been identified as barriers to engagement in HIV care (280–283). Social support, infant testing and disclosure to a partner (284) have a positive effect on retention. Perceived and experienced stigma is still an issue (283,285) and often prevents disclosure (249,279,286,287) with An et al reporting that fear of a positive result is strong enough that some women opted out of ANC services altogether rather than know their status (288). Mothers also reported fear of stigma related to giving their child medication and from their status being disclosed if they did not breastfeed their infant (289). Women that disclose their HIV status receive more support and are better engaged in care (290). However, women are less likely to disclose in situations where disclosure is viewed as too risky with the potential repercussions including violence, segregation or loss of social support (249,279,286,287). Women who have not disclosed their HIV status might also find it harder to remain engaged in care in the postpartum period once the cover of frequent clinic visits for ANC ceases and the convenient explanation is no longer available to them (245).

Furthermore, clinics may not be well adapted for the increased mobility that often accompanies pregnancy (for example, in many countries expectant mothers move back to their natal home because of the help they can receive in early childcare but later move back to their own homes to resume their lives) (18,102). After delivery, many women return to previous economic activities and place of residence which may come with their own stresses which may undermine HIV care engagement. Some women report feeling overwhelmed in this period and may become too busy with other activities to remain engaged in care (245,251,252). In South Africa, where labour migration is very common, this might include moving to metropolitan areas either to find or to resume work.

Poverty also plays a major role in engagement in care (291–293). Several logistics are involved in continued engagement such as funds for transportation to the clinic, and availability of food to aid in taking medication. Studies have identified a lack of transport as a barrier to engagement in care (234,245,255,282–284,294). Moreover, as patients are usually advised to take their medication with food (10), some patients have reported a lack of food as

a significant barrier to adequate adherence and continued engagement in care (255).

Health systems and services

These are the factors that shape access to ART and include concepts such as access, availability, quality of care and model of care. Regarding the model of care, women must navigate ANC, and HIV clinics in settings where these are not fully or well-integrated (295). Moreover, even in settings with better integrated clinics, transitioning back into general population HIV clinics in the postpartum period can be challenging (296). Integration of ANC and HIV care significantly improves ART uptake during pregnancy and has become the standard of care in most of sub-Saharan Africa (297–301). Some countries continue integrated maternal and child healthcare into the postpartum period which has been shown to improve engagement in the postpartum period (302–304). However, there is a hurdle of moving mothers from PMTCT programmes to routine care postpartum and the potential LTFU during this transition period. There is little available evidence to guide decisions on when women should be transferred back to routine ART care. As a result, decisions in many countries are based on various other practices. In South Africa, this transition happens 6-10 weeks postpartum (256), in Malawi this ranges from 6 weeks to 12 months (17,257), while in Mozambique, the United Republic of Tanzania and Zimbabwe this transition occurs up to two years postpartum (296,305) showing the heterogeneity in country implementation. Some settings offer a one-stop shop where ANC, postnatal care (PNC), child health care, and ART services are provided at the same facility (249,306). However, while women may not have to transfer geographically, they may need to transfer to a different part of the same clinic (249,306). This transfer period may come with higher susceptibility to disengagement from care (256,307–309). Furthermore, if a child tests positive, mothers must navigate both their own and their infant's clinic visits. If child and maternal care are not integrated, then the difficulty of juggling multiple clinic appointments might undermine women's continued engagement in care (238,255).

Regarding access and availability, infrastructure plays a significant role in engagement in care. Settings where roads can be washed away or made

impassable by rain for example make engagement in care a trickier prospect. Stockouts of ARVs also significantly affects adherence and engagement in care and stockouts increased in some sites following Option B+ roll-out (296). Furthermore, where patients are expected to pay for some services at health facilities, this has been shown to be detrimental to engagement in care (282,283). Distance to the facility and related transportation costs also played a significant role in LTFU among pregnant women (234,245,255,282–284,294).

Regarding quality of care, some studies have focused on the testing experience for pregnant women (288,310–312), including eliciting the contents of counselling sessions (310). Women appreciated the knowledge garnered from these HIV testing and counselling sessions (288). Healthcare workers (HCWs) also reported improved confidentiality as testing became routine which led to less stigma (288). One study also reported improved diffusion of the testing message for pregnant women into the community (288), as more mothers became knowledgeable and consequently shared this knowledge with other pregnant women. On the other hand, the routine nature of the HIV testing offer to pregnant women has also been identified as an early barrier to long-term engagement in care for some pregnant women. For example, some studies have shown that women may feel coerced to test, leading to subsequent disengagement from care for some of them in the future (288,310–312). Some mothers expressed discomfort in voicing their opinions regarding testing and counselling to practitioners (255,313). Several studies noted that the patient-practitioner relationship was not viewed as equal by patients or providers (288,294,313). Few women discussed health decisions in terms of exerting control over their own bodies and perceived the HCW as the health-related decision maker (288). A role HCWs may not relish but one which nonetheless has been thrust upon them by "a unilateral 'moral economy', which requires the compliance of patients who are newly initiated on treatment" (314–316). Many women reported feeling that testing was compulsory, sometimes interpreting the HIV test as an order from the Health Ministry (288). A supportive relationship with providers often translated to more autonomous decision making on the mothers' part (288). Maltreatment from clinic staff was a barrier to adherence and retention in care (237,317), suggesting, that the

patient-provider relationship plays a pivotal role in PMTCT service use (313). Omission of pre-test counselling also influenced women's ability to opt-out of HIV testing (313). With the need to initiate pregnant women on treatment immediately after they tested positive, feeling ready played a major role in acceptance of ART (237), with readiness influenced by previous knowledge of HIV status, patient-provider relationship and the partner relationship (237). Patients and HCWs expressed concerns with the speed of the initiation process which they feared would make it difficult for patients to digest a positive result (286). With regards to women who never returned for a clinic visit following ART initiation, some studies suggest that rapid ART initiation might leave patients overwhelmed and underprepared for the realities of lifelong treatment thereby making them less likely to return for follow-up clinic visits (239). In particular, studies have reported mixed results with regards to disengagement from care for women who initiate ART on the same day (42,43,203), with some women wanting to first discuss their diagnosis with their partner, get a CD4 count and get a confirmatory test at another facility. HCWs feared that some women were only initiating treatment to please them and that they would not take the treatment properly at home (239). Consequently, they were worried about LTFU and drug resistance. Fear of breach of confidentiality also played important roles in LTFU (286,313) with some women concerned about referrals to other facilities having established trust where they initiated ART (313). Facility type and size have also been reported as affecting engagement in care (318) although there have been mixed results with regards to facility size (249,318). Studies suggest that public facilities are a risk factor for disengagement compared to private facilities (318), hospitals have higher attrition than health centres (203), and urban facilities contribute to disengagement when compared to those located in rural settings (318). Finally, long lines, limited clinic hours and slow service contributing to long waiting times at the clinic have also been reported as barriers to engagement in care (245,319).

Other studies have identified several concerns throughout the Option B+ cascade. Specifically, there is fear of the potential adherence to old messaging around PMTCT and the subsequent problems that might arise as a result of starting ART with high CD4 (320). Postpartum women also need other

services including reproductive health services such as contraceptives for those not looking to get pregnant and safe conception for those who are. Unplanned pregnancy contributes to mother-to-child transmission and maternal engagement in care (321,322). Up to 70% of pregnancies between 2012 and 2016 were unplanned in African cohorts living with HIV (323–325). Multiple hypotheses have been postulated to explain better engagement during pregnancy compared to the postpartum period. Healthcare messaging on ART adherence has focused heavily on the health of the baby and prevention of transmission (235) and women report being motivated to remain in care and adherent for the sake of their unborn baby (237).

Many studies also found a significant number of mothers eligible under old guidelines who inexplicably slipped through the cracks (297,326–329) it is therefore plausible that this may also happen in Option B+ programmes. However, there were also good, contrasting results from South Africa (110) where a better resourced health care system likely played a role in the good performance of Option A compared to other countries. Questions remain regarding how a better resourced health system translates to an Option B+ programme. PMTCT is only effective if mothers and exposed infants remain in care and on therapy for the duration of MTCT risk (214) something more likely to happen with the simplified care continuum offered by Option B+ and supported by early findings from Malawi (36). Simplification of eligibility criteria could mean an improvement or, conversely, the increasing numbers of mothers being initiated could mean that more mothers slip through these cracks; supported by retention statistics from a number of studies showing that retention rates decline as Option B+ programmes age (34,36,227,318). Option B+ is a balancing act especially in scenarios in which poor adherence with consequent early virologic failure or high rates of loss to follow-up is common (193). 'Particularly pertinent consideration for resource-constrained nations that are balancing ART costs with other critical health expenditures' (31).

Individual-level factors

These include psychological, social, interpersonal, and economic factors that are proximal determinants of engagement in care among pregnant and

postpartum women. Young age is consistently reported as a risk factor for disengagement from care (69,249,305,317,330–332). Adolescents and young women have also been shown to have poorer adherence, worse HIV treatment outcomes, higher rates of vertical transmission and LTFU (11,17,50,203,333,334). This is possibly linked to poor health seeking behaviour as evidenced by late presentation at ANC and a higher likelihood of unplanned pregnancies (35,69,332,335). Young people may have lower impulse control (336), poorer grasp of the concept of actions and consequences, and poor ability for long-term risk benefit analyses (337) which also probably play an important role in this phenomenon.

Studies have also reported that several other individual level factors play an important role in engagement in care. The continuum of acceptance and denial plays a role in engagement in care (338). The process of acceptance of an HIV status is influenced by various events and experiences that are unique to each individual (338). Women who were newly diagnosed at their first ANC visit had worse adherence and treatment outcomes (66,331,332) with denial possibly partly explaining the mechanism of this observation. Women who had previous knowledge of their HIV status at their first ANC visit had had more time to move through the process of denial and acceptance (338). Women also spoke about feeling healthy when asked to initiate ART, with perceived lack of need for treatment undermining their engagement (239,339). Women with less education also had worse engagement in care (66,317). Some women attributed attrition to several factors including mothers' lack of knowledge regarding the benefits of ART for their own health, ignorance or irresponsibility, and that mothers only cared about the baby's health and not their own (245). Religious beliefs were also an important predictor of engagement in care (249). Mothers also expressed several motivating factors for remaining in care. Chief among these was the desire to have a healthy baby (238), mothers also wanted to remain healthy for themselves and in order to see their children grow up (239,240,251,319,340,341). Some women report that continuing on ART gives them hope for the future (280). Other motivators included stigma avoidance usually expressed as a desire to maintain their appearance, keep their status hidden and not be identifiable as HIV positive if their health deteriorated and they started to experience symptoms (239).

However, a fear of being seen at the clinic was a deterrent probably speaking to the setting with high social cohesion where social standing and social inclusion are often perceived as more important than individual wellbeing (342).

Regarding psychological factors, research is starting to emerge suggesting that postpartum depression is a risk factor for disengagement from care (343–345). Alcohol and substance abuse are also known to be associated with poor adherence and engagement and are prevalent among WLHIV (343–345). Other life stressors such as partner violence, crime, loss of employment, food and housing security can also disrupt treatment (17,346–348). Migration and travel can also disrupt treatment (349). This is particularly pertinent in South Africa where labour migration emerged due to the apartheid regime and quickly became an important source of income for families in the homelands and is still common even now (349,350). Furthermore, fitting clinic visits into their schedule when they were back at work was difficult as it often meant they had to disclose their HIV status to their employer (245).

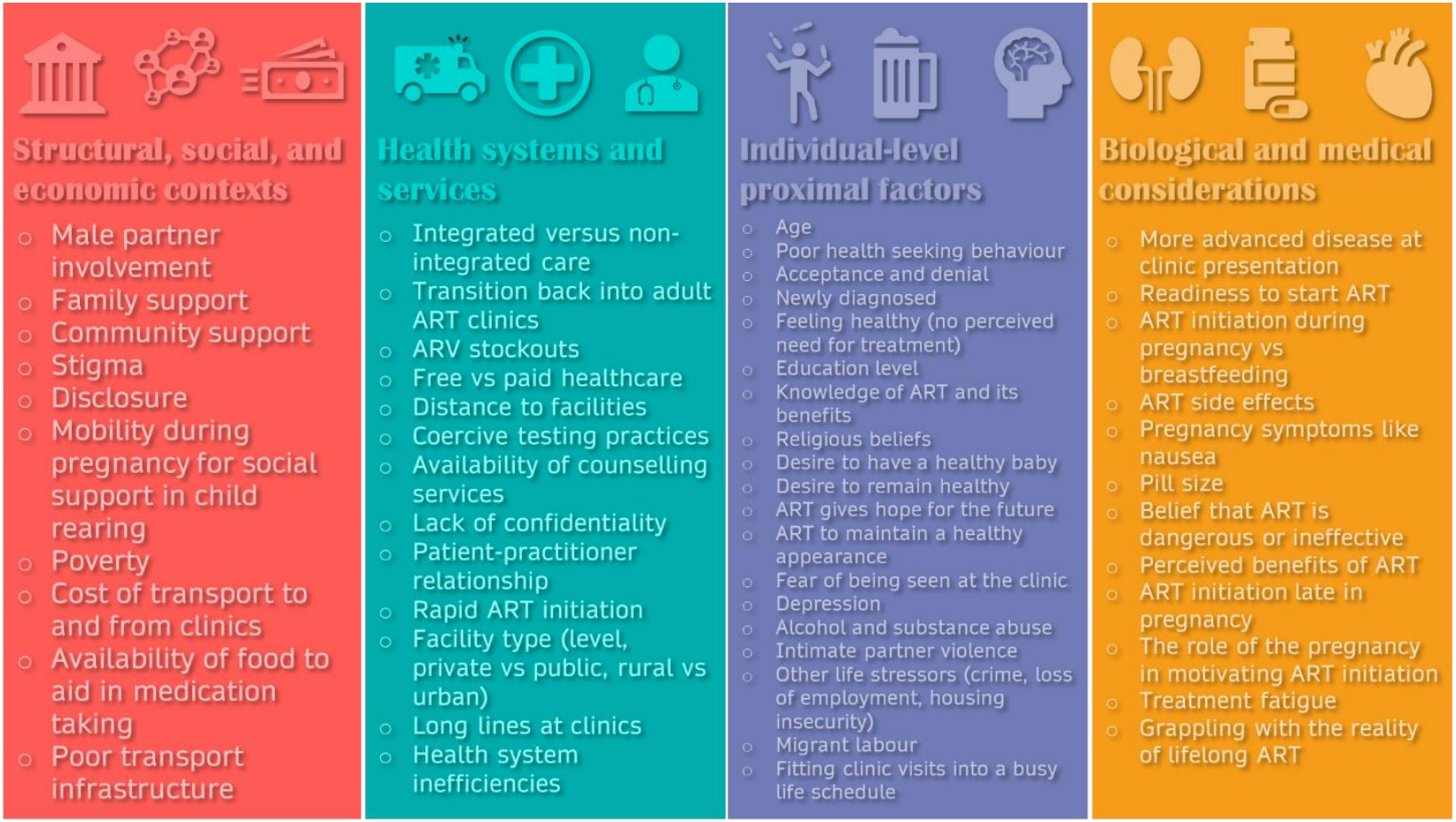
Biological and medical considerations

This looks at factors related to physiologic changes associated with HIV and pregnancy, obstetric and medical conditions, and anything related to disease management including the use of ART. Late presenters who are at a more advanced disease stage when they first enter HIV treatment programmes are more vulnerable to disengagement usually because they are experiencing symptoms including physical wasting (250,282,351) and also have higher mortality risk (352). The proportion of people initiating ART at an advanced disease stage has declined since the advent of ART in sub-Saharan Africa (258). Furthermore, pregnant women are generally healthier and are usually asymptomatic when they initiate ART (258,259). Nonetheless, some studies have reported more advanced disease as a risk factor for disengagement with patients being too weak/sick to take ART or attend clinic visits. Feeling healthy has also been reported as a risk factor for disengagement from care (240,252,283). Readiness to start ART is a concept that features heavily with regards to engagement in care (237) and is influenced by many factors including coercive testing, and previous knowledge of HIV status.

Women who initiate ART during pregnancy have higher disengagement rates than women who initiate during the breastfeeding period (17,204,250,318). This may point to the multiple pregnancy related symptoms like nausea and fatigue which are similar to the profile of side effects that patients might experience once they initiate ART. This might also explain why primigravida mothers disengage from care more frequently than more experienced mothers (69). With the novelty of the transitions of a first pregnancy, mothers are perhaps more likely to mistake pregnancy symptoms for ART side effects. However, one study reported higher gravida as barrier to engagement in care (305). Apart from ART side effects (238,251,289,317,319,353,354), pill size (238), beliefs that ART is dangerous (355), a lack of understanding of HIV (17,341), and doubts about the effectiveness of ART (354) have also been reported as barriers to optimal engagement in care. There have been some contrasting findings, some women have reported feeling more motivated because of noticeable improvements in their health following ART initiation, for example one study reported optimal engagement where mothers perceived benefits of lifelong treatment including falling ill less frequently and prolonged life (289), findings echoed in another study, where women also felt that they would acclimatize to the treatment (239). Women who initiated ART late in pregnancy were also reported to have higher risk of attrition (69,317,332). Their late attendance of ANC probably speaks to poor seeking behaviour which has been reported as a risk factor for disengagement from care (35,69,332,335).

Finally, the role of pregnancy in motivating initiation was important as this played a part in postnatal attrition with some women reporting loss of motivation after protecting the baby (289). Some mothers also expressed challenges with postnatal adherence (245,289) with some mothers reporting the pregnancy was a way to hide their status as they could easily explain that the reason for all the medication and frequent clinic visits was the pregnancy, but this option disappeared once the baby was delivered (245,257). Some women also mentioned treatment fatigue (289) and grappling with the fact that ART was a lifelong commitment (239,255,339) as reasons for disengagement from care.

Figure 2.5: Determinants of engagement in care under Option B+



2.4. Loss to follow-up and maternal treatment outcomes

2.4.1. The problem of LTFU

Usually, most HIV treatment programmes are most interested in retention and survival statistics. As such patients who become LTFU are censored and it is assumed that this censoring is uninformative and random (12,356). However, it is well established from early treatment programmes that this was not true (for example, patients LTFU had higher mortality). Therefore, the proportion of patients LTFU became an outcome of interest independent of retention and survival (58,61). As LTFU reflects patients not retained in care, it is increasingly used as a measure of the effectiveness on treatment programmes (57,61,165,357,358).

One study reported that the combination of outcomes that make up LTFU underestimate retention and death rates by as much as five-fold while default rates are overestimated (90). Understanding true outcomes among patients who are LTFU is important in order to accurately monitor and report on indicators for national ART programmes and better target tracing efforts. Accurate mortality estimates are also important as these are used as parameters for projections in software programmes such as the UNAIDS Spectrum package (91,92,359).

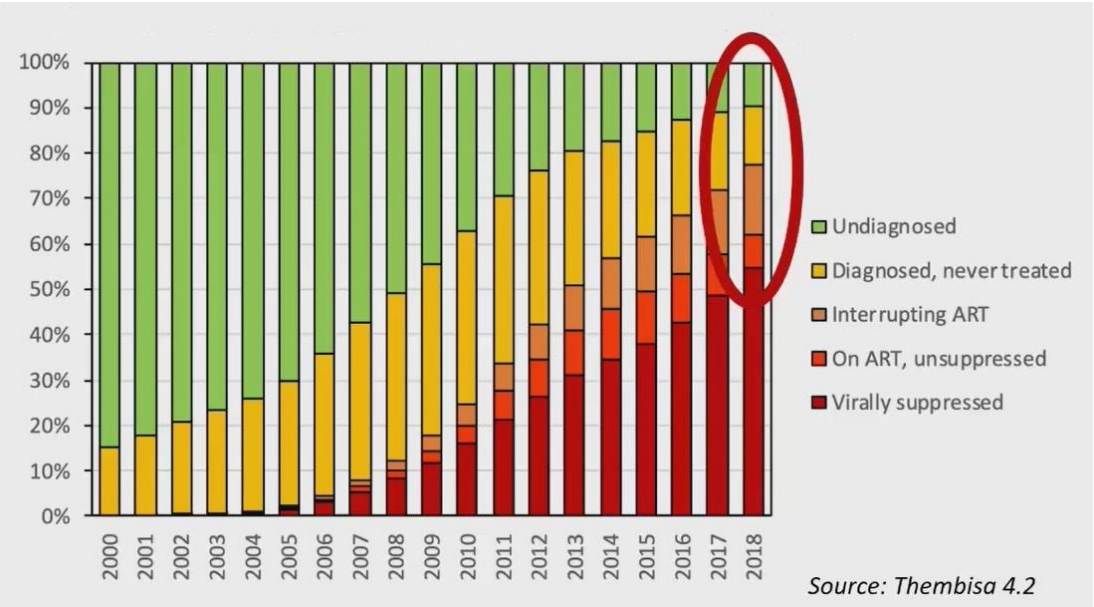
Furthermore, LTFU threatens the effectiveness of ART. A 2013 systematic review of ART patients in Africa estimated LTFU at 82%, 76%, 68% and 65% at 6, 12, 24, and 36 months respectively (199). While there was substantial variation in retention, given that ART is only effective if patients are retained and adherent, these numbers illustrate that retention is a substantial threat to ART effectiveness (61). For pregnant and breastfeeding women, this is two-fold as ART is not only for the health benefit to the mother but also a means to curtail vertical transmission.

Studies have reported increases in attrition as programmes expand and increasingly, more programme losses can be attributed to LTFU (13,57,360). One study reported an inverse relationship between LTFU rates and mortality, with the contribution of unascertained mortality decreasing as LTFU increased, and the proportion of attrition attributable to LTFU increasing with each additional year on ART (13). With estimates of programme attrition as

high as 40% after 3 years, LTFU is a considerable barrier to the achievement of the long-term goals of ART programmes (61).

Finally, in October 2017 the UNAIDS announced the 90-90-90 targets which aim to have 90% of people living with HIV know their status, 90% of those who know their status remain on ART, and 90% of those on ART achieving viral suppression by 2020 (41,97). As part of this initiative, improved HIV testing and linkage to care following an HIV diagnosis were identified as points of intervention. However, with this goal increasingly being met, programmes must now start looking at how best they can restructure themselves to allow patients to live productive lives. The gap in achieving the second 90 consists of people that do not link to care following an HIV diagnosis as well as people that initiate ART but are lost from care. In South Africa, it was estimated that in 2018 more than 50% of the diagnosed and untreated population had previously been on ART, a proportion which had been steadily increasing over the past few years (Johnson LF; SA AIDS conference, 2019) (Figure 2.6). Given the successes in testing and treatment scale-up as a result of universal ART combined with high rates of LTFU in most ART populations, understanding people who start ART but do not remain retained in care is of increasing importance to ART programmes. However, this group has received less attention than linkage to treatment in the context of the UNAIDS targets (41).

Figure 2.6: South Africa's progress towards the UNAIDS 90-90-90 targets *(Johnson LF, SA AIDS conference, 2019).*



2.4.2. Results from tracing studies

It is important to estimate the "true default" rate, which is loss to follow-up excluding those who have died or transferred out of the area and are receiving treatment in another health facility elsewhere. Most ART programmes do this by tracing patients lost to follow up. However, this is often done inconsistently more so in national governmental programmes (52,90,361) even with tracing policies in place. In addition, whereas some programmes try to trace all patients LTFU, some trace a random sample of patients and others trace a non-random sample (15). Wilkinson et al (15) in their systematic review of tracing studies reported a summary mortality estimate of 38.8% for patients LTFU, which was a reduction compared to a similar review done earlier by Brinkhof et al (14) which reported a summary mortality estimate of 42%. More recent studies have reported further reductions in mortality with Zürcher et al (16) finding that 32.4% of patients traced had died and Chammartin et al (362) reporting that 21.8% of patients that were LTFU had died four years after their last clinic visit.

Wilkinson et al also reported a summary estimate of 18.6% for self-transfers and 28.6% for patients that stopped ART ("true default") (15). Many of the studies included in these systematic reviews were done in the early stages of sub-Saharan African ART programmes when a large number of those initiating ART were much sicker. Scale up and decentralisation of these programmes also meant that ART could be provided closer to home (15) which potentially increased the rate of self-transfers in order to continue treatment at locations that were more convenient. This probably explains why LTFU is directly proportional to ART programme size (360) and may also explain why LTFU is higher at centralised health facilities compared to primary healthcare facilities (363). In 2017, Zürcher et al in their systematic review reported that 23.9% of LTFU patients successfully traced had transferred, representing an increase from the estimate reported by Wilkinson (16). However, an individual patient meta-analysis conducted in 2018 reported a reduction in both self-transfers and ART stoppage four years after a last clinic visit, with estimates of 14.8% and 22.6% respectively (362).

It is possible now that the percentage of those deceased has changed owing to growing ART access and coverage, leading to more healthy asymptomatic patients initiating ART. Wilkinson et al found a significant reduction in deaths – from 50% to 30% – identified by tracing studies when they compared studies before and after 2007 (15). Zürcher et al also reported that mortality following LTFU appeared to decrease each calendar year, while ART stoppage and self-transfer appeared to be increasing (16). One study reported that mortality associated with LTFU is inversely related to the proportion of patients lost (364). As the proportion of patients LTFU from a treatment programme increase, the proportion of LTFU attributable to mortality decreases. Furthermore, few studies have specifically traced mothers LTFU from PMTCT programmes (17,19,102). This population is different from the populations that have previously been traced in a number of ways; firstly, with Option B+, many mothers are initiating ART while asymptomatic which potentially increasing their risk of LTFU. In addition, adequate adherence drops postpartum (89) and childbirth can be a risk factor for default (365) which could be because of a myriad of reasons. For example, the added burden of travelling to the clinic with a young infant, postpartum depression or out-referral after delivery (245,257,366). Consider also that new mothers are often quite mobile (18,102). Because of this, we can postulate that they are more likely to self-transfer especially in situations where health facilities are not transfer friendly.

2.5. Data sources

The majority of PMTCT programmes and studies reviewed were implemented as clinical cohorts and relied heavily on paper-based registers and physical patient files (11,99,228,229). These paper-based registers suffer from several deficiencies. Firstly, these registers suffer from general data quality issues, such as incompleteness and duplicate records. These registers are also harder to store often getting lost or having torn or illegible pages. These issues limit the accuracy of results based on routinely collected data (99). Furthermore, the sheer number of registers complicate patient follow-up. In some settings, HIV test results, ART clinic visits, pregnancy data, and outcomes of tracing are recorded across several separate registers meaning information is often duplicated. Sometimes multiple versions of the same register exist at some

clinics which constitutes a high volume of paperwork and a significant workload for clinic staff, probably explaining the high levels of missing data. Finally, the lack of unique identifiers in these registers makes collating of all pertinent patient information difficult. Lack of unique identifiers also complicates tracking of women's outcomes throughout the PMTCT cascade. For example, it is hard to track patients as they move from one facility to another or in the case of postpartum women, when they transfer their treatment from ANC to the adult ART clinics. Some studies employed active patient tracing to mitigate loss to follow-up (201,367,368). However, this is also significantly impeded by data quality issues (17,369). Data linked across multiple clinics is recommended by the WHO (370) and could also help to catch silent transfers and identify patients who are highly mobile. However, these linked data systems are a rarity in sub-Saharan Africa (18,371). Investigating retention using other data sources is therefore an important consideration especially as data triangulation using multiple sources improves the accuracy of estimates and data quality as well (372).

2.5.1. The role of community cohorts in estimating outcomes among ART patients

Community cohort studies provide an opportunity to investigate engagement in Option B+ at a population level (20). These community cohorts collect demographic, behavioural and health information (including in and out migrations from the surveillance site) regularly using HDSS and have unique identifiers for each individual. Furthermore, they include information linking infants to their mothers making their identification simpler. Some of these community cohorts have also started linking clinical data from nearby clinics allowing the utilisation of more data (103,104). This linkage provides the opportunity to look at outcomes among mothers who are lost to follow-up from the HIV clinic where they initiated treatment, something which other clinic-based PMTCT cohort studies are unable to do (99). Finally, with the availability of verbal autopsies in some sites, presumptive causes of death for all patients found to have died can give an indication of predominant causes of death in mothers LTFU. Such an endeavour will allow for accurate estimation of Option B+ coverage rates in other settings with the availability

of population-wide estimates on undocumented transfers between clinics, deaths, outcome misclassifications and genuine ART discontinuation.

2.6. Summary

Whereas PMTCT programmes in sub-Saharan have come a long way since their inception, there are still improvements that could be made to support maternal engagement in HIV care. Pregnant and postpartum women have worse engagement in care. However, little is known about what happens to these women after they become LTFU. Furthermore, given that many mothers report protecting their unborn child as a major contributing factor to their starting treatment (237,251,319,340), little research has investigated how infant outcomes affect mothers' continued engagement in care in the postpartum period (373). By contributing to these research gaps, the work of this thesis will improve our understanding of pregnant and postpartum women's engagement in HIV care and provide recommendations for future practice to improve engagement in care in this group.

Table 2.3: Manuscripts reviewed for retention and engagement in care statistics for pregnant and postpartum women

Study	Year	Country	Study design	Source of retention data	Retention definition	N	Percent retained (%)
Ahoua (374)	2020	Mozambique	Retrospective cohort	Routine electronic patient-level databases	Facility visit 12 months after ART initiation	31186	12mo: 60
Ahoua (375)	2020	Mozambique	Retrospective cohort	ANC aggregated data	No facility visits for 30 days or more prior to expected 12-month visit date	31186	12mo: 74
Chaka (376)	2019	Ethiopia	Retrospective cohort	Individual medical records	Not defined in paper	248	96
Pellowski (108)	2019	South Africa	Prospective cohort	Routine facility data and self-report	Not defined in paper	260	80
Cichowitz (377)	2019	Tanzania	Retrospective cohort	Electronic patient medical records	No gap in care greater than 90 days	650	24mo: 41

Watt (378)	2019	Tanzania	Prospective cohort	Routine facility level data and patient surveys	In care 6 months postpartum with a VL<200	200	6mo: 79
Etoori (35)	2018	Eswatini	Prospective cohort	Review of facility registers and patient files	No gap in visits of 4.5 months or more	496	1st appt: 91, 6mo: 80, 12mo: 71, 24mo:53
Hauser (379)	2018	Malawi	Retrospective cohort	Routine facility registers and patient files	No gap greater than 60 days following a missed appointment	490	3mo: 73
Langwenya (43)	2018	South Africa	Prospective cohort	Routinely collected clinic, pharmacy and laboratory records	VL within a week before or after delivery	628	68
Phillips (18)	2018	South Africa	Retrospective cohort	Routine electronic medical records	Any visit after leaving integrated PMTCT clinic postpartum	671	12mo:71, 24mo: 65
Kiwanuka (380)	2018	Uganda	Retrospective cohort	Routine facility data	No gap greater than 60 days following a missed appointment	518	24mo: 46

Atanga (249)	2017	Cameroon	Prospective cohort	Facility level data on refill appointments	No gap of 90 days or more following a missed appointment	277	1st appt: 92, 3mo: 88, 6mo: 85, 12mo: 77
Hoffman (317)	2017	Malawi	Case-control	Review of facility records	No gap of 60 days or more after a missed appointment		
Hosseinipour (200)	2017	Malawi	Randomised control trial	Record review of facility registers and patient files	No gap of 60 days or more after a missed appointment	447	1st appt: 81, 6mo: 71, 12mo: 60, 24mo: 41
Mwapasa (332)	2017	Malawi	Cluster randomised trial	Record review of facility registers and patient files	No more than 14 days late for drug refills and attended 12-month postpartum visit	396	12mo: 69
Phiri (201)	2017	Malawi	Randomised control trial	Record review of facility registers and patient files	No gap of 60 days or more after a missed appointment	1269	1st appt: 85, 24mo: 65
Pfeiffer (381)	2017	Mozambique	Cluster randomised trial	Routine patient registers and forms	Medication refill +/- 5 days of scheduled visit (30-day refills)	761	3mo: 40

Oyeledun (382)	2017	Nigeria	Cluster randomised trial	Record review of facility registers and patient files	Full: Attended six-month postpartum visit (±30 days) and did not missed any previous scheduled visit by more than 30 days; Partial: Attended six-month postpartum visit (±30 days) but missed ≥1 previous scheduled visit by more than 30 days	247	6mo: 68
Sam-Agudu (383)	2017	Nigeria	Prospective cohort	Record review of facility registers and patient files	At least 3 visits between delivery and 180 days postpartum (30-day schedule)	497	44
Guillaine (303)	2017	Rwanda	Retrospective cohort	Routine electronic medical records	Facility visit 15 months postpartum	185	18mo: 98
Clouse (102)	2017	South Africa	Observational cohort	National laboratory database	At least one CD4, VL, or lab record after being considered LTFU	788	62*
Gamell (384)	2017	Tanzania	Prospective cohort	Routine electronic medical records	No gap of 60 days or more after a missed appointment	45	73

Koss (202)	2017	Uganda	Cross-sectional follow-up of a random sample of women in a randomised trial	Review of patient records combined with patient interviews	Attended the clinic in the 90 days preceding the interview	200	48mo: 68
Miller (385)	2017	Uganda	Retrospective cohort	Record review of facility registers and patient files	At least one clinic visit 12 months after pregnancy detection	373	12mo: 84
Muhumuza (386)	2017	Uganda	Retrospective cohort	Standardized facility-based records	No gap of 90 days or more without a visit	2169	6mo: 74, 12mo: 67, 18mo: 62
Musomba (331)	2017	Uganda	Retrospective cohort	Routine electronic medical records	No gap in visits of 3 months or more	856	92
Erlwanger (69)	2017	Zimbabwe	Cluster randomised trial	Routine facility registers and case report forms	Medication possession ratio or exhausted pill supply following last visit	1113	12mo: 68

Ford (330)	2017	Zimbabwe	Retrospective cohort	Record review of facility registers and patient files	No gap 90 days or more without a visit	386	1st appt: 97, 3mo: 92, 6mo: 86, 12mo: 85
Foster (387)	2017	Zimbabwe	Cluster randomised trial	Record review of facility registers and patient files	Visited the clinic at 12 months postpartum	348	12mo: 66
Joseph (388)	2017	Zimbabwe	Cluster randomised trial	Record review of facility registers and patient files	Having had an ART refill visit a minimum of 335 days post-ART initiation and on-time attendance (before, on or up to 14 days after the next scheduled date) for at least 75% of scheduled ART refill visits, up to and including the 12-month visit AND no gap in care >90 days.	547	1st appt: 96, 6mo: 69, 12mo: 63
Mitiku (203)	2016	Ethiopia	Retrospective cohort	Record review of facility registers and patient files	No gap of 90 days or more without a visit	346	1st appt: 95, 6mo: 88,

							12mo: 84, 24mo: 77
Chan (42)	2016	Malawi	Retrospective cohort	Record review of facility registers and patient files	Clinic visit within 2 months of last dispensed drugs running out	813	1st appt: 56, 3mo: 48, 6mo: 47
Haas (34)	2016	Malawi	Observational cohort	Routine electronic medical records	No gap greater than 60 days following a missed appointment	29313	6mo: 83, 12mo: 77, 24mo: 71, 36mo: 70
Landes (250)	2016	Malawi	Retrospective cohort	Review of standard ART monitoring tools	No gap of 60 days or more after a missed appointment	2955	1st appt: 87, 3mo:85
Auld (53)	2016	Mozambique	Observational cohort	Routine electronic programme data	60 days or more late for a scheduled appointment	14397	6mo: 69
Llenas-Garcia (204)	2016	Mozambique	Observational cohort	Routine HIV programme data	No gap in visits of 180 days or more	308	1st appt: 60, 12mo: 42
Woelk (389)	2016	Rwanda	Retrospective cohort	Record review of facility registers and patient files	At least one visit in each period 6wk, 3, 6, 9, and 12 months postpartum	457	1st appt: 67*, 3mo: 67*, 6mo: 64*, 9mo:

							62*, 12mo: 58*
Myer (244,390)	2016	South Africa	Prospective cohort	Combination of routine electronic HIV databases	VL around time of delivery	620	94*
Schnack (66)	2016	Uganda	Observational cohort	Facility level data on refill appointments and pill counts		124	1st appt: 64
Dzangare (305)	2016	Zimbabwe	Retrospective cohort	Record review of facility registers and patient files	Not defined in paper	148	1st appt: 93, 6mo: 77
Kim (391)	2015	Malawi	Quasi-experimental	Routine facility level data	Not defined in paper	810	6mo: 80
Schwartz (109)	2015	South Africa	Pilot intervention	Record review of facility registers and patient files	No gap of more than 6 weeks after a missed appointment	50	12mo: 76
Kamuyango (70)	2014	Malawi	Retrospective cohort	Record review of facility registers and patient files	No gap of 60 days or more after a missed appointment	190	12mo:97
Koole (392)	2014	Malawi	Retrospective cohort	Record review of facility registers and	No gap of 60 days or more after a missed appointment	586	6mo: 85

				patient records plus patient interviews			
Price (354)	2014	Malawi	Retrospective cohort	Record review of facility registers and self-reported	On ART at the time of the interview	63	1st appt: 67, 6mo: 60
Tenthani (318)	2014	Malawi	Retrospective cohort	Review of facility records aggregated for routine monitoring and evaluation, Routine electronic medical records	No gap of 60 days or more after a missed appointment	5357	6mo: 76
Tweya (17)	2014	Malawi	Retrospective cohort	Routine electronic medical records	No gap of 3 weeks or more after a missed appointment	2930	1st appt: 91, 3mo: 87, 9mo: 83
Van Lettow (257)	2014	Malawi	Observational cohort	Routine facility cohort reports	No gap of 2 months or more without ART	18207	6mo: 84, 12mo: 81
Kiweewa (393)	2013	Uganda	Randomised control trial	Record review of facility registers and patient files	VL 6-12 months post ART initiation	85	89*

(* Cohort may contain some pregnant and breastfeeding WLHIV who initiated ART under Option B or A)

3. Research methods

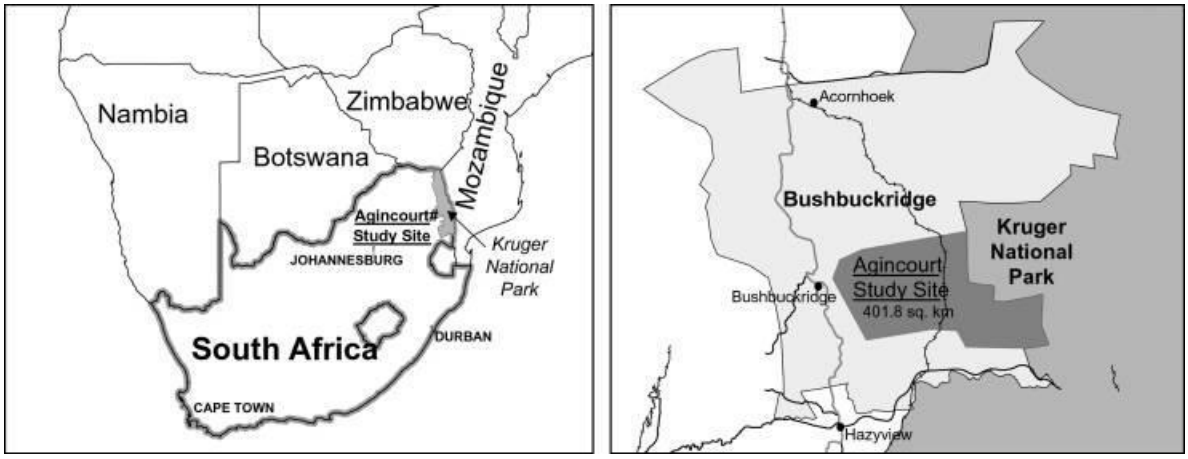
This chapter begins by introducing the context for this PhD research, including an overview of the study setting, details of the MRC/Wits Rural Public Health and Health Transitions Research Unit activities in the Agincourt HDSS and details of the health services offered in the HDSS. Methods for the collection of quantitative data and other specific information about the datasets are outlined. Statistical analysis methods are then presented. The second part of this chapter describes the methods used during the implementation of a qualitative study that I designed and implemented in in the second year of my research. I describe the data collection procedures and outline the methods used to analyse the data generated.

3.1. Context

3.1.1. Overview of the study setting

The research for this PhD was conducted in the Agincourt sub-district located in Bushbuckridge local municipality of Ehlanzeni district in the Mpumalanga province, in rural north-east South Africa. The Agincourt HDSS located in this area is run by the MRC/Wits Rural Public Health and Health Transitions Research Unit under the auspices of the School of Public Health at the University of the Witwatersrand. The HDSS has been tracking demographic and health events in the Tsonga or Shangaan people since 1992. Mozambicans comprise about 30% of the population and have culturally assimilated, primarily speaking Shangaan. They arrived as refugees in South Africa in the 1980s following the Mozambican National Resistance (RENAMO) – Mozambique Liberation Front (FRELIMO) civil war in Mozambique (350). At the time of this study, the HDSS covered an area of approximately 475 square kilometres, with an approximate population of 115,000 people living in 17,000 households located in 31 contiguous villages (394). The Agincourt HDSS is bordered by Kruger National Park to the east and is adjacent to the Mozambique border (Figure 3.1).

Figure 3.1: A map showing the regional location of the Agincourt health and demographic surveillance system *(Source: Kahn et al (395))*



3.1.2. Historic context

It is important to consider the historical context in order to better understand the nature of the HIV epidemic and national responses to it in a given setting. In South Africa, the National Party government introduced apartheid in 1948. As part of this system, legislation was enacted that included forced resettlement, movement restrictions for black South Africans, and separate development with the establishment of "homelands" or "Bantustans". Restriction of access to land, together with forced resettlement resulted in black South African settlements that were densely populated, but agriculturally and economically inhospitable (396). As a result, many of the inhabitants of these settlements were forced to migrate for work. Various laws were passed to restrict their movement. The pass system, for example, restricted free movement to those with employment, entrenching the separation of families because women and children often did not have the legal right to travel with their partners (396).

Gazankulu was a homeland situated in northeast South Africa. The Agincourt sub-district is situated in what was formally Mhala district of Gazankulu, the inhabitants of which belong to the Shangaan-speaking Tsonga ethnic group (396).

3.1.3. Current socioeconomic context

Located within a former Bantustan, the area still carries remnants of the Apartheid legacy of underdevelopment and inadequate education. Despite

improvements in the social situation following the collapse of Apartheid, and the move to more democratic governance, there are still issues with access to electricity, water and tarred roads (20). Because homelands were often found in areas of little industrial and agricultural activity or potential, lack of gainful employment opportunities has led to high unemployment rates. As a result, there are high rates of labour migration with reliance on remittances as an important income source (350). Formal employment involves mostly migrant men working in the mining sector, in construction and security firms in larger towns and on nearby agricultural and game farms (350). For many families, social benefits/allowances are a crucial source of income especially the "old age" pension and the "child support grant".

This political history has influenced current demographic patterns, including migration, that influence ART access patterns today. Whereas it was hoped that black South Africans would move and assimilate into economic centres and cities following the end of Apartheid, labour migration has remained the norm for most. Continued separation due to labour migration has had severe psycho-social impacts, especially with regards to alcoholism and violence (350). Sexually transmitted infections (STIs) are also highly prevalent and have been proliferated by behavioural traits that are more commonly found among migrant communities, such as the development of sexual networks at workplaces due to spousal separation. This has been exacerbated by the intersection of a weak health system and other social conditions like poverty in which HIV/AIDS thrived and became entrenched, bred by protracted colonialism and Apartheid, which a social and political transition period was unable to curtail.

The Agincourt HDSS had an estimated population of 115,000 residents in 2018, with 52% of them being female. Children under 5 years of age accounted for 10% of the population, with children and young adults 5-19 years of age making up 31% of the population. There were 2042 births recorded in 2017 and the crude birth rate (CBR) was estimated at 18 live births per 1000 people. The age-specific fertility rate was estimated at 60 births per 1000 women aged 15-19 and peaked at approximately 90 births per 1000 women in the 25-29 years age group. There were 542 deaths (52.3% males) recorded in the

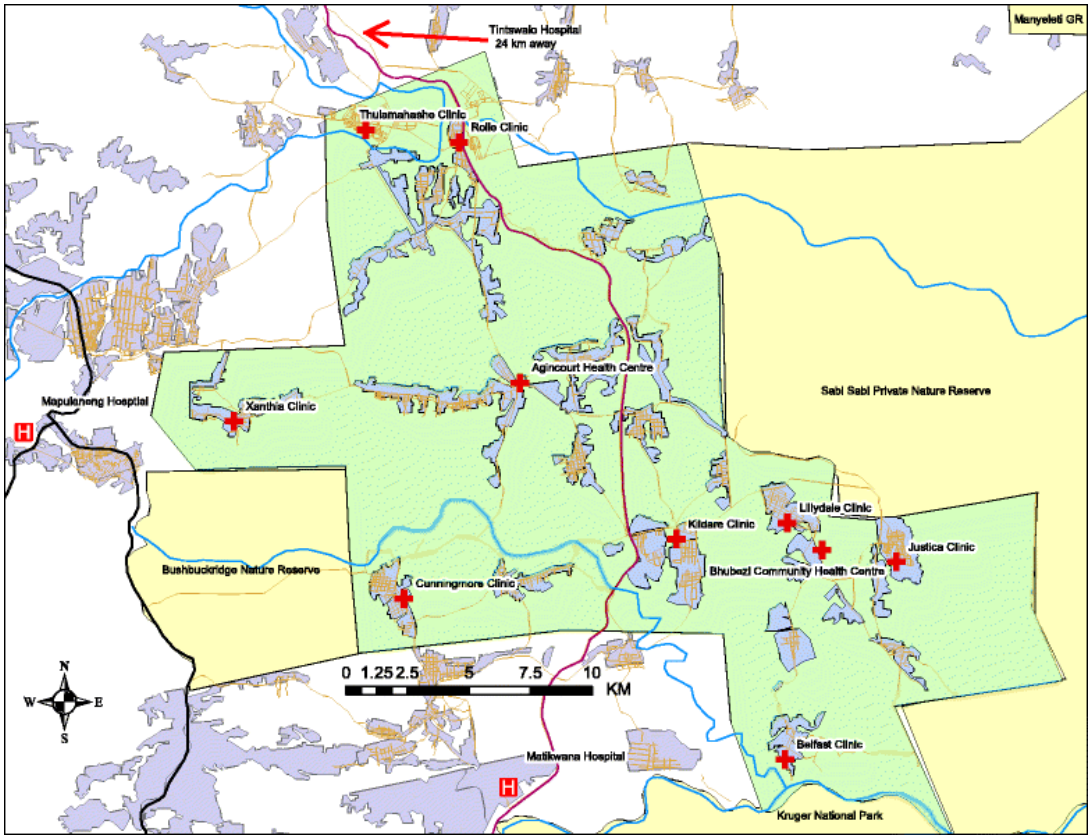
Agincourt HDSS in 2017, giving a crude death rate of 6 deaths per 1000 people. The Agincourt HDSS recorded 3049 total in-migrations and 4533 total out-migrations in 2017 (397).

Antenatal care (ANC) attendance is estimated at >95%. Estimates of HIV sero-prevalence in antenatal clinics in the province rose from 2% in 1992 to 35% in 2005 (396). In 2010, HIV prevalence among people 15 years of age or older was estimated at 19.4% in the Agincourt HDSS. Prevalence was characterised by a large gender difference (10.6% for men and 23.9% for women) and peaked at ages 35-39 among both men (45.3%) and women (46.1%), with 5.5% of women 15-19 years old estimated to be HIV infected (398).

3.1.4. Health services overview

The Agincourt HDSS includes eight government-run health facilities within its borders. Five of these facilities are primary healthcare (PHC) clinics and three are designated as community health centres (CHCs). These centres act primarily as referral centres for patients that require specialised healthcare services. The objective of this is two-fold, to make modern healthcare services available to rural populations and to reduce overcrowding at regional and district hospitals. The clinics offer ANC services, delivery, and child clinic services as well as offering STIs and tuberculosis screening and treatment. The facilities also offer HIV counselling and testing services, PMTCT and HIV care and treatment services for PLHIV. There has also been a push by the Department of Health to improve health services for other chronic diseases such as diabetes and hypertension and these services are now being implemented in most clinics. There are three government hospitals located near the Agincourt HDSS, Matikwana and Mapulaneng hospitals located about 5 kilometres outside the HDSS, and Tintswalo hospital located approximately 24 kilometres away (Figure 3.2).

Figure 3.2: Maps of Agincourt HDSS showing health facilities within the site and the surrounding area *(Source: Lippman et al (399))*



Note: Lillydale clinic and Bhubezi CHC merged in 2016, Thulamahashe is now designated as a CHC.

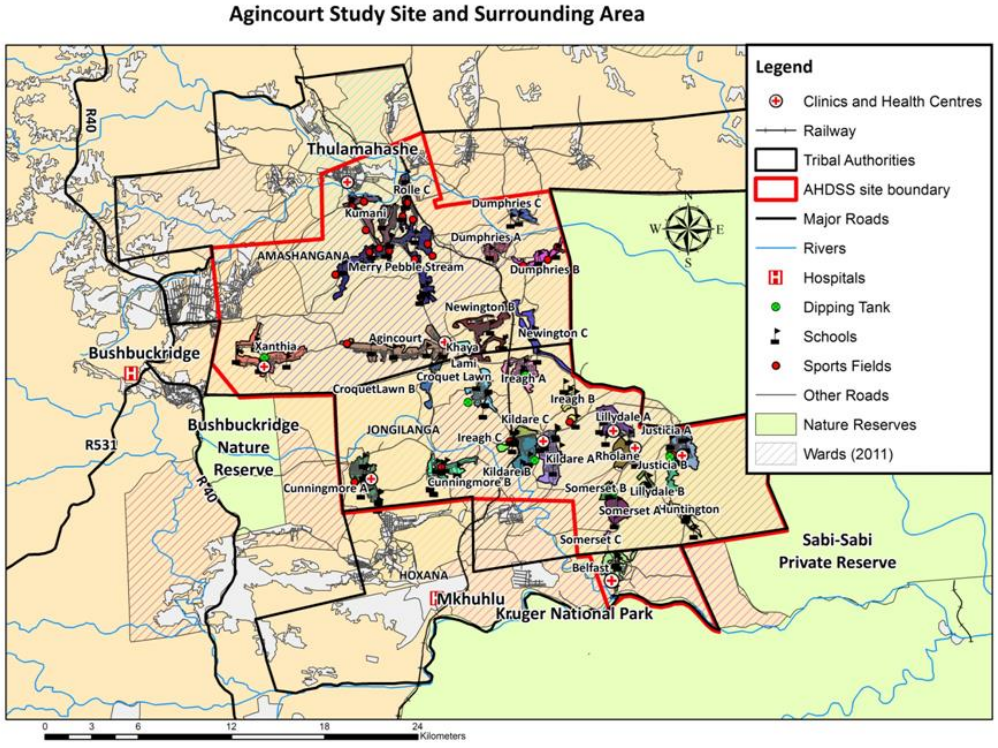


Figure 3.3: Images of Bhubezi CHC




Figure 3.4: Images of Xanthia PHC


3.1.5. HIV services

HIV counselling and testing

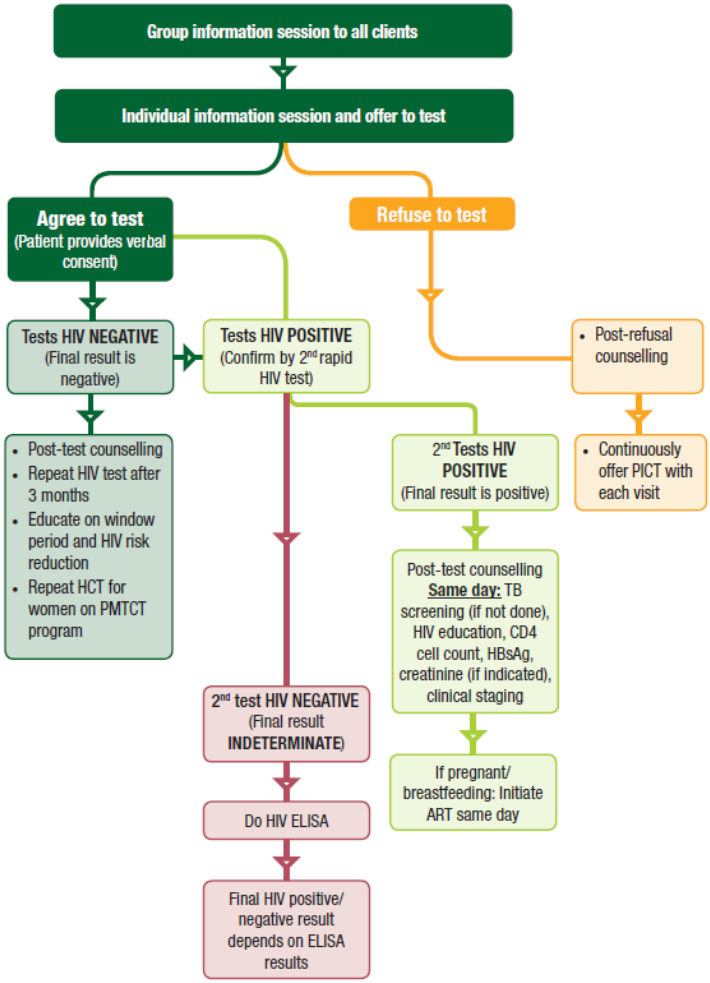
The HIV/AIDS and STI national strategic plan of 2007 emphasised a push to establish "a national culture in which all people in South Africa regularly seek voluntary testing and counselling for HIV" (400). The plan proposed interventions including the development of high-profile campaigns utilising peer influence to promote testing and disclosure, expansion of access to HIV testing beyond formal healthcare settings, and development of clear, consistent HIV prevention messaging. In 2009, as part of his World AIDS day address, President Jacob Zuma launched a new HIV counselling and testing (HTC) campaign. As part of the HTC campaign, the President publicly tested for HIV, being among 20 million South Africans to learn their status over the next 20 months (401). This represented a substantial increase in national testing rates (402).

In line with national policy on provider-initiated counselling and testing (PICT), facilities in Agincourt offer HCT to adults who do not know their HIV status if they have not tested in the past year, as part of any clinical care or screening, in cases of sexual assault or domestic violence, and as part of medical male circumcision. This is repeated annually for those who were HIV negative when they last tested, with more frequent testing for those with new sexual partners or those engaging in unprotected sex (402). HCT should be offered to all pregnant and breastfeeding women with unknown HIV status or those who tested HIV-negative 3 or more months prior. Children aged 12 years or older may consent to a test if they are considered by the health worker as sufficiently mature to understand the benefits, risks, and social implications of the HIV test result. In all other cases, a parent or caregiver must give consent.

The policy also stipulates that all patients receiving PICT or client-initiated counselling and testing (CICT) should provide verbal consent for HIV testing. HCT follows the Department of Health testing algorithm (Figure 3.5). A group session outlines the benefits of HCT to the patient, including in the context of PMTCT, if the patient is pregnant. Individual sessions should include an assessment of whether the information communicated in the group session

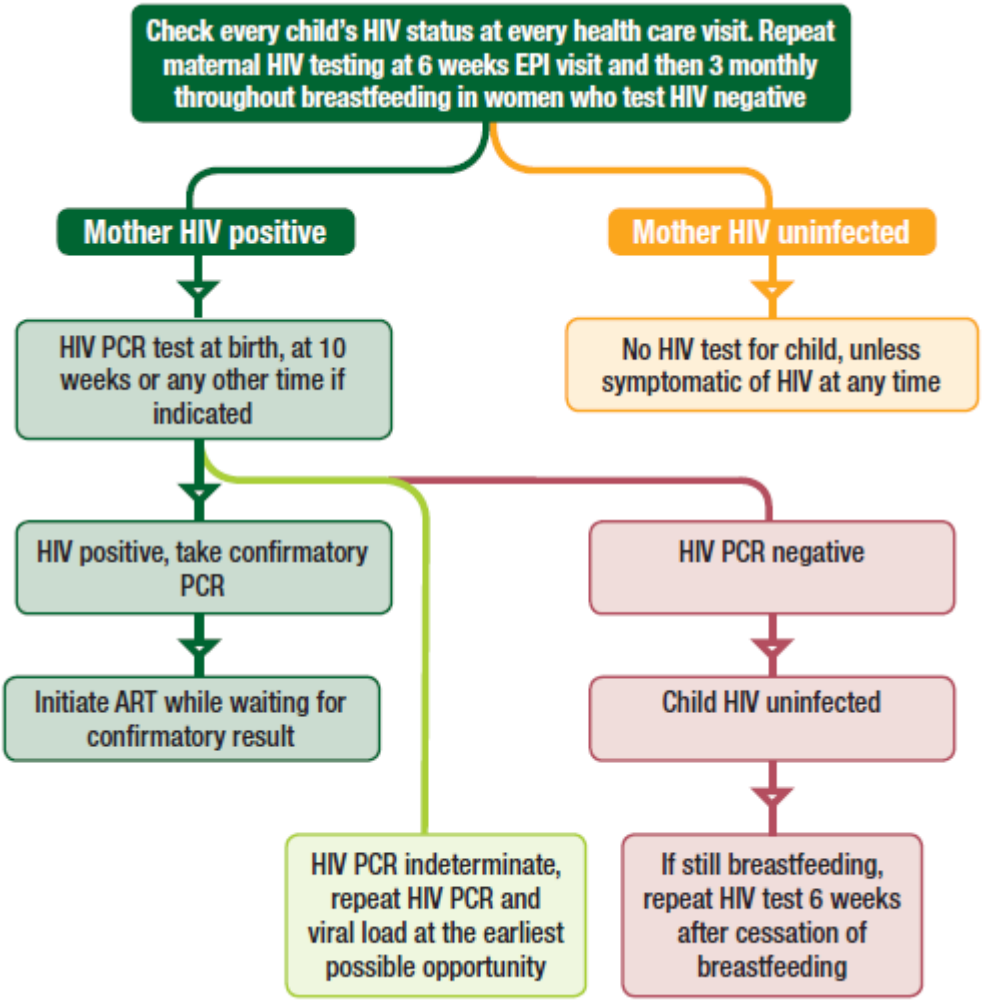
was understood, answering any questions, clarifying any misunderstanding, and addressing any concerns. Pregnant and breastfeeding women who test negative are considered part of the PMTCT programme and should retest every 3 months until breastfeeding cessation, unless HIV infection is diagnosed. All patients receive post-test counselling regardless of their result, which covers risks for HIV transmission, safe sex and condom use, contraception and family planning, HIV testing for sexual partners and children, repeat HIV testing for those who are HIV-negative, and PMTCT including safe infant feeding and infant prophylaxis. All patients who test for HIV are recorded in the HCT register. For those who test positive, details including full names, age, sex, and address are recorded in the pre-ART register to enable tracking of linkage to care.

Figure 3.5: Algorithm for HTC using rapid antibody test for adolescents and adults including pregnant and breastfeeding women *(Source: National consolidated guidelines (402))*



As part of PICT, all HIV-exposed neonates should receive an HIV polymerase chain reaction (PCR) test at birth, ten and eighteen weeks, and a rapid HIV antibody test at 18 months or older (Figure 3.6). Children should also be tested if they present with severe illness, are suspected to be HIV infected, are diagnosed with tuberculosis (TB), the mother's HIV status is unknown, the father or sibling tests HIV-positive, the mother, father or sibling dies, they are a suspected victim of sexual assault and if they are being considered for fostering or adoption. Parents can also request for the child to be tested.

Figure 3.6: Testing algorithm for routine testing in children <18 months of age



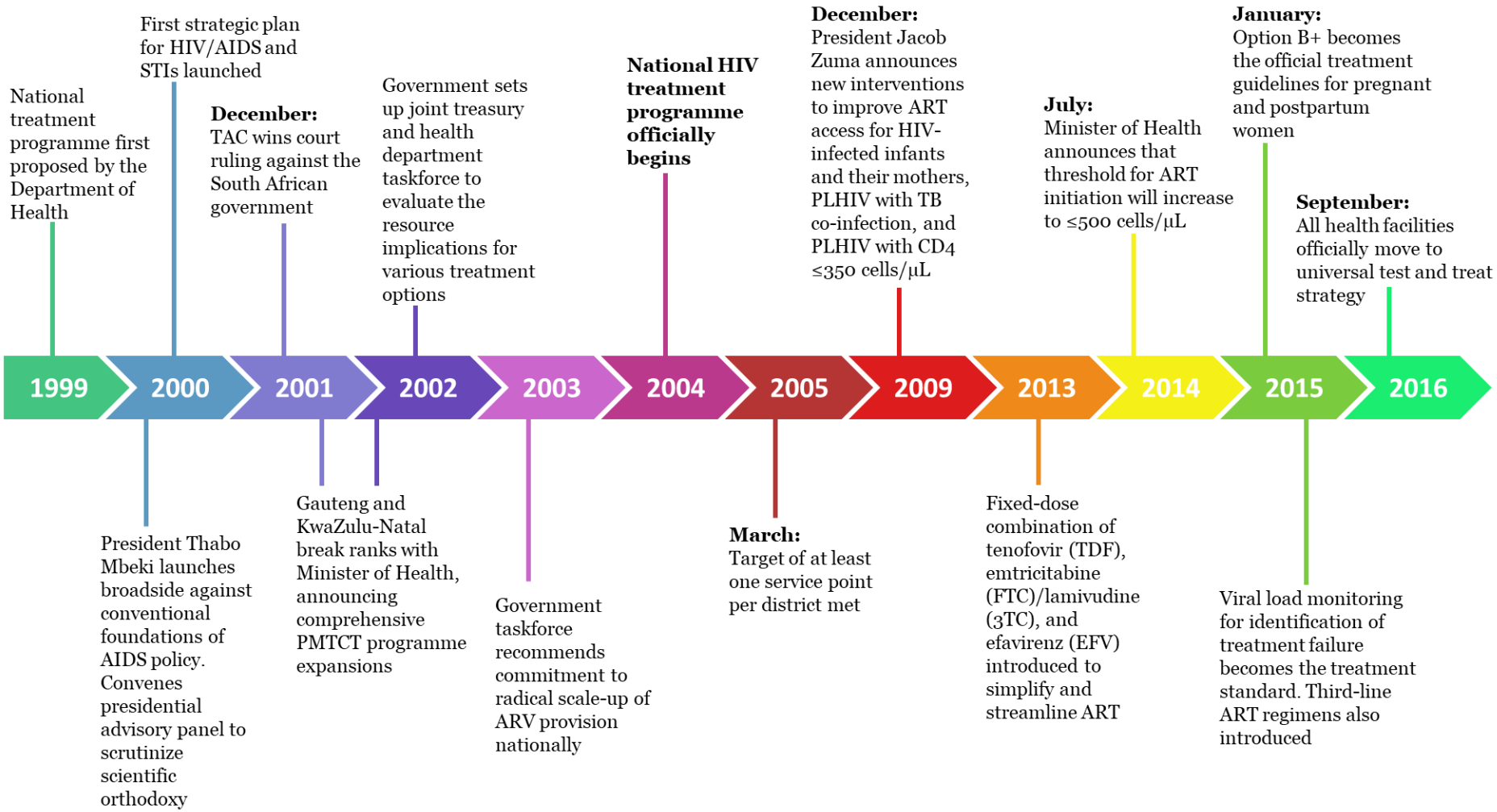
Depending on the size of the facility, testing is done in a separate room in the same building or in a different building within the clinic compound. However, for pregnant women, HCT is integrated into ANC.

Antiretroviral therapy (ART)

A national HIV treatment programme was first proposed in South Africa in late 1999 by the National Department of Health but did not materialise until 2004 following legal action by the Treatment Action Campaign (TAC) against the South African government (403). In November 2003, the South African Department of health proposed a plan to provide HIV/AIDS care and treatment in at least one service point in every health district in 2004, with the aim to expand the programme and achieve equitable access within local municipal areas by 2008. In total, 22500 new health workers would be

recruited over the five-year period, including 1100 new doctors (404). To begin with, ART was only offered to those with a CD4 count less than or equal to 200 cells/µl with the aim of achieving universal treatment coverage for all new AIDS cases by the end of 2008. By March 2005, the target of at least one service point per district had been met, but ART was largely provided through hospitals, most of which were tertiary facilities. On 1 December 2009, World AIDS day, then president Jacob Zuma announced new interventions to improve ART access to all HIV-positive infants, pregnant women, people with TB and HIV co-infection and PLHIV with CD4 counts less than or equal to 350 cells/µl (402). With the launch of a massive HIV counselling and testing campaign, and in anticipation of large numbers of new patients identified by the campaign, it was also announced that accreditation would be abandoned and that all public healthcare facilities would be equipped to provide ART. In 2013, a fixed-dose combination (FDC) of tenofovir (TDF), emtricitabine (FTC)/lamivudine (3TC), and efavirenz (EFV) was introduced to simplify and streamline ART (402). On July 23, 2014, the Minister of Health announced the threshold for ART initiation would increase to CD4 less than or equal to 500 cells/µl (402). This came into effect in January 2015. Furthermore in 2015, use of viral load for monitoring treatment success and early identification of treatment failure became the standard treatment and third-line drugs were introduced for patients failing second-line regimens. On 22 August 2016, all health facilities were instructed to move to universal test and treat starting on the 1st of September 2016 (93) (Figure 3.7).

Figure 3.7: The South African National treatment programme timeline showing major milestones



Most health facilities in Agincourt have been providing ART since 2010 (405). Patients who test HIV-positive are now eligible to initiate ART as soon as they are ready (402). According to national guidelines, at the time of diagnosis, the healthcare provider should involve the patient in the decision-making process regarding ART initiation and explain the entire treatment plan (402). In the case of pregnant women, they can initiate ART during ANC, usually on the same day. Non-pregnant patients are referred to HIV/ART services. Services are usually provided at the same facility but in some cases, the patient can be referred to another facility on request. In such instances, the sending facility makes an appointment directly with the receiving facility on behalf of the patient and provides the patient with an appointment date and referral letter. Most patients receive FDC as their first ART regimen. If FDC is contraindicated for pregnant women, they are considered high-risk pregnancies and are referred to HIV/ART services where they are usually offered AZT twice daily until a three-drug ART regimen can be initiated.

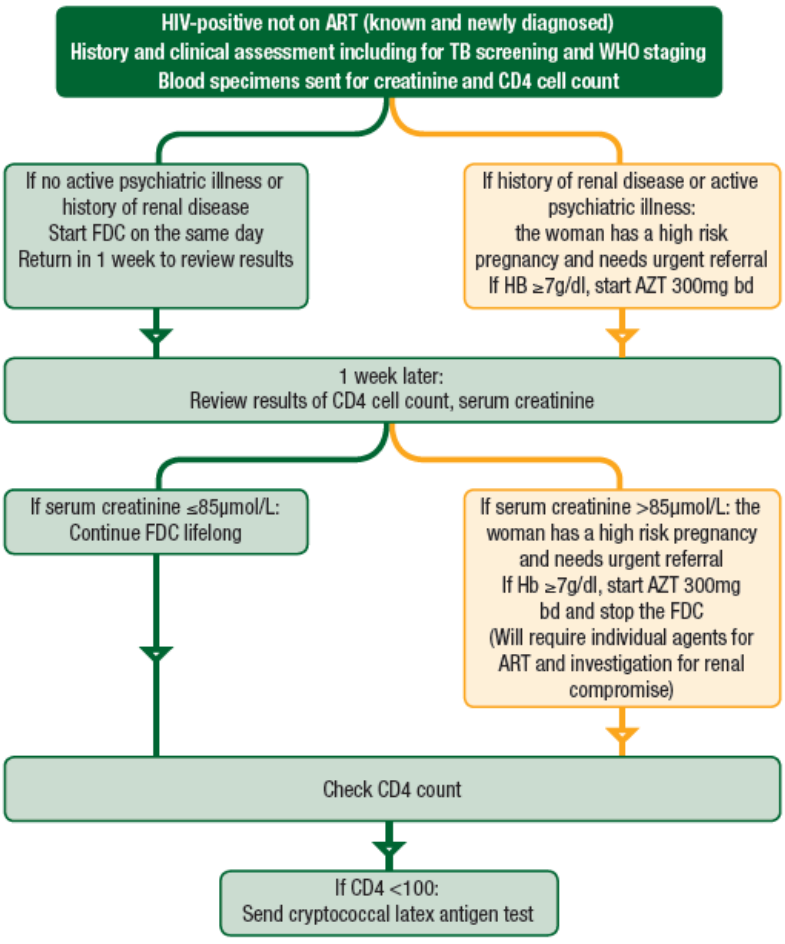
Patients should receive a viral load (VL) test at 6 and 12 months after ART initiation and annually thereafter (10). Pregnant women should receive VL tests more frequently usually every 3 months until breastfeeding cessation. Patients with suspected non -adherence (e.g. multiple missed appointments) or treatment failure (VL>1000 copies/mL) should receive step-up adherence counselling. This includes re-education about the importance of adherence, evaluation of support structures, advice on methods to improve adherence like pillboxes, encouragement to participate in a support group, a mental health assessment and in some cases home visits where spot pill counts can be done. Clinically stable patients defined as those receiving ART for at least one year, with no adverse drug reactions requiring monitoring, no current illnesses or pregnancy, a good understanding of lifelong adherence, and two consecutive undetectable viral load results are offered differentiated models of care (10). These include greater spacing between pill refill visits of up to 6 months, “fast-track” appointments, health worker run adherence clubs and Central Chronic Medicines Dispensing and Distribution programme (CCMDD) which allows patients to collect their treatment at multiple distribution points.

Prevention of mother-to-child transmission of HIV

On July 23, 2014, the Minister of health announced that the PMTCT programme would adopt the Option B+ approach and this was implemented from January 2015. The PMTCT programme should be fully integrated into ANC. HIV testing, ART, HIV care and treatment, labour and skilled delivery services should all be offered through a one-stop shop approach.

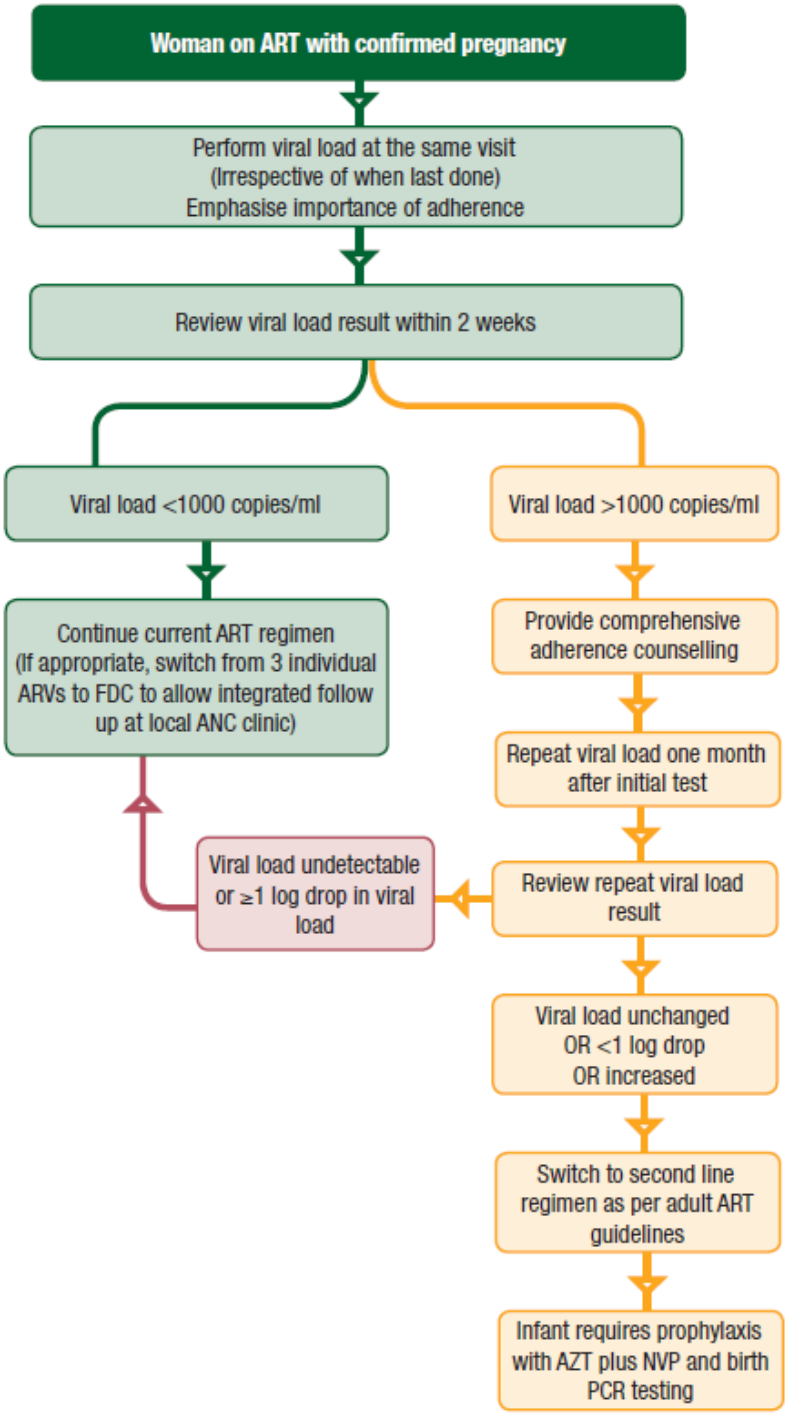
In South Africa, 4% of pregnant women who test negative at their first ANC visit seroconvert during the pregnancy (402). Women newly diagnosed with HIV receive several tests including CD4 count, Hepatitis B antigen, haemoglobin, creatinine and are assessed for ART eligibility and readiness. They are initiated on treatment following a specific treatment initiation algorithm (Figure 3.8).

Figure 3.8: Algorithm for initiation of ART for HIV-positive ART-naive women



For women already on ART with a confirmed pregnancy, a VL test should be done at the same visit of the confirmed pregnancy, with the results of the VL test used to indicate which interventions the mother requires (Figure 3.9).

Figure 3.9: Algorithm for the management of pregnant women already on ART for >3 months



All HIV-positive pregnant and breastfeeding women should receive a VL test every 3 months until breastfeeding cessation. All pregnant women are encouraged to deliver their baby at a health facility.

HIV-exposed infants for mothers on ART also receive nevirapine (NVP) at birth and then daily for 6 weeks. Infants whose mother did not receive ART are given NVP as soon as possible and then daily until the mother has been on ART for 12 weeks. Infants whose mother is diagnosed with HIV while breastfeeding or whose mother had their latest VL>1000 copies/mL receive NVP and AZT immediately. If the infant then tests HIV-negative by PCR, AZT is stopped and NVP continued until the mother has been on ART for 12 weeks. All infants who test HIV-positive are initiated on ART immediately.

Home-Based Carers organisations

Community home-based care for people who had advanced AIDS was first proposed in an effort to mitigate the impact of the HIV epidemic. In 2000, home-based carers were recognised as de facto healthcare sector labour force with the government initiating a non-governmental organisation-based contracting system to provide community-based services (406). In 2010, in order to formalise the community-based care sector, home-based care was recognised by the South African National Department of Health as a primary healthcare strategy to reduce pressures on hospitals and other healthcare resources (407). Under a programme to re-engineer primary healthcare, home-based care was expanded (408). Since it was first proposed, many of these volunteer caregivers have organised themselves into non-profit organisations that are affiliated with specific villages. They recruit and train community health workers to assist families with homecare, participate in income-generating activities including agriculture (Figure 3.10) and receive donations from various charities (409,410). Home-Based Carers are sometimes HIV-positive patients themselves, with experience of engaging with HIV services (usually referred to as “expert clients”), these groups are seen to have their hand on the pulse of their community and to be most knowledgeable about most inhabitants of their villages.

These organisations provide comprehensive services ranging from health education to palliative care. Home-based care also includes preventative,

therapeutic, rehabilitative, long-term maintenance, and other social services with the aim of empowering patients to take ownership of their health. In some clinics, home-based care workers are utilised in routine tracing and adherence monitoring through pills counts and direct observation of treatment taking. These organisations are not formally employed healthcare cadres and receive a stipend rather than remuneration from the Department of Health (411). There were sixteen home-based carer organisations operating in the Agincourt HDSS at the time of this research.

Figure 3.10: Images of Lillydale home-based carers compound situated opposite Bhubezi CHC

Routine patient tracing

All health facilities in Agincourt routinely trace HIV patients who are LTFU, defined in this setting as being more than 90 days late for a scheduled appointment in accordance with national policy (412). In practice, each health facility manager is responsible for ensuring that there is a functioning paper-

based or electronic appointment system, such that clinical files for patients who are expected the following day are retrieved from the filing room. Files for patients who do not attend a scheduled visit should be kept aside for further action. A list of patients who did not attend a scheduled appointment should be generated every week, either through the facility's appointment register or through querying the facility-level electronic database (TIER.Net). If a patient has not attended the facility within 5 working days to follow-up on a missed scheduled appointment, the patient's name should be registered in the facility tracing register to be traced.

This list is signed off by the facility manager and transferred to the person responsible for tracing patients, usually a designated nurse, community health worker (CHW) or the ward-based outreach team (WBOT) lead. The delegated nominee will extract contact information including addresses and telephone numbers (which should be updated at every clinic visit) of the individuals on the list (and their treatment supporter where available) from the patient files and enter this information into the facility tracing register. The facility telephone is then used to contact all the individuals who were added to the tracing register that week, with the date the phone call was attempted and the outcome of the phone call, and patient outcomes recorded in the register when obtained. Six facilities receive assistance with telephone tracing from a non-profit organisation called Right-to-Care (RtC)[2]. Three calls should be attempted within 14 days after each patient's missed visit. Patients who are alive, and who have not transferred to another clinic are encouraged to return to treatment. Self-transfers are further investigated usually through a phone call to the facility they have transferred to. The names of patients who cannot be reached after three attempts by phone are transferred to a list of those to be traced through outreach and home visits.

Patient consent for a home visit should be verified in the patient file. WBOTs, CHWs and home-based carers (HBCs) linked to the facility are involved to physically trace defaulters. Details of each home visit, including the outcome of the visit, are reported to the facility manager. Each outreach tracing effort

[2] See https://www.righttocare.org/ [accessed 27 August 2020]

should be marked in the facility tracing register, indicating the date and outcome of the tracing visit.

Patients who return to the facility after tracing are actively referred for psychosocial support to either a social worker, psychologist, peer support or other support groups. Patients in differentiated care models are returned to normal care if they cannot be found after 30 days of tracing. They can return to differentiated care if they meet the criteria in the future.

Patients who have not reported back to the clinic for 90 days since their last scheduled visit and do not have a tracing outcome e.g. transferred out, died or stopped treatment are registered as LTFU. Before this entry is made, one more attempt at phoning or visiting the patient should be made. Information from this entire exercise is in principle fed back into the patients' electronic record.

3.1.6. MRC/Wits Agincourt unit activities

Annual demographic surveillance

The Agincourt HDSS was initiated in 1992. A baseline census was conducted in 20 villages chosen for their rural living conditions, limited access to public services, underperforming primary care clinics and communities of Mozambican refugees displaced by the civil war (413,414). Following the baseline demographic surveillance survey and three update rounds that occurred up to 1998, the site has conducted annual surveys since 1999. An annual update of the HDSS household rosters is made of every birth, death and migration within the HDSS households. A household roster showing current members (based on the previous year's census) is printed onto each census form before the annual update. Trained fieldworkers visit each household and interview the most knowledgeable adult available. During the visit, individual-level information on all household members is checked and updated and any events that have occurred since the last census round are recorded. Fieldworkers also record maternity histories of all in-migrant women aged 15-55 years, as well as residence histories and other pertinent data modules built into the census. Census updates are supported by geographic information system (GIS) based maps to guarantee that every

household is covered. Maps are kept updated by recording global positioning system (GPS) coordinates for every new dwelling each year.

For each death, a verbal autopsy should be conducted to establish a probable cause of death. A structured interview is conducted with people who were closely related to or cared for the deceased during the final illness and could report on symptoms and signs they observed during this period. The interview is conducted using a World Health Organisation validated tool, in the local language. Until 2010, two medical doctors independently reviewed the data to assign a cause of death based on international classification of diseases (ICD-10) conventions (415), with a third doctor used in the event of a lack of consensus. The cause was coded 'undetermined' if this failed to yield any agreement (20,416). Since 2011, causes of death are assigned using the InterVA-4 probabilistic model (106). The database is stored in Microsoft SQL server in a relational database. Starting in 2017, the HDSS migrated from paper-based census forms to electronic forms administered on tablets.

Ethics approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg, South Africa, for surveillance activities in the Agincourt HDSS (Appendix 11.2.1). Informed verbal consent is obtained at every surveillance visit from the household head or another eligible adult present (417). The person giving consent is noted in the household roster, with pertinent details and the date recorded by the fieldworker.

Point-of-contact Interactive Record Linkage (PIRL)

In parallel to demographic surveillance, chronic care HIV patient visit logs are collected by study fieldworkers in the eight health facilities that provide ART in the HDSS area. Fieldworkers also log other chronic care (diabetes and hypertension) patient visits. This work started in April 2014 at seven government facilities and was extended in 2015 to include one additional health facility. In addition to logging patient visits, these records are linked to the Agincourt HDSS demographic surveillance records using a procedure named Point-of-contact Interactive Record Linkage (PIRL) (103,104).

This approach uses a probabilistic search algorithm to identify possible matches in the HDSS database for patients who visit any of the clinics. Possible

matches are subjected to a review in the presence of the patients whose records are being linked. This allows for any uncertainty to be resolved during a brief interaction where names of other household members or other unique information is used as a key attribute to adjudicate between possible matches. This also allows for ethical and privacy concerns to be addressed as informed consent is sought at the time of record linkage and given their participation in the process, individuals become fully aware of how their data are being used and can have any issues clarified.

Ethics approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg, South Africa, for linkage of Agincourt HDSS demographic surveillance records and individual clinic records (Appendix 11.2.1). Informed written consent is obtained at every record linkage event from the individual whose records are being linked.

3.2. Fieldwork operations

Between August 2017 and December 2018, I undertook fieldwork in the Agincourt HDSS that aimed to determine the true outcomes of patients that had disengaged from HIV care and explore their experiences with HIV treatment in this setting through IDIs. As part of this fieldwork, I recruited and trained two teams of fieldworkers (quantitative team of four fieldworkers and a qualitative team of five fieldworkers). The quantitative team was trained on the aims of the study, the data that were required from the clinics, how to approach clinic staff during fieldwork, and data entry procedures. The qualitative team was trained on how to approach potential study participants, obtain informed consent, and conduct interviews using the study topic guide.

The fieldwork was split into three different trips equating to approximately 6 months (Table 3.1).

Table 3.1: Fieldwork trips

Trip number	Date of arrival	Duration of stay	Achievements
1	19/08/2017	4 months	• Interviewed, hired, and trained four quantitative fieldworkers to perform the comprehensive record review • Created a Microsoft Access database to capture data from the record review • Liaised with clinics, RtC and HBCs to gain access to pertinent data • Supervised the collection of all data from the comprehensive record review in 8 clinics
2	05/01/2018	1 month	• Interviewed, hired and trained five qualitative fieldworkers • Handed lists of patients requiring supplementary tracing to the respective clinics • Supervised 31 IDIs. This involved daily debriefings to gain an understanding of the fieldworkers experiences each day
3	25/11/2018	1 month	• Revisited all the clinics to check TIER.Net, speak to RtC representatives and HBCs in an attempt to locate a last group of patients who remained LTFU after supplementary tracing.

3.3. Quantitative research methods

This section provides an overview of the quantitative research methods used. It includes information on the record review and tracing study (through which most of the data used in this research were generated) as well design of data collection tools, fieldworker recruitment and training, data collection and management, preparation of the data, ethical considerations for this work and analysis methods.

3.3.1. Record review and tracing study

Study design

The study was an observational cohort study of PLHIV who initiated ART after record linkage began in 2014 and were considered LTFU on August 15, 2017 to ascertain their treatment and vital status following disengagement from HIV services at eight clinics located within the Agincourt HDSS. All HIV-positive adults (18 years or older[3]) who had declared residency in the HDSS

[3] Girls aged 14-17 were excluded due to ethical concerns as they are minors under South African law

and who had enrolled in HIV care since record linkage began in 2014 were eligible for the study. I only considered patients who had enrolled after record linkage began to account for survivor bias. Considering patients who initiated treatment before record linkage began would include only patients who had survived up to that point and exclude patients who had died, a group that would have different characteristics that merit investigation.

Loss to follow-up was defined using the South African definition which is all patients who are more than 90 days late for a scheduled clinic appointment (412). For those without the date of the next scheduled clinic visit documented in their file, they were assumed to be on a month-long refill schedule and their next scheduled visit was set to 28 days after their last actual clinic visit. I used the PIRL database to identify and extract a list of patients who met the eligibility criteria and were more than 90 days late for a scheduled clinic appointment as of August 15, 2017 (the date of data extraction). These patients were recruited into a cohort and followed up until December 2018 to ascertain their treatment and vital status (Figure 3.11).

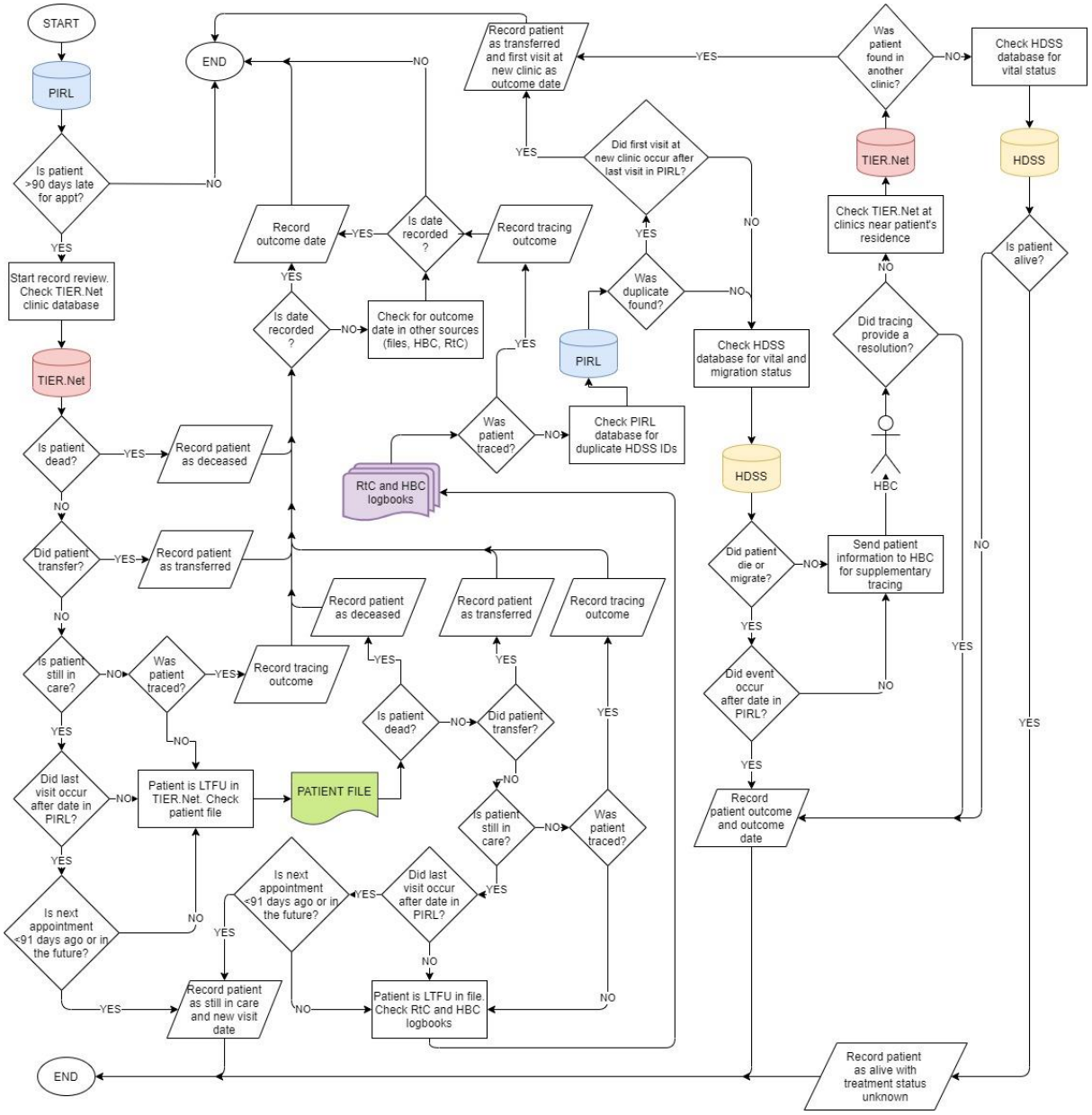
The treatment and vital status of patients deemed LTFU was ascertained via:

(i) Record review: I recruited, trained and supervised fieldworkers who compared the lists of patients LTFU against (a) TIER.Net (b) patient clinic files, (c) logbooks kept by RtC and HBCs. I then reviewed the PIRL database for duplicate patients (the same HDSS resident linked to multiple clinic records, which probably indicated a silent transfer). Finally, I reviewed residency and vital status from the demographic surveillance data collected by the HDSS. This was done on a case-by-case basis.

(ii) Supplementary tracing: For all patients for whom a satisfactory outcome could not be established, I conducted additional tracing in collaboration with HBCs. List of these patients were separated by clinic and given to the sisters-in-charge at each clinic. The sisters then liaised with HBCs to conduct physical tracing.

(iii) A final attempt was made to search TIER.Net at clinics in the vicinity of patient's homes to find any that might have transferred unofficially and who the record review and supplementary tracing had missed.

Figure 3.11: Record review and tracing flow chart



Data collection

All the data were entered either at the clinic or at the HBC compound. Fieldworkers worked in a room within the clinic designated by the clinic staff as available and without disruptions to their work. In order to collect data from clinic files, the fieldworkers retrieved individual files from the filing rooms at each clinic, with the permission of clinic staff (Figure 3.12). Files were returned to their rightful place once the pertinent data had been retrieved and entered. In order to collect data from TIER.Net, fieldworkers had to work around the schedule of the clinic data clerk in order not to disrupt their work. Fieldworkers received instructions on how to query the database and then

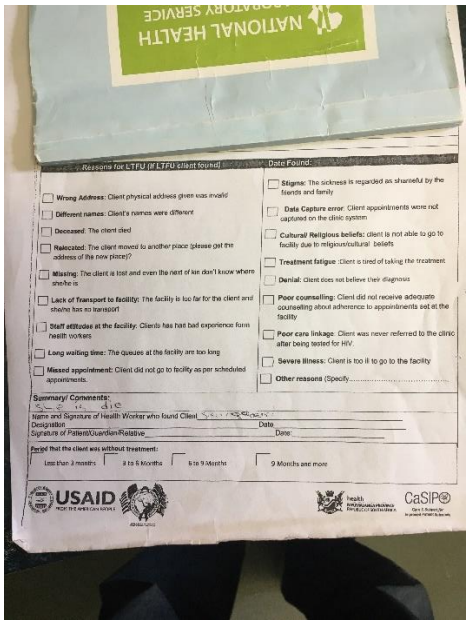
were signed into the database as a visitor with read-only rights. Permission to access RtC data was obtained from the province programme manager. Fieldworkers queried logbooks kept by RtC linkage officers.

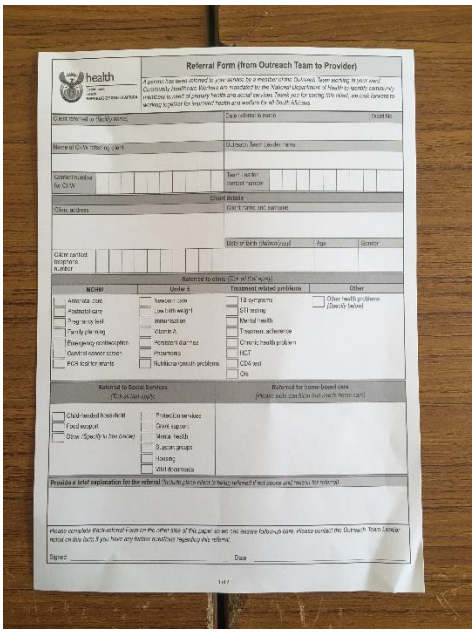
Figure 3.12: Fieldworkers retrieving files from Belfast Clinic (left), Bhubezi CHC (centre), and Thulamahashe CHC (right)

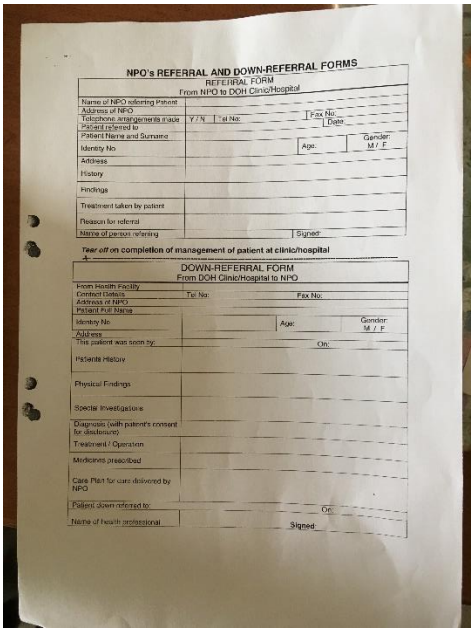
At each clinic, I obtained permission from the sister-in-charge before we commenced work. The fieldworkers worked in pairs. For the first 1-3 days at each clinic, one pair retrieved data from TIER.Net while the other pair

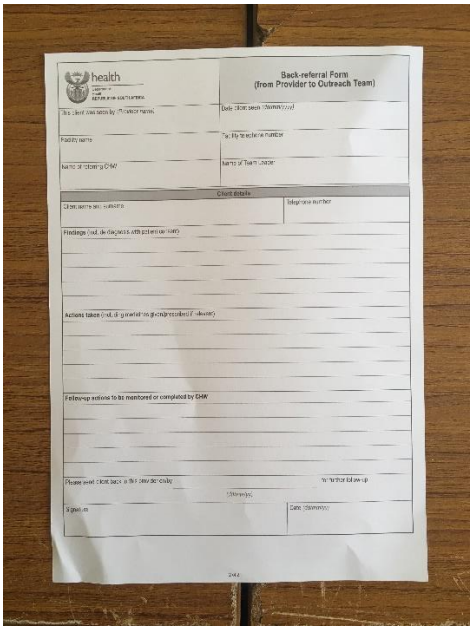
retrieved data from physical patient files. After this was completed, the fieldworkers reviewed RtC logbooks kept by RtC linkage officers if there was a RtC presence in the clinic (not all clinics were assisted by RtC). Finally, the fieldworkers reviewed HBC logbooks as well as physical tracing forms (Figure 3.13) if these were available.

Figure 3.13: Images showing examples of forms used by community outreach teams like HBCs *(these were from Lillydale HBC, Bhubezi CHC and Agincourt CHC)*









Data entry and management

I designed a Microsoft Access database to collect data from the record review. This database contained a table for each data source (TIER.Net, patient clinic files, HBC, RtC). Each table had a Visual Basic front-end data entry form (Appendix 11.3.1). The forms included skip patterns and basic data checks like date validity and consistency (for example the tracing date could not happen before the last visit date in the PIRL database) to streamline data entry and make it more intuitive. Each clinic had a separate database. I recruited and trained four fieldworkers on how to use the database for data entry.

I populated the tables and forms with the Patient IDs, file numbers, health facility, date of HIV diagnosis, ART initiation date, and the last visit date according to the PIRL database for all the patients that were LTFU. Additionally, fieldworkers received a list containing the patient ID, file number, first name, last name and date of birth of these patients. Names were not added to the database to ensure the data remained anonymised. The name lists were given to the fieldworkers at the beginning of the day and retrieved at the end of each workday. I personally kept the name lists during fieldwork and these lists were shredded at the end of the fieldwork.

All eight health facility databases were stored on password-protected fieldwork laptops. At the end of each day, these laptops remained in either my possession or that of the Agincourt data supervisor until the next workday. Once data collection had ended at a clinic, the databases for that clinic (TIER.Net, patient files, RtC, and HBC) were transferred to my password protected laptop and deleted from the fieldwork laptops. I applied edit checks on the data. These included checks for missing data and any other inconsistencies. Where these were identified, I retrieved and entered the data into the database on my computer.

At the end of data entry, I extracted the tables from each database and imported them into Stata. I then merged data from the different tables into one dataset for each clinic. All eight clinic datasets were then appended to form one dataset for analysis.

3.3.2. Statistical analysis methods

All statistical analyses were conducted in Stata 15 (418) and R (419). Analyses for paper C included all patients who were more than 90 days late for a scheduled clinic appointment as well as a sample of patients recorded as still in care to act as a comparison group. Paper A and B included all patients that were LTFU excluding 57 patients who did not have an ART initiation date. Patients who had not yet initiated ART were excluded from analyses as they often did not have a next scheduled visit specified and as such it was impossible to determine whether they were LTFU or just visited the clinics less frequently. Furthermore, this population would not be comparable to patients who had potentially accrued some benefits from taking ART in terms of reductions in morbidity and mortality.

The linkage rate for clinic and HDSS records for our cohort of patients was 88%. The probabilistic algorithm for finding matches is not perfect and unfortunately in 12% of cases, even in the presence of the patient, the records of those reporting residence in the HDSS could not be linked to the HDSS dataset. There are various reasons that could explain this. It is possible that patients misunderstood the question regarding their residency, or that they thought that there might be some incentives for answering in the affirmative, or that they were genuine residents whose record could not be retrieved for a myriad of reasons including differently spelled names, or they had migrated into the HDSS after the last census round. It is impossible to differentiate the different groups, so to minimise bias, patients whose records had not been linked were included in all analyses. The implications of this choice are considered in further detail in the discussion chapter.

All CD4 data were retrieved from patient clinic records (TIER.Net or patient files). All other clinical data were retrieved from the PIRL database, if any data were missing, this was cross-checked in the clinic records. Demographic data such as age and sex were retrieved from the PIRL database and cross-checked in the clinic and HDSS records. All socioeconomic data were retrieved from the HDSS records.

Table 3.2: Definition of terms used

Term	Definition
The last appointment	The last scheduled appointment for each patient as of August 15, 2017, when we generated the list of patients deemed LTFU.
TIER.Net treatment status	The treatment status of the patient as recorded in TIER.Net during the comprehensive record review.
The final outcome	The outcome ascertained for each patient through the record review and tracing process.
Data error	A situation in which a patient was found still in care and <90 days late for their last appointment. Some data errors occurred because visit dates had not been properly entered in the PIRL database. Patients categorised as a data error were excluded from our analyses.
Deceased	A patient was considered to have died if they were reported as deceased in their patient file or in TIER.Net or if they were reported to have died through HDSS surveillance data.
Re-engagement	A patient was considered to have re-engaged in care if they were found to be still in care at the same clinic where they initiated treatment but were >90 days late for their last appointment (had previously been LTFU).
Transfer out	A patient was considered to have transferred if they had either reported taking treatment at another clinic (for clinics outside the Agincourt HDSS), if their ART initiation clinic had communicated with and ascertained their transfer to another clinic, or if there was record of them collecting treatment at another clinic within the Agincourt HDSS.
Migration	A patient was classified as having migrated out of the study site if they were recorded as having migrated through the Agincourt HDSS demographic surveillance, this migration event happened after their last clinic visit date and there was no proof that they were taking treatment at another facility.
Stopped ART	A patient was considered alive and not on ART if they had been found and had reported that they had stopped ART, denied their HIV status or refused to return to the clinic.
Alive with ART status unknown	A patient was considered alive with ART status unknown if additional tracing yielded no definitive outcome, but they were found to still be alive through the most recent Agincourt HDSS demographic surveillance, with a surveillance date after their last clinic visit and there was no proof that they were taking treatment at any facility.

Source of resolution	A source of resolution was the data source from which the final outcome for each patient was ascertained.
Origin health facility	The health facility at which a patient initiated ART and was recorded as LTFU
Destination health facility	The health facility to which a patient transferred their care after being recorded as lost to follow-up

A descriptive analysis of outcomes following loss to follow-up was conducted for paper A, with outcomes stratified by sex, clinic variables such as baseline CD4 and pregnancy status at ART initiation in order to compare Option B+ women to the rest of the treatment population. With regards to the reasons for ART initiation, whereas specific reasons for ART initiation such as CD4 and presence of opportunistic infections were listed for the general population, this was not always consistently done and so non-PMTCT patients were all grouped together. A descriptive analysis of sources of resolution was also conducted with possible sources being through record review, through demographic surveillance data (migrations, deaths, alive with treatment status unknown), through subsequent updates to visit data in the PIRL database, through supplementary tracing, identification as duplicates in the PIRL database (one person matching to multiple clinic records), and through a search of patient records in clinics in close proximity to the patient's residence. A descriptive analysis for causes of death was conducted for all patients for whom verbal autopsy data was available.

For paper A, competing risk survival analysis methods were used to estimate the cumulative incidence of death, transfer, migration, ART stoppage and re-engagement following LTFU. As we suspected that many deaths leading to loss to follow-up would occur closely after a last clinic visit, follow-up time began on the date of each patient's last recorded clinic visit to account for any outcomes that might have occurred before patients would have been categorised as LTFU. These cumulative probabilities were used to produce status plots stratified by sex, pregnancy status at ART initiation and baseline CD4.

Factors associated with mortality following LTFU were determined using a Cox regression model with all other outcomes considered as right censored. All models accounted for clustering at the clinic level with robust standard

errors. Bivariate analyses were conducted using an a priori list of variables, with all variables with $p<0.1$ included in the multivariable model. A parsimonious model was achieved using Wald tests. A similar analysis was conducted in paper B for factors associated with transferring to another facility following LTFU. However, in this model all variables with $p<0.2$ were included in the multivariable model.

For paper C, to assess the degree and direction of misreporting of patient outcomes in TIER.Net, each patient was assigned a treatment status based on their current TIER.Net status (still in care, deceased, transferred out, lost to follow-up) and this was compared to their final outcome. A misclassification was defined as any instance where the patient's TIER.Net treatment status did not match their final outcome. The variables produced from these two sources were cross-tabulated. A Pearson's chi-square test was used to compare whether TIER.Net treatment status and the final outcome varied by age, sex, pregnancy status at ART initiation, ART initiation year, baseline CD4, time on ART, clinic visit schedule (used as a proxy for patient stability), health facility, and time since the patient's last scheduled visit.

To visualise this data, TIER.Net treatment status and the final outcome were aggregated by ART initiation status and reason, and time since the last missed appointment using the *collapse* command in Stata. These collapsed datasets were imported into R where the *ggplot* package was used to plot bar graphs of these data.

As patients recorded as LTFU in TIER.Net were the most likely to be misclassified, a binary outcome variable was created to identify whether a patient was recorded as LTFU in TIER.Net. Logistic regression was used to assess the factors associated with being recorded as LTFU in TIER.Net. Logistic regression was also used to assess the factors associated with being misclassified in TIER.Net, with a binary outcome variable being created to indicate whether TIER.Net had misclassified a patient's treatment status. Because we could not find a TIER.Net record for every patient, all cases where an electronic record could not be found were excluded from these analyses.

For paper B, an undocumented transfer was defined as one where the origin health facility was unaware and therefore did not have this recorded as a patient outcome within its system. Patients' village of residence was ascertained through health facility and Agincourt HDSS records. A mid-point GPS coordinate of the village was used as each patient's residence. I also obtained decimal degree coordinates for origin and destination health facilities by querying Google Maps. Geographic distances were calculated (i) between patients' residence and both their origin and destination health facility, and (ii) between the origin and destination clinic. Kruskal-Wallis test was used to compare median distances disaggregated by age, sex, pregnancy status at ART initiation, type of transfer (documented or undocumented), ART initiation year, baseline CD4 count, time on ART, clinic visit schedule, health facility, and time since the patient's last scheduled visit. Using ArcMap® 10.3.1 (420), the health facility coordinates were imported to shapefiles with a WGS 1984 coordinate system. I then used ArcMap to spatially visualise the locations of destination health facilities.

The Circlize package in R (419,421) was also used to visualise the main corridors of movement between facilities. I created a matrix containing the transfer flow data with the input data calculated using Stata. Separate flow matrices were created for Option B+ women, other women, and men's transfers as well as for documented and undocumented transfers. Each health facility was then allocated a circle segment with all transfers outside the HDSS aggregated under other facilities. I then created a data frame to store information on each segment of the circle plot. The *circlize* command was then used to plot the circle plots.

3.3.3. Ethical considerations

Permissions were obtained from the Mpumalanga Department of Health to collect and process data from the clinics. The district manager sent a letter to the PHC manager for the Bushbuckridge Department of Health. The PHC manager then sent a letter to each clinic explaining the study and its aims and objectives and authorising the data collection process. Ethical approval was obtained for the LSHTM, the University of Witwatersrand and the

Mpumalanga department of health ethical review boards for the collection and use of these quantitative datasets (Appendix 11.2.2).

Fieldworkers who entered the clinic data were trained on the importance of protecting patient confidentiality.

The name lists did not contain any sensitive information about HIV status or receipt of ART in case they inadvertently fell into the wrong hands. Separate lists were generated for each clinic, handed to fieldworkers at the beginning of a workday and retrieved at the end of the day. All lists remained in my possession throughout the duration of fieldwork. The database used for data collection as well as datasets generated from these databases only included ID numbers (Patient ID, file number) without names. During fieldwork, the databases were stored on password-protected laptops which were kept by me or the Agincourt data supervisor at the end of each workday. At the end of data collection these databases and datasets generated from them were stored in independent files on a secure laptop with password restricted access and deleted from the fieldwork laptops. All name lists were shredded at the end of data collection.

The supplementary tracing component was intentionally nested into routine care as patients must give consent to be physically traced at their homes. As such, HBCs would have first consulted patient files to make sure they had consented to tracing before a supplementary tracing visit was attempted.

3.4. Qualitative research methods

This section provides an overview of the aims of the qualitative research and methods used, the objectives and design of the data collection tools, fieldwork recruitment and training, piloting, sampling and recruitment, data collection, preparation of the data and analysis of results.

3.4.1. Aims and overview

The overall aim of the qualitative study conducted for this thesis was to investigate patients experiences of HCT, HIV treatment including interruptions and re-engagement in care, and pregnant and breastfeeding women's experiences with infant testing with a view to understanding if any of their experiences with HIV care and treatment were linked to interruptions or re-engagement in care. Data were generated through IDIs with HIV-positive

patients and structured observations of public areas at health facilities in the Agincourt HDSS to achieve this aim.

The use of qualitative methods in this thesis allowed for a broader understanding of engagement in care in this setting. Fieldwork took place from January to February 2018. The design of data collection tools, fieldwork procedures and final analysis of results was done in collaboration with local fieldworkers and scientists. The fieldworkers helped to improve the data collection tools based their knowledge of the context which enhanced the relevance of the work. For example, they played a role in translating the IDI topic guide into Shangaan.

3.4.2. Objectives and design of the data collection tools

In-depth interviews

In-depth interviews were chosen as a data collection method to enable a private and detailed discussion of their personal experiences of the HIV care and treatment programme. This allowed us to explore personal challenges faced while using the programme, barriers and motivators to remaining engaged with the programme. Interviews with non-pregnant women and men aimed to explore their HIV testing experience, ART treatment and follow-up, and any interruptions during treatment. I also aimed to understand re-engagement in care in this setting to get a better understanding of the barriers and facilitators to re-engagement in care following treatment interruptions. These interviews were undertaken to understand how experiences among pregnant and breastfeeding women differed from those of PHIV who received their services outside of PMTCT. For pregnant and breastfeeding women infant testing was explored as an additional topic. Since research has shown that many pregnant women initiate ART for the sake of the baby(237), I hypothesised that infant testing and the results from infant testing could play a major role in their disengagement from care.

The topic guide (Appendix 11.3.4) for the IDIs was divided into six sections reflecting the study objectives: life history (serving as an 'ice-breaker' and a way to build rapport), testing experience, ART treatment and follow-up, loss to follow-up, re-engagement in care, and infant testing. Fieldworkers were

encouraged to ask questions in the third person to ease anxiety around the discussion of sensitive topics.

Observations

Observations were conducted to enhance my understanding of how the health system may potentially affect participants engagement in care. Observations also helped me to understand how programmes actually operate in relation to standard operating procedures, guidelines and protocols issued by the national Department of Health. Furthermore, observations also helped to improve the IDI topic guide. For example, some questions about attitudes towards breastfeeding were added to the IDI topic guide after observing aggressive campaign posters against bottle-feeding in one clinic (Figure 3.14).

Observations were recorded in a fieldwork notebook and in some cases, photographs were taken with the permission of clinic staff.

Figure 3.14: Posters observed in one clinic campaigning against bottle-feeding

3.4.3. Fieldworker recruitment and training

Five Shangaan-speaking female fieldworkers were recruited. These fieldworkers were recruited from an existing pool of qualitative fieldworkers who were usually contractually employed by the Agincourt HDSS. There were no men available at the time of fieldwork. Four of the selected fieldworkers had

prior experience of conducting qualitative research in the Agincourt HDSS and this mostly included IDIs (the fifth had prior quantitative fieldwork experience). Fieldworkers had some knowledge of the HIV care and treatment services available in the clinics, but training revised the basics of HIV transmission, prevention, care and treatment.

Training was conducted over a week and included a discussion on the aims of the study, discussions on approaching potential participants for the study, how to ensure that participants' consent was truly informed, protecting anonymity and confidentiality, other ethical concerns (Figure 3.15). The training approaches included practical sessions and group discussions to facilitate learning. I designed all the fieldwork training tools which included PowerPoint slides, printing information sheets, and exercises to improve interviewing techniques. I also delivered the training sessions. Training sessions were interactive, and fieldworkers were encouraged to be at ease and to share their experiences from other projects. The fieldworker with no prior qualitative experience benefitted a lot from these sessions giving her an idea of what to expect and how to handle different scenarios during the interview process.

All the data collection tools, and the information sheet (Appendix 11.3.3 and Appendix 11.3.4) were translated by the fieldworkers. This allowed them to become more familiar with the tools and gave them a chance to practice what translation would best be suited to asking the questions so that respondents clearly understood them. Translations were shared with the Agincourt HDSS translator in order to verify their integrity.

Figure 3.15: Images showing fieldworker training

3.4.4. Piloting

One day of training included the review, practice, and piloting of the topic guide. One fieldworker interviewed another while the rest watched with feedback being shared throughout the process. I observed these sessions and discussed difficulties encountered and potential refinements with the team.

3.4.5. Sampling and recruitment

Participants were recruited purposively for interview from the Agincourt HDSS community by fieldworkers to ensure a sample of patients with varying engagement in care profiles. For example, patients might have recently transferred their care to a new health facility, might have recently re-engaged in care, or might have currently been disengaged from care. The sample was chosen to ensure that patients with all these different treatment outcomes were included. In order to recruit patients who were currently disengaged from

care or who had previously disengaged from care, I utilised the PIRL database to identify patients that met these criteria.

It was expected that patients currently disengaged from care would be hard to recruit as other studies have demonstrated previously (422). Many of these patients have been lost to the health system and are difficult to locate through the clinics. Furthermore, it was feared that an approach from the clinic could influence participation, firstly if potential participants mistook the researchers for clinic or healthcare system staff, secondly if they feared that this was an attempt to coerce or re-engage them into care and they were not ready, and finally if clinic staff were biased in who they approached to participate. These were people whose experiences I was particularly interested in eliciting because they have been under-represented in research on HIV treatment experiences. Therefore, I decided to utilise all data available through the potential participants' HDSS records. Potential recruits' HDSS records were used to retrieve the location of their home which was then located on maps showing all the dwellings in the HDSS. They were then contacted and were informed of the aims of the study and asked if they would be willing to participate. They were not coerced to participate but given an opportunity to share their opinions. The study was not framed as an HIV study but more as one to understand their experiences with using the healthcare system. If they agreed to participate, an appointment would then be scheduled.

3.4.6. Data collection procedures

In-depth interviews

Thirty-one IDIs were conducted in total: 20 with women who were pregnant or breastfeeding when they initiated ART, 6 with non-pregnant women, and 5 with men. A summary of the IDI sample size and recruitment procedures is provided in table 3.3 and basic demographic characteristics of all the participants recruited are shown in table 3.4.

Table 3.3: Summary of sample size and recruitment procedures for IDIs

Method	Total sample size	Respondent type and numbers	Recruitment
IDIs	20	HIV+ women who were pregnant or gave birth since 2015 (Option B+)	Purposive to ensure diversity in terms of age, parity, clinic attended, and treatment outcomes (11 reengaged, 3 transferred, 6 not in care). All community recruits.
IDIs	6	HIV+ women who had not been pregnant since 2015	Purposive to include as many treatment outcomes as possible (2 reengaged, 4 transferred). All community recruits.
IDIs	5	HIV+ men	Purposive to include as many treatment outcomes as possible (2 reengaged, 3 transferred). All community recruits.

All interviews were conducted in Shangaan. All IDIs were audio-recorded following written consent from each participant. To begin with, three IDIs were conducted and transcribed into English. These three transcripts were manually open coded by myself with regular discussions with my supervisor (AW), and advisor (JR) to get a sense of the data that was being generated. Information garnered from this process was used to improve the topic guide and brief/support the fieldworkers in order to improve their interviewing technique. After each IDI, I held a debriefing session with the fieldworker involved to discuss how the interview went and identify any obstacles or ways to improve the process. Fieldworkers also made detailed field notes about the IDIs and these were reviewed at the end of each IDI.

Table 3.4: Summary of characteristics of participants and non-participants

Characteristic	Participants (n=31)			Non-participants (n=29)		
	Option B+	Non-pregnant women	Men	Option B+	Non-pregnant women	Men
	20	6	5	12	10	8
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Age						
19-24	7 (35.0)	1 (16.7)	1 (20.0)	5 (41.7)	0 (0.0)	1 (12.5)
25-29	6 (30.0)	0 (0.0)	0 (0.0)	4 (33.3)	2 (20.0)	2 (25.0)
30-34	5 (25.0)	0 (0.0)	0 (0.0)	2 (16.7)	3 (30.0)	0 (0.0)
35+	2 (10.0)	5 (83.3)	4 (80.0)	1 (8.3)	5 (50.0)	5 (62.5)
Mean (range)	28 (21-37)	45.2 (23-59)	37.4 (23-43)	26.5 (19-43)	39.7 (25-91)	38.2 (24-59)
Marital Status						
Single	3 (15.0)	1 (16.7)	4 (80.0)	7 (58.3)	3 (30.0)	3 (37.5)
Married	4 (20.0)	1 (16.7)	0 (0.0)	1 (8.3)	1 (10.0)	0 (0.0)
Informal	12 (60.0)	1 (16.7)	1 (20.0)	1 (8.3)	2 (20.0)	2 (25.0)
Separated or Divorced	1 (5.0)	1 (16.7)	0 (0.0)	1 (8.3)	1 (10.0)	3 (37.5))
Widowed	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	2 (20.0)	0 (0.0)
Unknown	0 (0.0)	0 (0)	0 (0.0)	2 (16.7)	1 (10.0)	0 (0.0)
Education status						
No formal education	0 (0.0)	1 (16.7)	0 (0.0)	1 (8.3)	1 (10.0)	0 (0.0)
Primary	3 (15.0)	2 (33.3)	2 (40.0)	6 (50.0)	4 (40.0)	6 (75.0)
Secondary	15 (75.0)	1 (16.7)	3 (60.0)	2 (16.7)	3 (30.0)	1 (12.5)
Tertiary	2 (10.0)	1 (16.7)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	1 (16.7)	0 (0.0)	2 (16.7)	2 (20.0)	1 (12.5)
Parity						
0	0 (0.0)	1 (16.7)				
1 to 2	17 (85.0)	0 (0.0)	__	__	__	__
3 to 4	3 (15.0)	2 (33.3)	__	__	__	__
5+	0 (0)	3 (50.0)				
Self-reported treatment status						
In care	13 (65.0)	5 (83.3)	4 (80.0)	__	__	__
Not in care	7 (35.0)	1 (16.7)	1 (20.0)	__	__	__
Clinic treatment status						
Re-engaged	11 (55.0)	3 (50.0)	2 (40.0)	5 (41.7)	3 (30.0)	1 (12.5)
Transferred	3 (15.0)	3 (50.0)	3 (60.0)	2 (16.7)	7 (70.0)	6 (75.0)
Not in care	6 (30.0)	0 (0.0)	0 (0.0)	5 (41.7)	0 (0.0)	1 (12.5)

Timing of HIV diagnosis						
Newly diagnosed	12 (60.0)	5 (83.3)	2 (40.0)	5 (41.7)	6 (60.0)	8 (100.0)
Previously diagnosed	8 (40.0)	1 (16.7)	3 (60.0)	7 (58.3)	4 (40.0)	0 (0.0)
EID done						
Yes	14 (70.0)	__	__	__	__	__
No	4 (20.0)	__	__	__	__	__
Incomplete (<18 months)	2 (10.0)	__	__	__	__	__
Infant's HIV status at the time of the interview						
Negative	15 (75.0)	__	__	__	__	__
Positive	1 (5.0)	__	__	__	__	__
Unknown	4 (20.0)	__	__	__	__	__
Reason for non-participation						
Not at home	__	__	__	3 (25.0)	3 (30.0)	5 (62.5)
Migrated	__	__	__	5 (41.7)	5 (50.0)	2 (25.0)
Could not be found	__	__	__	1 (8.3)	1 (10.0)	0 (0.0)
Refusal	__	__	__	3 (25.0)	1 (10.0)	1 (12.5)

Observations

I conducted observations at all the clinics and at some of the HBC compounds. In instances where I was observing HBCs, I was accompanied by a fieldworker who was fluent in Shangaan to assist with translating questions and answers. I kept fieldnotes and in some instances with the permission of clinic staff or HBCs also took some photographs. Observations did not follow any systematic or predetermined format but were done informally, and all observation notes were recorded in English.

3.4.7. Data preparation and analysis

Audio recordings from IDIs were translated and transcribed directly into English by the qualitative fieldworkers. The translated transcripts were uploaded to Nvivo11.

Preliminary analysis was conducted in the field to identify emerging themes from the data generated. Information from the debriefing sessions and fieldworker notes was used to modify the remaining interviews with probes added to add more clarity or to explore new emerging concepts. Probes included questions on infant testing counselling sessions at the clinics

including when during the pregnancy these sessions occurred and the content of these sessions.

The final analysis stage aimed to explore maternal engagement in care and infant outcomes in detail. Only the 20 IDIs conducted with HIV+ women who had given birth since 2015 were extensively analysed (while the IDIs conducted with men and non-pregnant women generated interesting findings, the themes did not align with my objectives and were therefore excluded). I analysed the data generated thematically drawing on the principles of inductive coding to identify themes. I coded all the transcripts with the aid of Nvivo11. The coding framework was continually refined as more transcripts were analysed to capture new codes as they emerged. Codes were then grouped and conceptualised to identify themes. Two themes were considered for further analysis those relating to women's engagement in care and those relating to infant testing. As mentioned in chapter two, practice theory (83,85,87) was identified as an appropriate theoretical framework with which to present and relate the findings. Participants' accounts and social practices were presented in relation to engagement in care and infant testing, the main social practices of interest. Interpretations were built by exploring relationships between the engagement in care, infant testing and other social practices mentioned by the participants and considering the meanings they gave to these practices and the competences they described in relation to enacting them.

3.4.8. Ethical considerations for the qualitative research

Ethical approval for the qualitative study was received from the LSHTM, the University of Witwatersrand and the Mpumalanga Department of Health ethical review boards (Appendix 11.2.2). Members of the HDSS give consent to be approached at home using contact information provided to the HDSS team and to be invited to participate in relevant studies with the understanding that they have the right to refuse to participate. As the population of the HDSS is studied all year round, it was not unusual for HDSS staff to approach participants at the homes and as a result of this, patient confidentiality was kept. Interviews took place in private at a location of the participant's choosing.

All IDI participants were informed about the study before commencing the interviews. They were informed of their right to refuse to participate and that their refusal would not affect the services they received through the healthcare system or result in any loss of benefits regarding medical treatment. They were also advised that all discussions were confidential and that they could refuse to answer any questions or leave the interview at any time. Written informed consent was obtained for all the IDIs.

Interviews were transcribed on password protected fieldwork computers. All transcripts were also individually password protected. All documentation was labelled with codes. Interviews were labelled with a number, followed by the status of the patient, the initial of the first name of the fieldworker and the date of the interview. For example, the fourth interview was with a patient who had re-engaged in care and the label was 04RE24/01/2018. The list of all people that were approached to participate as well as all participants was kept in a password protected Excel spreadsheet on my personal laptop which also has password-restricted access. Published quotations by participants were anonymised and documented observations were not linked to the participants. Audio recordings were stored on a secured Agincourt HDSS server and deleted from the recorders after transcription. Translations, notes and other outputs were also stored on the secure server. I also kept transcripts and fieldnotes on my personal laptop which has password-restricted access.

4. Paper A: Outcomes after being lost to follow-up differ for pregnant and postpartum women when compared to the general HIV treatment population in rural South Africa

Introduction to the paper:

This paper (A) utilises data from the record review and tracing study described in chapter 3 to investigate objective 1. The paper provides estimates of the outcomes for patients that were considered to be lost to follow-up through the linked clinic-HDSS dataset. This paper was conceived as a means to explore LTFU among pregnant WLHIV (particularly under Option B+) which has not been widely researched. As such, outcomes are disaggregated by sex and pregnancy status at ART initiation. I disaggregated the outcomes in order to compare these groups with the rationale that any differences observed might explain why pregnant and postpartum women disengage from care at higher rates than other adults on ART.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1603703	**Title**	Mr
First Name(s)	David		
Surname/Family Name	Etoori		
Thesis Title	A mixed methods study using linked demographic surveillance and health facility data to investigate and compare loss to follow-up among women living with HIV who initiated antiretroviral therapy during pregnancy under Option B+ in Agincourt, South Africa		
Primary Supervisor	Alison Wringe		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	JAIDS		
When was the work published?	2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	No		
Have you retained the copyright for the work?*	Yes	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	

Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the study, planned and executed the fieldwork. Supervised data collection in the field. I conducted all the pertinent analyses and interpreted the findings. I drafted the manuscript.

SECTION E

Student Signature	[redacted]
Date	14/07/2020

Supervisor Signature	[redacted]
Date	14/07/2020

4.1. Abstract

Background: Undetermined attrition prohibits a full understanding of the coverage and effectiveness of HIV programmes. Outcomes following loss to follow-up (LTFU) among antiretroviral therapy (ART) patients may differ according to their reasons for ART initiation.

Setting: We compare the true outcomes of adult patients previously identified as LTFU by reason for ART initiation in eight health facilities in north eastern South Africa.

Methods: Adult HIV patient records were linked to health and demographic surveillance system (HDSS) data from 2014 to 2017.

Outcomes of adults categorised as LTFU (>90 days late for the last scheduled clinic visit) were determined through clinic and routine tracing record reviews, consultation of HDSS data, and supplementary tracing.

We calculated the proportion of patients per outcome category and performed competing risk survival analysis to estimate the cumulative incidence of death, transfer, migration, ART interruption and re-engagement following LTFU.

Results: Of 895/1017 patients LTFU with an outcome ascertained, 120 (13.4%) had died, 225 (25.1%) re-engaged, 50 (5.6%) migrated out of the HDSS, 75 (8.4%) were alive and not on treatment, and 315 (35.1%) transferred their treatment. These outcomes varied by sex and pregnancy status at ART initiation. Mortality was less likely among pregnant women, patients with higher baseline CD4, and more likely among older patients.

Conclusion: Patient survival and transfers to other facilities are considerably higher than those suggested in earlier studies. Outcomes differ for women who were pregnant or postpartum when initiating ART, with this population less likely to have died and more likely to have migrated out of the HDSS.

4.2. Introduction

As HIV programmes in sub-Saharan Africa have expanded, emphasis has been put on initiating patients on antiretroviral therapy (ART) as early as possible in the course of HIV infection (5,6). Eligibility for ART has changed since the adoption of Option B+ which made all pregnant and postpartum women eligible for ART as soon as they tested HIV positive and "Treat all" which extended this eligibility to all people living with HIV (PLHIV) (9). Although ART initiation rates among people diagnosed with HIV have increased (360,423,424), many programmes have experienced high attrition rates, especially among women who initiate ART for prevention of mother-to-child transmission of HIV (PMTCT) (11). Many of these patients are classified as lost to follow-up (LTFU), a general term for unknown outcomes of patients who have not returned for a scheduled clinic visit. LTFU is often an amalgamation of "silent" (undocumented) clinic transfers, treatment interruptions or stoppages, and deaths (15,51,52,55,56), which are challenging to accurately document using routine reporting mechanism (16,102,367).

Misclassification of patients as being LTFU can lead to as much as a five-fold underestimation of retention and deaths (425). Understanding true outcomes among patients who are reported as LTFU is important in order to accurately monitor and report on indicators for national ART programmes and better target tracing efforts (52). Accurate mortality estimates are also important for parameterising epidemic projections in software programmes such as the UNAIDS Spectrum package (91).

A systematic review of HIV patient tracing studies conducted in sub-Saharan Africa from 2001 to 2012 reported that 39% of patients documented as LTFU in clinic records had died, 18.6% had self-transferred to other HIV clinics, and 28.6% had stopped ART but were still alive (15). An earlier review covering studies in sub-Saharan Africa undertaken between 2004 and 2008 reported that 42% of patients documented as LTFU in HIV clinics had died (14).

These two reviews were conducted in the earlier stages of sub-Saharan African ART programmes when ART patient profiles included a higher proportion with severe immunosuppression at treatment initiation and before universal ART for HIV positive pregnant women (Option B+) had been introduced

(259). In addition, decentralisation of ART programmes means ART can be provided closer to patients' homes (15), which may have increased the number of "silent" transfers taking place within these programmes. Furthermore, the proportion of pregnant and postpartum women in ART programmes has increased since the adoption of Option B+. This population differs from the general adult population on ART in several ways that are likely to impact the true outcomes among those LTFU, yet few studies have traced women LTFU from PMTCT programmes (17). Firstly, ART initiation eligibility criteria for pregnant women have included higher CD4 counts in many settings over the past decade, such that on average they are more likely to initiate treatment while still asymptomatic (258). In addition, childbirth is a risk factor for default from treatment programmes (89,365) for reasons including postpartum depression or out-referral from PMTCT programmes after delivery (245,257,366).

With recent randomised control trials of universal test and treat showing modest and mixed results regarding reducing HIV incidence (94,96,426), it is imperative that we understand outcomes among non-adherent patients including those LTFU. This will help to develop and direct innovative ways to identify and reach those who have truly disengaged from care. In this context, we conducted a tracing study in Agincourt in rural north-eastern South Africa to ascertain the true outcomes of patients who were LTFU, disaggregated by whether they were pregnant or postpartum when initiating ART (PMTCT) or not, to better understand the outcomes of this group and compare them to the adult ART population who met other criteria for ART initiation.

4.3. Methods

4.3.1. Setting

The Agincourt Health and Demographic Surveillance System (HDSS) is located in Mpumalanga province in rural north-eastern South Africa. Established in 1992, the site is approximately 475 square kilometres and has conducted annual demographic surveys within the HDSS population to capture births, deaths and migrations since 1999 (20,413). In 2013, HIV

prevalence in the HDSS population aged 15 years or older was estimated at 19.4% (398).

The HDSS also collects verbal autopsy (VA) data to ascertain probable causes of death (105). In brief, a structured interview was conducted with people who were closely related to or cared for the deceased during the final illness and could report on symptoms and signs they observed during this period. The interview was conducted using a locally validated tool, in the local language. Until 2010, two medical doctors independently reviewed the data to assign a cause of death based on international classification of diseases (ICD-10) conventions (415), with a third doctor used in the event of a lack of consensus. The cause was coded 'undetermined' if this failed to yield any agreement (20,416). Since 2011, causes of death are assigned using the InterVA-4 probabilistic model (106).

There are five primary health facilities and three secondary community health centres located within the Agincourt HDSS, all of which offer HIV services including testing and treatment. All health facilities routinely trace patients that are late for a scheduled appointment, with some clinics receiving tracing support from two non-profit organisations, Right-to-Care (RtC) (6 facilities) and Home-Based Carers (HBC) (7 facilities). Routine tracing is described in detail elsewhere (412). Briefly, tracing procedures are triggered once a patient is more than five working days late for a scheduled visit and usually involves two steps, three phone calls and a home visit if the phone calls do not yield a satisfactory outcome. Patients are considered LTFU if they have not returned to the clinic 90 days after their scheduled visit.

In 2014, an initiative was started to identify registered HDSS residents when they visited local health facilities. The point-of-contact interactive record linkage (PIRL) matches chronic care (HIV, diabetic and hypertensive) patient information at the health facility to their HDSS record. This is done in the presence of the patient to resolve any indecision about their identity in the event of multiple resident matches (104).

4.3.2. Record review and tracing study

Using the PIRL database, we identified patients who were more than 90 days late for a scheduled HIV clinic appointment on August 15, 2017 at any of the

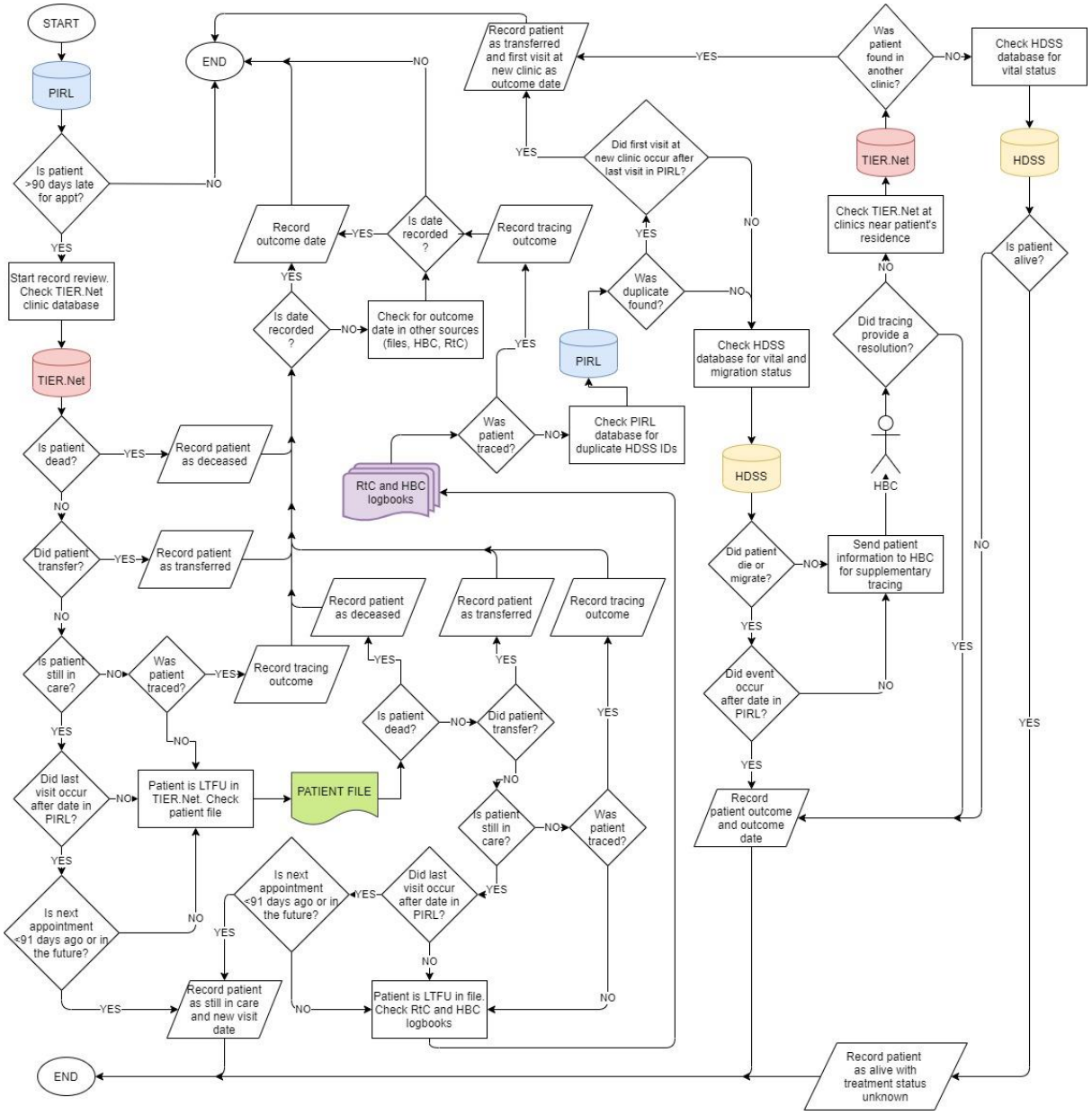
eight health facilities located in the Agincourt HDSS. Patients were included in the cohort if they were 18 years or older, had ever declared residency in the HDSS, and had enrolled in HIV treatment after PIRL was established at the health facilities.

Patients who had not yet initiated ART were excluded from our analyses as they did not have a next scheduled visit and as such it was impossible to determine whether they were LTFU or just visited the clinics less frequently. Furthermore, this population would not be comparable to patients who had potentially accrued some benefits from taking ART.

Patients were followed up to ascertain whether they were still alive and still on treatment. Trained fieldworkers conducted a thorough record review, on a case-by-case basis, to resolve each patient outcome by comparing the list of patients LTFU against (i) TIER.Net (the electronic medical records database for health facilities in South Africa) (100) (ii) paper-based patient clinic files, and (iii) logbooks kept by RtC and HBC. The PIRL database was also reviewed for duplicate patients who were then considered silent transfers. Residency and vital status were also checked in the HDSS demographic surveillance database.

Home-Based Carers conducted a further home visit for all patients without an outcome resolution (i.e. no definitive outcome after the record review and for whom routine tracing had not previously been done). For all patients remaining LTFU, searches were undertaken in TIER.Net databases of clinics in close proximity to their residence to capture any further silent transfers (Figure 4.1).

Figure 4.1: Record review and tracing flow chart



4.3.3. Definitions

A patient was considered to have <u>died</u> if they were reported as deceased in their patient file or in TIER.Net or if they were reported to have died through HDSS surveillance data.

A patient was considered to have <u>re-engaged</u> in care if they were found to still be in care at the same clinic where they initiated treatment but were >90 days late for their last appointment.

A patient was defined as having transferred if they had either reported taking treatment at another clinic, if the clinic at which they initiated ART had communicated with and ascertained their transfer to another clinic, or if there was a record of them collecting treatment from another clinic within the Agincourt HDSS.

Patients were defined as having migrated if they were recorded as such (movement outside the study area) through the HDSS, the migration event happened after their last clinic visit and there was no evidence of them taking treatment at another clinic.

A patient had stopped ART if they had been found and reported that they stopped ART, denied their HIV status or refused to return to the clinic.

A patient was alive with ART status unknown if additional tracing yielded no definitive outcome, but they were found to still be alive through the most recent demographic surveillance round, with a surveillance date after their last clinic visit.

A data error was a situation where a patient was <90 days late for their next scheduled appointment but was erroneously classified as LTFU.

4.3.4. Statistical analyses

Counts and proportions were calculated for socio-demographic, baseline clinical characteristics, patient tracing outcomes, and verbal autopsy causes of death. A Pearson's chi-square test was used to compare categorical variables.

Competing risk survival analysis methods were used to estimate the cumulative incidence of death, transfer, migration, ART stoppage and re-engagement following loss to follow-up (LTFU). Follow-up time began on the date of each patient's last recorded clinic visit as we suspected that some outcomes especially deaths would occur closely following a last visit and before patients would have been categorised as LTFU. Using these cumulative probabilities, status plots were produced stratified by sex, pregnancy status at ART initiation and baseline CD4.

A Cox regression model was used to determine the factors associated with death, with all other outcomes considered to be right-censored. Bi-variate

analyses were conducted with a priori selected variables that had been shown to be associated with death in previous studies (14,427–429). All variables with $p<0.1$ were included in the multivariable Cox regression model. A parsimonious model was achieved using Wald tests. All analyses were conducted using Stata 15 (418). All models accounted for clustering at the clinic level and utilised robust standard errors.

4.3.5. Ethics

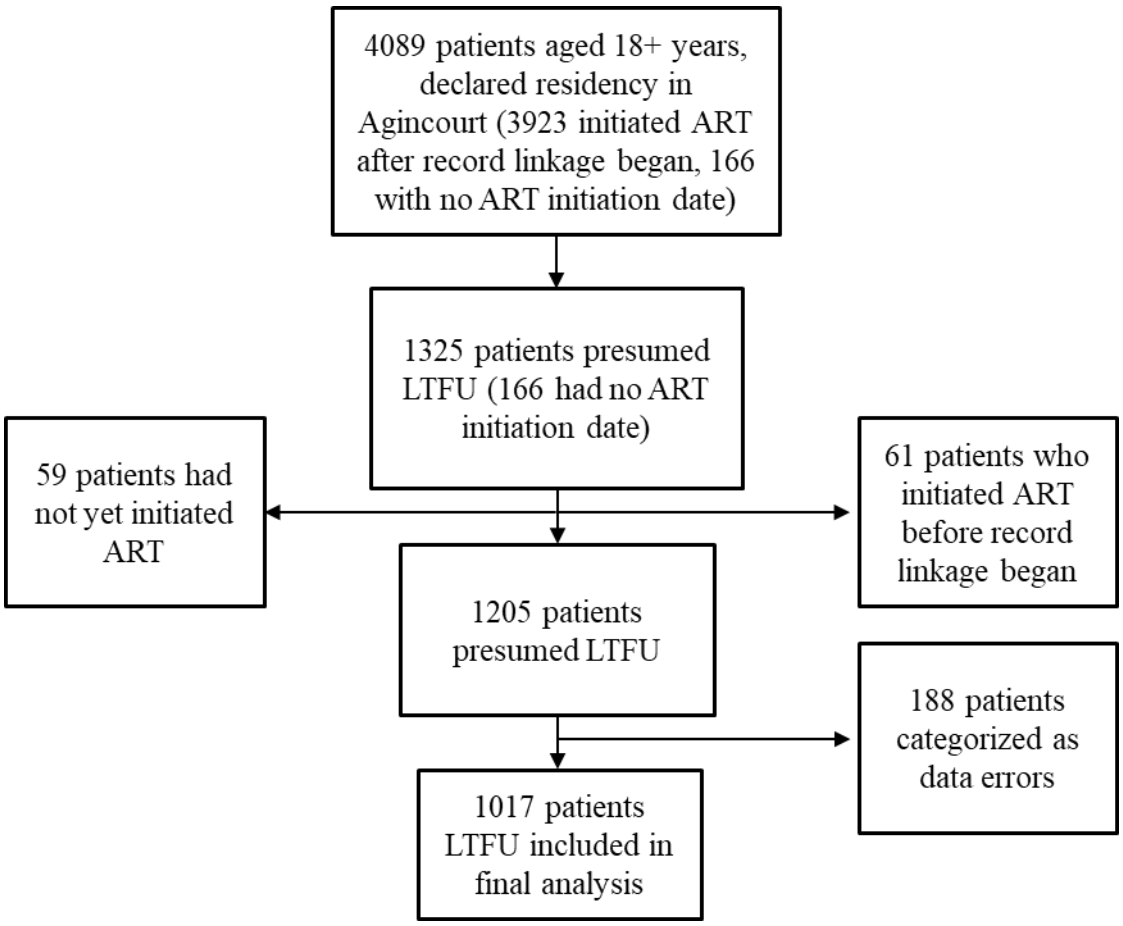
Ethical approval was obtained from the London School of Hygiene and Tropical Medicine, the University of Witwatersrand and the Mpumalanga Department of Health.

4.4. Results

4.4.1. Population characteristics

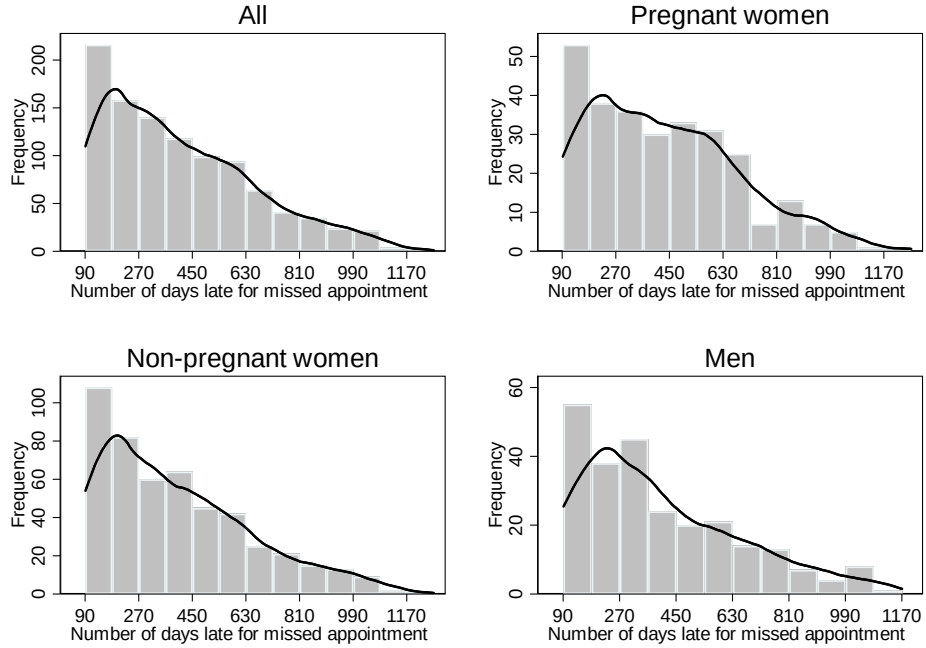
Over the study period, 4089 patients were added to the PIRL database and met the inclusion criteria. Of these 4089, 1325 (32.4%) met the LTFU criteria and were eligible for inclusion in the record review and tracing study. Of these 1325 patients, 166 (12.5%) did not have an ART initiation date. Further investigation of these 166 patients found 46 (27.7%) had initiated ART after record linkage, 59 (35.5%) had not yet initiated ART and 61(36.7%) had initiated ART before record linkage began. These 61 patients and the 59 non-ART patients were excluded from further analyses. Of the remaining 1205 patients, 188 (15.6%) were misclassified as LTFU due to data errors (missed clinic visits in the PIRL database) and were excluded from further analysis (Figure 4.2).

Figure 4.2: Number of patients that were eligible at each stage and the number of patients excluded at each stage



Of 188 patients who were categorised as data errors, 39 (20.7%) returned early (before their next scheduled visit), 58 (30.9%) returned on the exact date of their next scheduled visit, 30 (16.0%) were between 1 to 7 days late for their next scheduled visit, and 61 (32.4%) were more than 7 days late for their next scheduled visit and were a median of 43 days late (IQR: 27, 58). These 61 probably indicate the utility of routine tracing as tracing procedures would have in theory been performed for them. The 91 patients that were late for their scheduled visit, were late for a median of 27 days (IQR: 6, 55). The remaining 1017 patients were 91 to 1188 days late (Figure 4.3).

Figure 4.3: Histogram and kernel density plots of the distribution of days late for a missed appointment disaggregated by pregnancy status at ART initiation



Of the 1017 remaining patients, 280 (27.5%) initiated ART for PMTCT, 767 (75.4%) were females and 849 (83.5%) linked to an HDSS record (Table 4.1). Pregnant women were younger with a median age of 29 years (IQR: 25, 33) compared to non-pregnant women, 33 years (IQR: 28, 42) and men, 41 years (IQR: 34, 48). Of 280 patients who initiated ART for PMTCT, 52 (18.6%) had a baseline CD4 <200 cells/ μL compared with 193 of 487 (39.6%) non-pregnant women and 146 of 250 (58.4%) men. None of the patients who initiated ART for PMTCT with baseline CD4 <200 cells/ μL were categorised as WHO stage III/IV compared to 53 of 193 (27.5%) non-pregnant women and 45 of 146 (30.8%) men. Furthermore, 5.0% of women who initiated treatment for PMTCT had a CD4 less than 100 cells/μL compared to 21.8% of non-pregnant women and 34.4% of men. The main reason for ART initiation for non-pregnant patients was CD4 count criteria (74.5%) (Table 4.1).

Table 4.1: Patient demographic and clinical characteristics, and final outcomes disaggregated by pregnancy status at ART initiation

	LTFU	Pregnant women	Non-pregnant women	Men
	1017	280	487	250
	N (%)	N (%)	N (%)	N (%)
Age				
18-29	333 (32.7)	150 (53.6)	157 (32.2)	26 (10.4)
30-44	484 (47.6)	124 (44.3)	226 (46.4)	134 (53.6)
45-59	141 (13.9)	6 (2.1)	70 (14.4)	65 (26.0)
60+	58 (5.7)	0 (0)	33 (6.8)	25 (10.0)
Missing	1 (0.1)	0 (0)	1 (0.2)	0 (0)
ART reason				
CD4	549 (54.0)	0 (0)	376 (77.2)	173 (69.2)
PMTCT	280 (27.5)	280 (100.0)	0 (0)	0 (0)
WHO stage	77 (7.6)	0 (0)	45 (9.2)	32 (12.8)
Test and treat	43 (4.2)	0 (0)	23 (4.7)	20 (8.0)
TB	39 (3.8)	0 (0)	17 (3.5)	22 (8.8)
Missing	29 (2.9)	0 (0)	26 (5.3)	3 (1.2)
ART start year				
2014	211 (20.8)	58 (20.7)	101 (20.7)	52 (20.8)
2015	414 (40.7)	105 (37.5)	212 (43.5)	97 (38.8)
2016	350 (34.4)	107 (38.2)	157 (32.2)	86 (34.4)
2017	42 (4.1)	10 (3.6)	17 (3.5)	15 (6.0)
Time on ART				
≤3 months	325 (32.0)	89 (31.8)	136 (27.9)	100 (40.0)
3-6 months	190 (18.7)	70 (25.0)	88 (18.1)	32 (12.8)
6-12 months	228 (22.4)	70 (25.0)	114 (23.4)	44 (17.6)
12-24 months	219 (21.5)	39 (13.9)	120 (24.6)	60 (24.0)
>24 months	55 (5.4)	12 (4.3)	29 (6.0)	14 (5.6)
Baseline CD4				
<100	206 (20.2)	14 (5.0)	106 (21.8)	86 (34.4)
100-199	185 (18.2)	38 (13.6)	87 (17.9)	60 (24.0)
200-349	261 (25.7)	71 (25.4)	129 (26.5)	61 (24.4)
350-499	193 (19.0)	74 (26.4)	95 (19.5)	24 (9.6)
500+	145 (14.3)	64 (22.9)	64 (13.1)	17 (6.8)
Missing	27 (2.6)	19 (6.8)	6 (1.2)	2 (0.8)
Baseline WHO stage				
I	722 (71.9)	261 (93.2)	329 (67.6)	132 (52.8)
II	143 (14.1)	17 (6.1)	73 (15.0)	53 (21.2)
III	129 (12.7)	2 (0.7)	70 (14.4)	57 (22.8)
IV	10 (1.0)	0 (0)	6 (1.2)	4 (1.6)
Missing	13 (1.3)	0 (0)	9 (1.8)	4 (1.6)
Refill schedule				
1 month	672 (66.1)	188 (67.1)	322 (66.1)	162 (64.8)
2 months	233 (22.9)	68 (24.3)	102 (20.9)	63 (25.2)
3 months	79 (7.8)	20 (7.1)	44 (9.0)	15 (6.0)

>3 months	33 (3.2)	4 (1.4)	19 (3.9)	10 (4.0)
Health Facility				
Agincourt	272 (26.7)	74 (26.4)	141 (28.9)	57 (22.8)
Belfast	186 (18.3)	64 (22.9)	80 (16.4)	42 (16.8)
Cunningmore	58 (5.7)	16 (5.7)	32 (6.6)	10 (4.0)
Justicia	120 (11.8)	42 (15.0)	42 (8.6)	36 (14.4)
Kildare	117 (11.5)	25 (8.9)	62 (12.7)	30 (12.0)
Lillydale	166 (16.3)	32 (11.4)	81 (16.6)	53 (21.2)
Thulamahashe	25 (2.5)	9 (3.2)	12 (2.5)	4 (1.6)
Xanthia	73 (7.2)	18 (6.4)	32 (7.6)	18 (7.2)
Time since last appointment				
≤1 year	526 (51.7)	130 (46.4)	255 (52.4)	141 (56.4)
1-2 years	369 (36.3)	117 (41.8)	176 (36.1)	76 (30.4)
>2 years	122 (12.0)	33 (11.8)	56 (11.5)	33 (13.2)
AHDSS outcome				
Still in HDSS	505 (49.7)	142 (50.7)	237 (48.7)	126 (50.4)
Deceased	74 (7.3)	6 (2.1)	42 (8.6)	26 (10.4)
Migrated	270 (26.5)	99 (35.4)	125 (25.7)	46 (18.4)
Not linked	168 (16.5)	33 (11.8)	83 (17.0)	52 (20.8)
Final Outcome				
Deceased	120 (11.8)	10 (3.6)	60 (12.3)	50 (20.0)
Transferred out	315 (31.0)	82 (29.3)	176 (36.1)	57 (22.8)
Stopped ART	75 (7.4)	28 (10.0)	20 (4.1)	27 (10.8)
Migrated	49 (4.8)	21 (7.5)	22 (4.5)	6 (2.4)
Reengaged	225 (22.1)	54 (19.3)	110 (22.6)	61 (24.4)
Alive: ART unknown	111 (10.9)	45 (16.1)	45 (9.2)	21 (8.4)
LTFU	122 (12.0)	40 (14.3)	54 (11.1)	28 11.2)

4.4.2. Sources of resolution

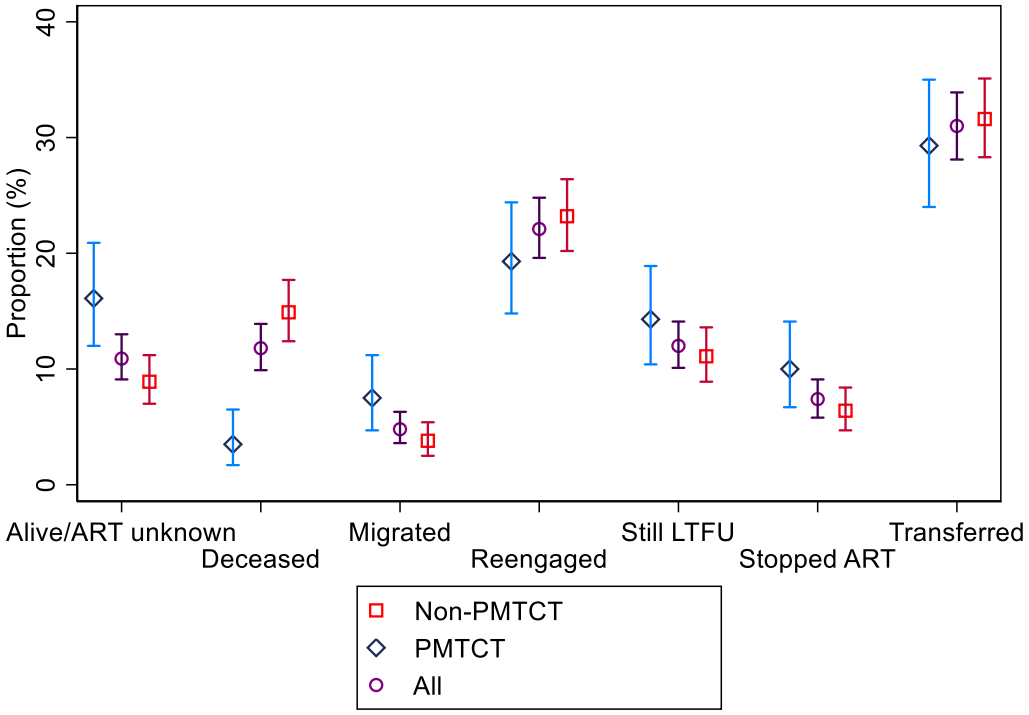
Of the 1017 patients LTFU, 895 (88.0%) were resolved, with 536 (59.9%) of these occurring through record review, 155 (17.3%) through demographic surveillance data (23 migrations, 21 deaths, 111 alive), 72 (8.0%) through subsequent visit data in the PIRL database, 53 (5.9%) through supplementary tracing, 57 (6.4%) identified as duplicates in the PIRL database (one person matching to multiple clinic records), and 22 (2.5%) through a search of patient records in clinics in close proximity to the patient's residence.

4.4.3. Patient outcomes

Of 1017 patients LTFU, 120 (11.8%, 95% C.I: 9.9-13.9) had died , 315 (31.0%, C.I: 28.1-33.9) had transferred to another facility, 75 (7.4%, C.I: 5.8-9.1) had stopped ART, 49 (4.8%, C.I: 3.6-6.3) had migrated, 225 (22.1%, C.I: 19.6-24.8) re-engaged in care, 111 (10.9%, C.I: 9.1-13.0) were alive with an unknown

treatment status and 122 (12.0%) remained LTFU. These outcomes differed (all p<0.001) by sex, age, baseline CD4 count, time on ART, clinic visit schedule, health facility, time since a missed appointment, and ART initiation reason. Women who initiated treatment while pregnant or postpartum were less likely to have died (3.6% (C.I: 1.7-6.5) compared to 14.9% (C.I: 12.4-17.7)) and more likely to have migrated (7.5% (C.I: 4.7-11.2) compared to 3.8% (C.I: 2.5-5.4)), to be alive with their ART status unknown (16.1% (C.I: 12.0-20.9) compared to 8.9% (C.I: 7.0-11.2)) or stopped ART (10.0% (C.I: 6.7-14.1) compared to 6.4% (C.I: 4.7-8.4)) (Table 4.2 & Figure 4.4).

Figure 4.4: Outcome estimates and confidence intervals disaggregated by pregnancy status at ART initiation



Most deaths occurred in the groups where baseline CD4<200 cells/μL (Figure 4.5). Men were at highest risk of mortality, and pregnant women were at the lowest risk (Figure 4.6). Men and pregnant women also had higher risks of being alive and not in care compared to non-pregnant women (Figure 4.6). The mortality risk appeared to be similar for all CD4 categories for pregnant women unlike for non-pregnant women (Figure 4.7 and 4.8).

Figure 4.5: Status of patients by baseline CD4 and years since their last clinic visit

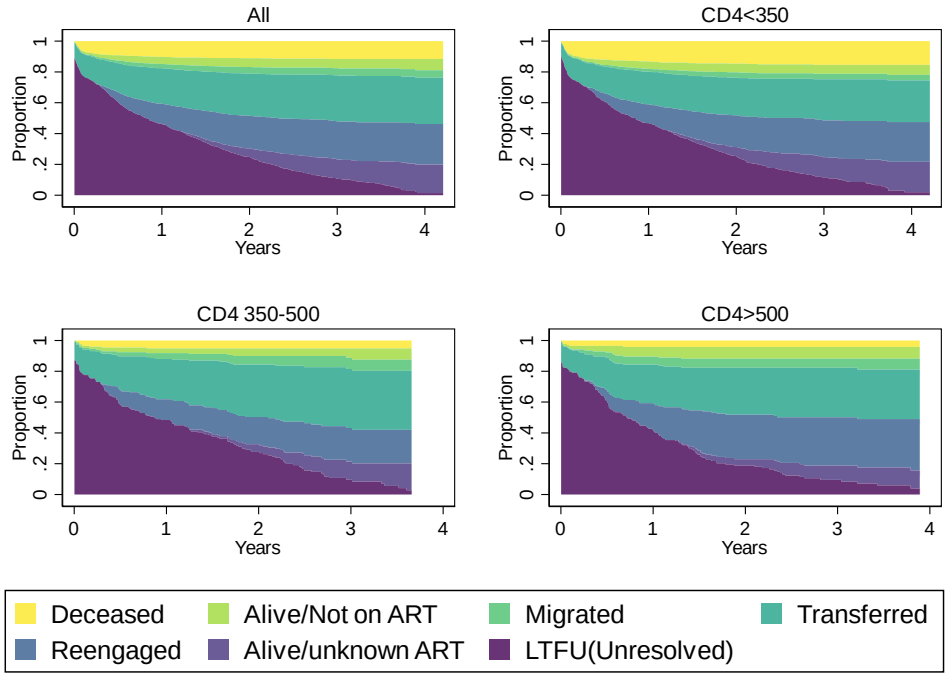


Figure 4.6: Status of patients by sex, pregnancy status at ART initiation and years since their last clinic visit

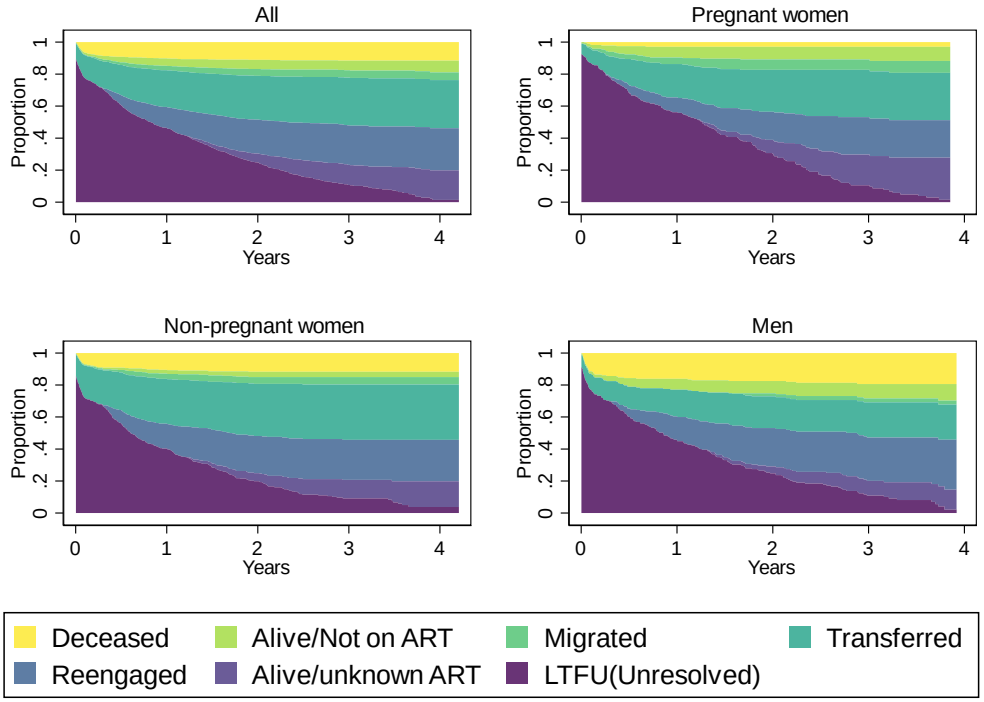


Table 4.2: Patient outcomes disaggregated by patient demographic and clinical characteristics

	Outcome							Total
	Deceased	Transferred out	Stopped ART	Migrated	Reengaged	Alive: ART unknown	Still LTFU	**All LTFU**
	120	315	75	49	225	111	122	**1017**
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
Sex (p<0.001)								
Female	70 (9.1)	258 (33.6)	48 (6.3)	43 (5.6)	164 (21.4)	90 (11.7)	94 (12.2)	**767 (75.4)**
Male	50 (20.0)	57 (22.8)	27 (10.8)	6 (2.4)	61 (24.4)	21 (8.4)	28 (11.2)	**250 (24.6)**
Age (p<0.001)								
18-29	17 (5.1)	117 (35.1)	24 (7.2)	25 (7.5)	61 (18.3)	46 (13.8)	43 (12.9)	**333 (32.7)**
30-44	55 (11.4)	147 (30.4)	37 (7.6)	21 (4.3)	116 (24.0)	50 (10.3)	58 (12.0)	**484 (47.6)**
45-59	27 (19.1)	38 (26.9)	11 (7.8)	2 (1.4)	35 (24.8)	13 (9.2)	15 (10.6)	**141 (13.9)**
60+	21 (36.2)	13 (22.4)	3 (5.2)	1 (1.7)	12 (20.7)	2 (3.4)	6 (10.3)	**58 (5.7)**
Missing	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	**1 (0.1)**
ART reason (p<0.001)								
Non-PMTCT	110 (14.9)	233 (31.6)	47 (6.4)	28 (3.8)	171 (23.2)	66 (8.9)	82 (11.1)	**737 (72.5)**
PMTCT	10 (3.6)	82 (29.3)	28 (10.0)	21 (7.5)	54 (19.3)	45 (16.1)	40 (14.3)	**280 (27.5)**
ART start year (p=0.251)								
2014	28 (13.3)	58 (27.5)	14 (6.6)	18 (8.5)	50 (23.7)	19 (9.0)	24 (11.4)	**211 (20.7)**
2015	41 (9.9)	149 (36.0)	33 (8.0)	16 (3.9)	82 (19.8)	44 (10.6)	49 (11.8)	**414 (40.7)**
2016	46 (13.1)	100 (28.6)	24 (6.9)	14 (4.0)	82 (23.4)	41 (11.7)	43 (12.3)	**350 (34.4)**
2017	5 (11.9)	8 (19.0)	4 (9.5)	1 (2.4)	11 (26.2)	7 (16.7)	6 (14.3)	**42 (4.1)**
Time on ART (p<0.001)								
≤3 months	54 (16.6)	89 (27.3)	29 (8.9)	13 (4.0)	47 (14.5)	41 (12.6)	52 (16.0)	**325 (32.0)**
3-6 months	18 (9.5)	62 (32.6)	13 (6.8)	8 (4.2)	31 (16.3)	30 (15.8)	28 (14.7)	**190 (18.7)**
6-12 months	25 (11.0)	79 (34.6)	12 (5.3)	17 (7.5)	42 (18.4)	25 (11.0)	28 (12.3)	**228 (22.4)**
12-24 months	16 (7.3)	76 (34.7)	17 (7.8)	9 (4.1)	75 (34.2)	13 (5.9)	13 (5.9)	**219 (21.5)**

>24 months	7 (12.7)	9 (16.4)	4 (7.3)	2 (3.6)	30 (54.5)	2 (3.6)	1 (1.8)	**55 (5.4)**
Baseline CD4 (p<0.001)								
<100	50 (24.3)	64 (31.1)	8 (3.9)	4 (1.9)	38 (18.4)	13 (6.3)	29 (14.1)	**206 (20.2)**
100-199	32 (17.3)	46 (24.9)	16 (8.6)	8 (4.3)	41 (22.2)	19 (10.3)	23 (12.4)	**185 (18.2)**
200-349	19 (7.3)	69 (26.4)	23 (8.8)	12 (4.6)	63 (24.1)	43 (16.5)	32 (12.3)	**261 (25.7)**
350-499	11 (5.7)	72 (37.3)	16 (8.3)	14 (7.3)	36 (18.6)	20 (10.4)	24 (12.4)	**193 (19.0)**
500+	8 (5.5)	53 (36.5)	11 (7.6)	10 (6.9)	41 (28.3)	12 (8.3)	10 (6.9)	**145 (14.3)**
Missing	0 (0)	11 (40.7)	1 (3.7)	1 (3.7)	6 (22.2)	4 (14.8)	4 (14.8)	**27 (2.6)**
Baseline WHO stage (p=0.017)								
I	65 (9.0)	230 (31.8)	55 (7.6)	38 (5.3)	159 (22.0)	88 (12.2)	87 (12.0)	**722 (71.0)**
II	21 (14.7)	42 (29.4)	12 (8.4)	6 (4.2)	34 (23.8)	11 (7.7)	17 (11.9)	**143 (14.1)**
III	26 (20.1)	39 (30.2)	7 (5.4)	4 (3.1)	28 (21.7)	9 (7.0)	16 (12.4)	**129 (12.7)**
IV	5 (50.0)	1 (10.0)	1 (10.0)	0 (0)	2 (20.0)	0 (0)	1 (10.0)	**10 (1.0)**
Missing	3 (23.1)	3 (23.1)	0 (0)	1 (7.7)	2 (15.4)	3 (23.1)	1 (7.7)	**13 (1.3)**
Refill schedule (p<0.001)								
1 month	84 (12.5)	210 (31.2)	48 (7.1)	30 (4.5)	143 (21.3)	77 (11.4)	80 (11.9)	**672 (66.1)**
2 months	24 (10.3)	71 (30.5)	21 (9.0)	14 (6.0)	43 (18.4)	24 (10.3)	36 (15.5)	**233 (22.9)**
3 months	9 (11.4)	30 (38.0)	3 (3.8)	5 (6.3)	18 (22.8)	9 (11.4)	5 (6.3)	**79 (7.8)**
>3 months	3 (9.1)	4 (12.1)	3 (9.1)	0 (0)	21 (63.6)	1 (3.0)	1 (3.0)	**33 (3.2)**
Health Facility (p<0.001)								
Agincourt	27 (9.9)	66 (24.3)	15 (5.5)	11 (4.0)	110 (37.1)	21 (7.7)	22 (8.1)	**272 (26.7)**
Belfast	16 (8.6)	52 (28.0)	13 (7.0)	12 (6.4)	32 (17.2)	29 (15.6)	32 (17.2)	**186 (18.3)**
Cunningmore	11 (19.0)	21 (36.2)	8 (13.8)	1 (1.7)	7 (12.1)	5 (8.6)	5 (8.6)	**58 (5.7)**
Justicia	20 (16.7)	30 (25.0)	13 (10.8)	7 (5.8)	14 (11.7)	11 (9.2)	25 (20.8)	**120 (11.8)**
Kildare	16 (13.7)	50 (42.7)	10 (8.5)	8 (6.8)	14 (12.0)	9 (7.7)	10 (8.5)	**117 (11.5)**
Lillydale	19 (11.4)	51 (30.7)	9 (5.4)	7 (4.2)	37 (22.3)	24 (14.5)	19 (11.4)	**166 (16.3)**
Thulamahashe	3 (12.0)	4 (16.0)	1 (4.0)	0 (0)	7 (28.0)	6 (24.0)	4 (16.0)	**25 (2.4)**
Xanthia	9 (12.2)	41 (55.4)	6 (8.1)	3 (4.0)	4 (5.4)	6 (8.1)	5 (6.8)	**74 (7.3)**

Time since last appointment (p<0.001)								
≤1 year	48 (9.1)	146 (27.8)	40 (7.6)	16 (3.0)	171 (32.5)	51 (9.7)	54 (10.3)	**526 (51.7)**
1-2 years	53 (14.4)	134 (36.3)	26 (7.0)	19 (5.1)	46 (12.5)	44 (11.9)	47 (12.7)	**369 (36.3)**
>2 years	19 (15.6)	35 (28.7)	9 (7.4)	14 (11.5)	8 (6.6)	16 (13.1)	21 (17.2)	**122 (12.0)**
AHDSS outcome (p<0.001)								
Still in HDSS	17 (3.4)	177 (35.0)	52 (10.3)	7 (1.4)	141 (27.9)	111 (22.0)	0 (0)	**505 (49.7)**
Deceased	70 (94.6)	4 (5.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**74 (7.3)**
Migrated	22 (8.1)	86 (31.8)	19 (7.0)	34 (12.6)	58 (21.5)	0 (0)	51 (18.9)	**270 (26.5)**
Not linked	11 (6.5)	48 (28.6)	4 (2.4)	8 (4.8)	26 (15.5)	0 (0)	71 (42.3)	**168 (16.5)**

Figure 4.7: Status of patients who were pregnant at ART initiation stratified by baseline CD4 count and years since their last clinic visit

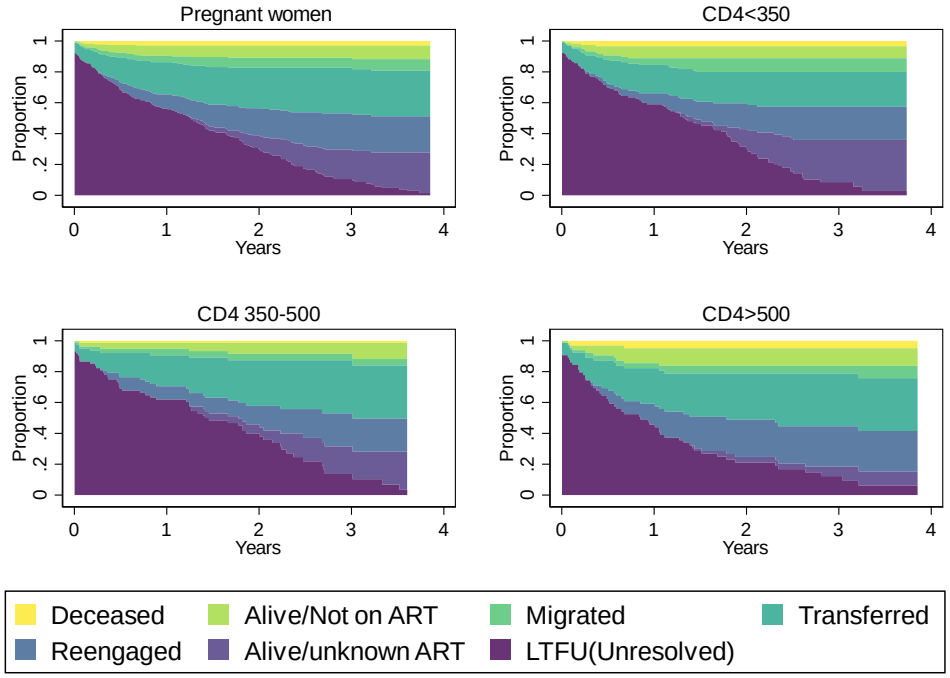
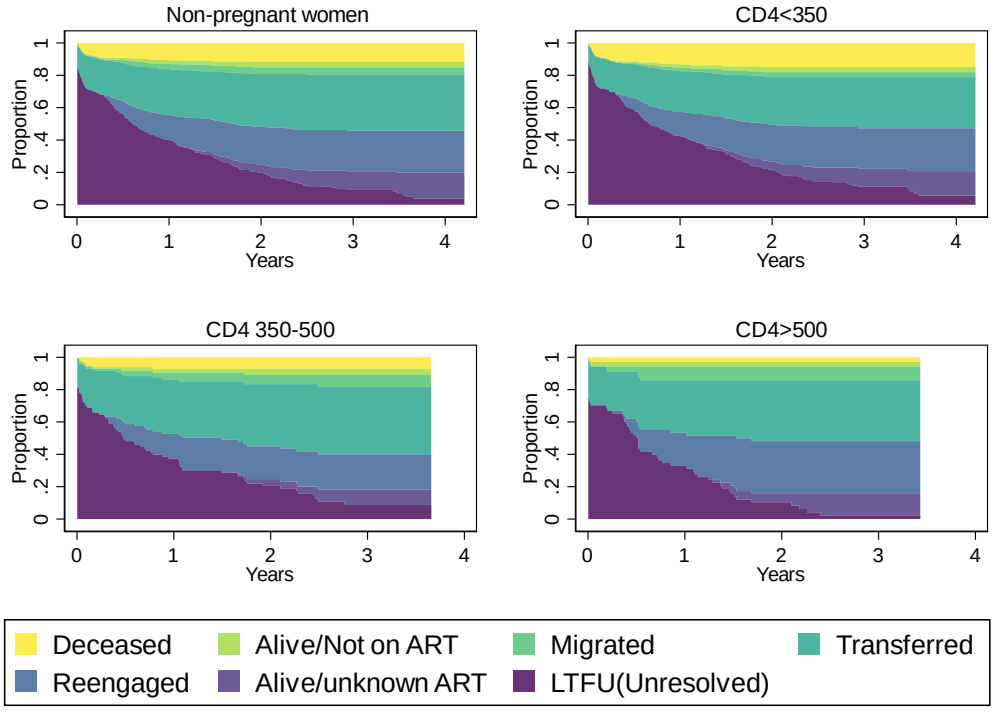


Figure 4.8: Status of non-pregnant female patients stratified by baseline CD4 count and years since their last clinic visit



4.4.4. Causes of death

We managed to ascertain the probable cause of death for 58 (48.3%) of 120 deaths through verbal autopsy data from the HDSS. HIV/AIDS was indicated as the main cause of death for 10 (17.2%) deaths and acute respiratory infection for 11 (19.0%) deaths. Other causes included tuberculosis, malaria, cardiovascular disease, and neoplasms. These causes of death varied by ART initiation reason (Table 4.3).

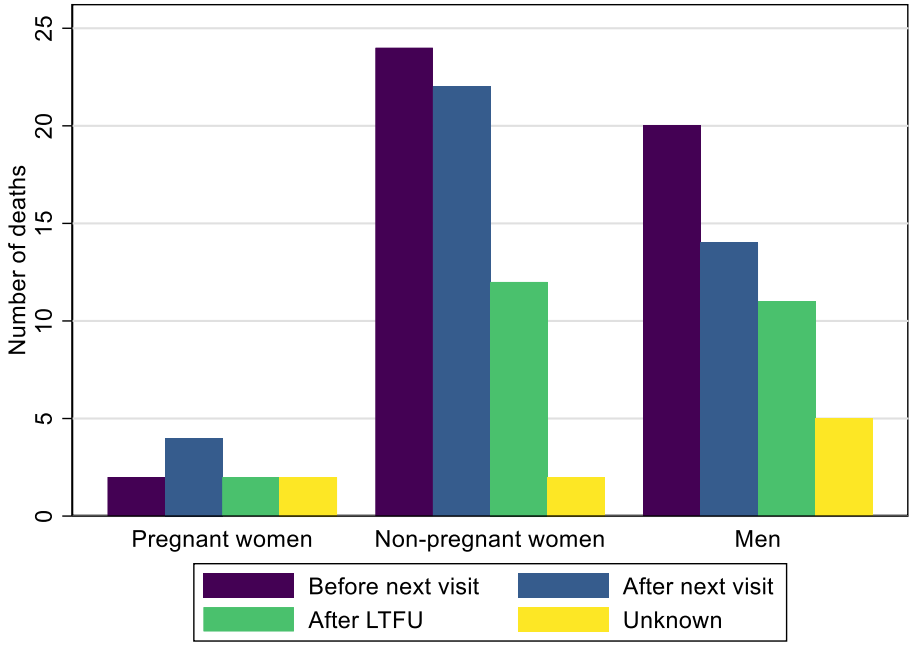
Table 4.3: Probable causes of death as indicated by verbal autopsy data

	Pregnant women	Non-pregnant women	Men	Total
Primary cause	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Acute respiratory infection (including pneumonia)	2 (20.0)	6 (10.0)	3 (6.0)	11 (9.2)
HIV/AIDS related death	0 (0)	8 (13.3)	2 (4.0)	10 (8.3)
Pulmonary tuberculosis	1 (10.0)	0 (0)	4 (8.0)	5 (4.2)
Malaria	0 (0)	3 (5.0)	0 (0)	3 (2.5)
Oral neoplasms	0 (0)	0 (0)	1 (2.0)	1 (0.8)
Digestive neoplasms	1 (10.0)	0 (0)	4 (8.0)	5 (4.2)
Reproductive neoplasms	0 (0)	2 (3.3)	0 (0)	2 (1.7)
Severe malnutrition	0 (0)	1 (1.7)	0 (0)	1 (0.8)
Diabetes mellitus	0 (0)	0 (0)	2 (4.0)	2 (1.7)
Acute cardiac disease	0 (0)	1 (1.7)	3 (6.0)	4 (3.3)
Stroke	0 (0)	2 (3.3)	0 (0)	2 (1.7)
Other and unspecified cardiac disease	0 (0)	2 (3.3)	1 (2.0)	3 (2.5)
Asthma	0 (0)	2 (3.3)	0 (0)	2 (1.7)
Acute abdominal condition	0 (0)	1 (1.7)	0 (0)	1 (0.8)
Pregnancy induced hypertension	0 (0)	1 (1.7)	0 (0)	1 (0.8)
Obstetric haemorrhage	1 (10.0)	0 (0)	0 (0)	1 (0.8)
Pregnancy related sepsis	0 (0)	1 (1.7)	0 (0)	1 (0.8)
Anaemia of pregnancy	1 (10.0)	1 (1.7)	0 (0)	2 (1.7)
Accidental exposure to smoke fire and flames	0 (0)	1 (1.7)	0 (0)	1 (0.8)
No verbal autopsy data	4 (40.0)	28 (46.7)	30 (60.0)	62 (51.7)
Total	10	60	50	120

4.4.5. Factors associated with death

Of 120 deaths, 48 (37.2%) occurred before the patient's next visit date, 42 (32.6%) occurred after the patient's next scheduled visit date but before they would have met the criteria for LTFU, 30 (23.3%) occurred after the patient had met the criteria for LTFU, and 9 (7.0%) had a missing date of death (Figure 4.9).

Figure 4.9: Timing of deaths disaggregated by sex and pregnancy status at ART initiation



In multivariable competing risk regression, being pregnant at ART initiation (aHR: 0.36, 95% C.I: 0.15-0.87), and longer time on ART (12-24 months aHR: 0.44, 0.23-0.85) were associated with lower hazard of death following LTFU. Older age (≥60 years aHR: 8.86, 3.90-20.14) and lower CD4 at ART initiation (<100 cells/μL aHR: 3.77, 2.31-6.15; 100-199 cells/μL aHR: 2.35, 1.49-3.69) were associated with a higher hazard of death (Table 4.4).

Table 4.4: Factors associated with death

	HR (95% CI)	p-value	aHR (95% CI) n=932	p-value
Sex				
Female	Reference	__		
Male	2.10 (1.57, 2.81)	<0.001		
Age				
18-29	Reference	__	Reference	__
30-44	2.68 (1.30, 5.51)	0.007	2.37 (0.98, 5.75)	0.056
45-59	4.73 (3.13, 7.15)	<0.001	2.96 (1.44, 6.08)	0.003
60+	11.31 (5.32, 24.06)	<0.001	8.86 (3.90, 20.14)	<0.001
ART reason				
Non-PMTCT	Reference	__	Reference	__
PMTCT	0.17 (0.07, 0.43)	<0.001	0.36 (0.15, 0.87)	0.022
ART start year				
2014	1.29 (0.82, 2.04)	0.268		
2015	Reference	__		
2016	1.20 (0.67, 2.14)	0.536		
2017	1.28 (0.83, 1.97)	0.258		
Time on ART				
≤3 months	Reference	__	Reference	__
3-6 months	0.56 (0.31, 0.99)	0.048	0.76 (0.46, 1.25)	0.276
6-12 months	0.74 (0.49, 1.13)	0.167	0.82 (0.56, 1.20)	0.307
12-24 months	0.53 (0.31, 0.91)	0.023	0.44 (0.23, 0.85)	0.015
>24 months	0.91 (0.41, 2.05)	0.828	0.60 (0.23, 1.56)	0.297
Baseline CD4				
<100	4.26 (3.11, 5.82)	<0.001	3.77 (2.31, 6.15)	<0.001
100-199	2.57 (1.60, 4.12)	<0.001	2.35 (1.49, 3.69)	<0.001
200-349	Reference	__	Reference	__
350-499	0.78 (0.39, 1.55)	0.483	1.11 (0.53, 2.36)	0.776
500+	0.82 (0.24, 2.79)	0.756	1.13 (0.35, 3.67)	0.840
Baseline WHO stage				
I	Reference	__	Reference	__
II	1.71 (0.98, 3.00)	0.061	0.86 (0.40, 1.86)	0.706
III	2.70 (1.77, 4.14)	<0.001	1.36 (0.94, 1.96)	0.102
IV	6.64 (3.08, 14.32)	<0.001	3.14 (1.14, 8.59)	0.026
Refill schedule				
1 month	Reference	__		
2 months	0.83 (0.37, 1.86)	0.647		
3 months	0.93 (0.49, 1.75)	0.824		
>3 months	0.74 (0.22, 2.42)	0.615		
Health Facility				
Agincourt	Reference	__	Reference	__
Belfast	1.03 (0.97, 1.09)	0.345	0.80 (0.61, 1.05)	0.108
Cunningmore	3.14 (2.98, 3.31)	<0.001	3.39 (2.92, 3.94)	<0.001
Justicia	2.10 (1.98, 2.24)	<0.001	1.70 (1.55, 1.86)	<0.001
Kildare	1.90 (1.84, 1.95)	<0.001	1.08 (0.78, 1.50)	0.639
Bhubezi	1.26 (1.19, 1.34)	<0.001	0.96 (0.73, 1.28)	0.810

Thulamahashe	0.93 (0.91, 0.95)	<0.001	1.59 (1.15, 2.22)	0.005
Xanthia	1.75 (0.70, 1.80)	<0.001	1.98 (1.64, 2.38)	<0.001
Time since last appointment				
≤1 year	Reference	__	Reference	__
1-2 years	1.57 (1.03, 2.39)	0.037	1.75 (1.10, 2.78)	0.018
>2 years	1.65 (0.73, 3.75)	0.228	0.81 (0.39, 1.67)	0.564

4.5. Discussion

We describe the treatment outcomes of HIV patients enrolled in care between April 2014 and August 2017 who had become LTFU in a rural South African setting as determined through a comprehensive record review and tracing study. Using multiple data sources and methods, we managed to ascertain the outcomes of 88% of the patients LTFU, a figure that is higher than most studies included in a recent systematic review of tracing studies in sub-Saharan Africa (15). We found that 31% of patients LTFU had transferred to another facility, 22% had re-engaged in care, and 12% of patients had died. These percentages varied by sex, reason for ART initiation and baseline CD4 cell count. The differences for pregnant and postpartum women are particularly pertinent given that they represent the first iterations of treatment as prevention and could provide an indication for what to expect with the move to test and treat for all PLHIV.

The proportion of patients reported as LTFU who had died in our study was substantially lower than the 42% and 39% reported in earlier systematic reviews of tracing studies from sub-Saharan Africa (14,15). Even if all the patients remaining LTFU after record review and tracing had died, mortality in our study would only rise to 24%. This lower percentage of deaths compared to the previous reviews is likely to be due to a healthier cohort of patients initiating treatment. We found that pregnant women were less likely to have died, an encouraging trend if it does translate to the general ART treatment population as less immunocompromised people begin to initiate ART. Mortality following LTFU may decrease further as universal test and treat policies result in growing proportions of asymptomatic patients initiating ART.

In competing risk survival analysis, being pregnant at ART initiation, higher baseline CD4 and longer time on ART were protective against death, while older age was found to be associated with a higher hazard of death following LTFU. Our findings suggest baseline CD4 cell count, WHO stage, and older age remain accurate measures for determining which patients are at highest risk for death (357,429,430), and these characteristics could be used to help prioritise tracing interventions. Whereas mortality risk appeared to wane with increasing CD4 at baseline for non-pregnant women and men, mortality appeared to be similar for all CD4 categories for women who initiated treatment for PMTCT. This may reflect the fact that their mortality risk was more influenced by other factors such as pregnancy related complications than by HIV (431,432). This could also be due to the fact that pregnant women were healthier in terms of WHO staging compared to non-pregnant women and men, given the same CD4 at baseline, also reflected by the lower proportion of pregnant patients with a baseline CD4 <100 cells/μL. This discrepancy could also be related to temporary declines in CD4 count during pregnancy (433).

Patients lost early on in treatment were at higher risk of death and this remained statistically significant even when controlling for baseline CD4, indicating that a longer duration on ART prior to attrition may reduce the risk of death. This protective effect appeared to be strongest for those who had been on ART 12-24 months before they became LTFU. This suggests that in settings with limited resources, tracing should be considered most urgent for newly ART-initiated patients who drop out of care. On the other hand, it might also indicate that some patients are still initiating treatment too late. In this study, 11% of non-pregnant patients had a CD4 cell count >500 cells/μL (compared to 23% of pregnant women), reflecting the fact that universal test and treat was not adopted in South Africa until September 2016 (93,434). Men were disproportionately over-represented in the <200 cells/μL baseline CD4 category despite South African guidelines for ART initiation with CD4<500 cells/μL having been in effect since January 2015 (435). Men especially appear to be harder to reach and come into care later, similar to findings from other studies (13,436–438), and emphasises the need to reach men earlier with ART (112,439,440).

However, as the proportion of LTFU attributable to mortality dwindles, other outcomes are likely to become more prevalent. In our study, transfer to another facility accounted for 31% of patients who were reported as LTFU, which is higher than a previous systematic review (15). Other studies have suggested transfers become more common as programmes expand and offer ART closer to patients' homes (15,441,442). Women were more likely to have transferred their care to another clinic. For pregnant women, this could reflect the higher mobility common during pregnancy and childbirth (102,443,444). Furthermore, given that the majority of these transfers were not reported to the sending facility similar to previous studies (15,16), these types of transfers could potentially lead to the spread of drug resistance in situations where ART experienced patients are offered regimens that have lost any therapeutic value due to drug resistance (445). Silent transfers may also lead to over-estimates of the number of people newly initiating ART and the number of people who have ever initiated ART. The current system of transferring patients could be improved by better referral systems, patient education, regular information exchange between clinics, and provider training (364).

We found that 7.4% of patients had stopped treatment, with this being more common for women who initiated ART while pregnant, which adds to findings from previous studies that suggest that feeling healthy contributes to attrition for pregnant women (240,339). This figure is lower than the 28.6% of treatment interruptions reported in a recent systematic review (15). This may suggest that interventions to reduce interruptions, including routine tracing, are working well in this setting, further supported by the number of re-engagements in care that were observed in our study.

Our data showed that pregnant women and the general treatment cohort still differ significantly especially with regards to immune system markers such as CD4. However, with the advent of test and treat, these groups may increasingly become similar in this regard and hence outcomes for pregnant women living with HIV could represent what treatment programmes may expect to see in the future with regards to patients that become LTFU especially those of a similar age. With ART programmes in sub-Saharan Africa maturing, and with less immunologically compromised patients initiating ART, patients that

become LTFU will be less likely to have died, while ART cessation or interruption and re-engagement in care are likely to become more common. Treatment programmes will increasingly need to reallocate resources to deal with improving the clinic transfer process and invest in tracing and psychosocial support to get patients back in care or else risk having high community viral load which may increase the probability of onward transmission. We showed that 6% of patients who were late for a scheduled appointment returned before they officially became categorised as LTFU. These patients in theory would have received the routine tracing intervention offering further evidence of its utility, in line with a previous study that has highlighted how early active tracing of patients LTFU may improve patient outcomes and retention in care (55).

Furthermore, given that most resolutions came through record review of tracing logbooks and clinic records, this study demonstrates that routine patient tracing still has utility for improving the completeness and accuracy of patient records. The availability of these data within the clinics suggests that routinely-collected data, especially those from the two organisations that assist in patient tracing needs to be better collated, integrated and recorded in order to ensure that patient outcomes are reflected in their clinic files and on TIER.Net. This study also demonstrates the utility of other data sources such as HDSS data. Given the push to integrate national ID numbers in patient profiles, clinics operating within similar health and demographic surveillance sites should consider liaising with these sites to improve the capture of deaths and migrations. Policy makers should also consider using South Africa's national death registry within clinics as this has been shown to be useful in other studies (446,447).

This study had several limitations. Firstly, the record review was cross-sectional; we only consulted clinic records at one point in time, whereas, some of these records might have subsequently been updated. Furthermore, we only consulted HBC and RtC logbooks that were afforded to us and it is possible that we might have missed some with information on patients we were trying to find. The observational nature of the study limited our ability to assess predictive factors and causality. We failed to ascertain the outcomes for 12%

of our cohort and this might introduce some downward bias to our estimates. Finally, as we only resolved cause of death in 48.3% of patients found to have died, this data should be interpreted with caution. As we attempted to trace all adult patients LTFU, rather than a sample, these results are likely to be generalisable to other rural sub-Saharan settings. A strength of this study is the utilisation of multiple data sources.

4.6. Conclusions

Our study offers evidence for the growing utility for routine patient tracing. The different distribution of outcomes among Option B+ women suggests that different programme mortality and attrition correction factors will be needed as universal test and treat becomes more established. Higher mortality among men emphasises the importance of programmatic efforts to reach men earlier and treatment programmes need to improve transfer procedures to make it more conducive for patients to move between clinics.

5. Paper B: Getting on with their lives: Understanding clinic transfers among HIV patients considered lost to follow-up in rural South Africa

Introduction to chapter:

This paper (B) utilises data from the record review and tracing study described in chapter 3 to examine objective 1. In this chapter, I comprehensively investigate transfer of care to another facility following LTFU. Transfers represented the most common outcome for patients considered LTFU through the PIRL database. The paper includes comparisons by sex and pregnancy status at ART initiation in order to examine transfers for Option B+ women in comparison to other adults on ART. The paper also presents factors that contribute to transfer of care following LTFU.

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Student ID Number	1603703	**Title**	Mr
First Name(s)	David		
Surname/Family Name	Etoori		
Thesis Title	A mixed methods study using linked demographic surveillance and health facility data to investigate and compare loss to follow-up among women living with HIV who initiated antiretroviral therapy during pregnancy under Option B+ in Agincourt, South Africa		
Primary Supervisor	Alison Wringe		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the study, planned and executed the fieldwork. Supervised data collection in the field. I conducted all the pertinent analyses and interpreted the findings. I drafted the manuscript.

SECTION E

Student Signature	[redacted]
Date	14/07/2020

Supervisor Signature	[redacted]
Date	14/07/2020

5.1. Abstract

Investigating transfers is important for accurate estimates of retention and informing interventions to support patients. We investigate clinic transfers for adults lost to follow-up (LTFU) from eight HIV care facilities in the Agincourt health and demographic surveillance system (HDSS), South Africa.

Using linked clinic and HDSS records, outcomes of adults more than 90 days late for their last scheduled clinic visit were determined through clinic and routine tracing record reviews, HDSS data, and supplementary tracing. Factors associated with transferring to another clinic were determined through Cox regression models. We also graphically and geospatially visualise these transfers.

Transfers were more common for women, patients living further from the clinic, and patients with higher baseline CD4. Transfers to clinics within the HDSS were more likely to be undocumented and were more common for women pregnant at ART initiation. Transfers outside the HDSS appeared to cluster around economic hubs, suggesting labour migration.

Patients transferring to health facilities within the HDSS may be shopping for better or more convenient care, whereas those who transfer out of the HDSS may be migrating for work. Treatment programmes should facilitate transfer processes for patients, ensure continuity of care among those migrating, and improve tracking of undocumented transfers.

5.2. Introduction

In 2016, the South African government launched the "test and treat" strategy providing antiretroviral therapy (ART) to all people living with HIV (PLHIV) regardless of CD4 count (93,95). By 2018, approximately 68% of the estimated 7.2 million PLHIV in South Africa were on ART (24,448).

Although ART expansion has improved life expectancy (174,449), several ART programmes in sub-Saharan Africa have reported higher rates of loss to follow-up (LTFU) among patients who initiated ART in more recent years (114,450,451). Increasing patient numbers have placed pressure on health systems, leading to longer waiting times and shorter counselling consultations for patients, which may increase LTFU (102,452). Asymptomatic or less severely ill patients initiating ART may not see the merits of remaining engaged in care (452,453), and higher rates of asymptomatic disease are linked to increased LTFU among women who initiate ART for prevention of mother-to-child transmission (PMTCT) compared to the general population (89,454). High rates of LTFU present multiple challenges, including mortality and HIV transmission risk (56,455–457).

Misclassification of patients as LTFU may lead to biased estimates of death and retention. One study reported a five-fold underestimation of death and retention rates and an overestimation of attrition due to LTFU (425). As more healthy people initiate ART, less LTFU will be attributable to mortality (14,15). "Silent transfers" whereby sending facilities are unaware of the transfer, so it is unreported, majorly contribute to LTFU (15,90). This is exacerbated by decentralised ART provision in sub-Saharan Africa, reliance on paper-based registers, a lack of unique identifiers and poorly implemented electronic databases, making patients' movement between clinics difficult to track and document (99). Silent transfers might also be driven by patient practices, such as "clinic shopping" as programmes expand, and ART becomes increasingly available (15,53). One South African study reported an increase in transfers from 1.4% among patients enrolled in care between 2002-2004 to 8.9% for patients enrolled in 2009, following ART expansion (442).

Previous studies reported high mortality immediately following clinic transfers and return migration, attributed to patients with severe illness

moving closer to home to be cared for in the expectation of death (405,428,458–460), or to better equipped facilities which could handle severely ill patients (428). However, evidence now shows a reduction in mortality for migrants following ART rollout (460). A similar trend may occur for clinic transfers more broadly. Patients can actively seek better quality care, hoping for improved outcomes (428,461). Whereas historically, migration selection effect has favoured participation of healthy individuals (462), studies are reporting increased participation in migration by physically healthier PLHIV (463). This has important implications for their continuity of care and consequently the potential transmission of HIV (464–466).

Recent research into patient mobility shows evidence of continued HIV care among patients considered LTFU after ART initiation (18,102). However, it is pertinent to understand how this mobility affects retention and the preventative benefits of ART (467), and contributes to silent transfers and over-estimation of LTFU.

We undertook a record review and patient tracing study in rural north-eastern South Africa to understand the outcomes of patients considered LTFU, from a network of eight public sector ART facilities. We utilised routinely collected data from the Agincourt Health and Demographic Surveillance System (HDSS), linked to patient records from health facilities, to track patients' movement between health facilities. In this paper, we describe mobility of residents of the HDSS who initiated ART and who were recorded as LTFU, using geographic information system (GIS) mapping techniques and circular migration plots.

5.3. Methods

5.3.1. Setting

The Agincourt HDSS comprises 115,000 residents in 31 villages, located in Mpumalanga province, South Africa where HIV prevalence is 14.1% across all ages (20,468,469).

There are five primary health facilities (Belfast, Cunningmore, Justicia, Kildare and Xanthia) and three secondary community health centres (Agincourt, Bhubezi and Thulamahashe) within the HDSS. All health facilities

routinely trace patients who are late for a scheduled clinic appointment, in conjunction with two non-profit organisations, Right to Care (RtC) and Home-Based Carers (HBC). Health facility staff contact patients by phone, with a home visit organised if necessary. Patients are classified LTFU 90 days after their scheduled visit if they have not returned or do not have an outcome ascertained through tracing.

Demographic surveillance

Fertility, mortality and migration data are collected annually from residents, based on a comprehensive household registration system, in operation since 1992 (20,413,414,470). Fieldworkers visit each household and interview the most knowledgeable adult available to obtain information on demographic events occurring since the last census (471).

Point-of-contact interactive record linkage (PIRL)

Since 2014, HIV patient visits to ART clinics in the area are logged by fieldworkers and linked to the HDSS using Point-of-Contact Interactive Record Linkage (PIRL) (103,104). In brief, a fieldworker conducts a short uptake interview with patients in the clinic waiting area. Consenting patients are asked for personal identifiers, used to search the HDSS database using a probabilistic algorithm. Matches are confirmed in interaction with the patients, and names of household members are used as a key attribute to adjudicate between possible matches.

5.3.2. Record review and tracing study

Through the PIRL database, we identified HDSS residents aged 18 years or older, enrolled after record linkage was established and more than 90 days late for a scheduled ART clinic appointment (LTFU) on August 15, 2017 (data extraction date).

Trained fieldworkers conducted a thorough record review on a case-by-case basis, comparing LTFU patients (against (a) TIER.Net (the South African national HIV treatment electronic database (100)) (b) patient clinic files, and (c) logbooks kept by RtC and HBC. The PIRL database was reviewed for duplicate patients (different clinical records linking to the same individual in the HDSS database, which was taken as evidence of silent transfers), and residency and vital status were extracted from the HDSS database. This was

supplemented by an HBC home visit if no outcome could be ascertained and a further TIER.Net search at clinics close to patients' residences to capture further silent transfer. Data collection concluded in December 2018.

5.3.3. Definitions

A patient was defined as having transferred if they had reported taking treatment at another health facility, if the health facility at which they initiated ART had communicated with and ascertained their transfer to another health facility, or if there was a record of them collecting treatment from another health facility within the HDSS. An undocumented transfer was defined as one where the sending (origin) health facility was unaware and therefore did not have this recorded as a patient outcome within its system.

Socioeconomic status is an assets-based indicator constructed using household assets data collected by the HDSS (469).

5.3.4. Statistical analyses

Patient characteristics were summarised using counts and proportions for categorical variables and medians and interquartile ranges (IQR) for continuous variables. A Pearson's chi-square test was used to test for differences in categorical variables, while a rank sum test was used for continuous variables.

A Cox regression model was used to determine the factors associated with transfer to another health facility, with all other outcomes treated as right censored. Bi-variate analyses were conducted with variables that were hypothesised to have a relationship with health facility transfer. All variables with $p<0.2$ were included in the multivariable Cox regression model. A parsimonious model was achieved using Wald tests. All analyses accounted for clustering at the clinic level with robust standard errors. These analyses were performed in Stata 15 (418).

Patients' village of residence was ascertained through health facility and Agincourt HDSS records. A mid-point Global Positioning System (GPS) coordinate of the village was used to calculate the distance between patients' residence and the health facility where they initiated ART. To assess the patterns of movement between health facilities, we obtained decimal degree coordinates for origin and destination health facilities by querying Google

Maps. Using ArcMap® 10.3.1 (420), the coordinates were imported to shapefiles with a WGS 1984 coordinate system. We then used ArcMap to spatially visualise the movements between health facilities.

We calculated geographical distances between the GPS coordinates for sending and destination health facilities. We compared the median transfer distances using the Kruskal-Wallis test for the equality of populations.

To visualise movements between health facilities within Agincourt HDSS, we used the Circlize package in R (419,421). A matrix of the volume of movements between health facilities was calculated for all transfers, stratified by the type of transfer (documented versus undocumented), and sex and pregnancy status at the time of ART initiation. These matrices were used to visualise flows between health facilities.

5.3.5. Ethics

Ethical approval was obtained from the London School of Hygiene and Tropical Medicine, the University of Witwatersrand and the Mpumalanga Department of Health.

5.4. Results

5.4.1. Population characteristics

Over the study period, 1017 patients met the LTFU criteria and were eligible for inclusion. Of these 1017 patients, 280 (27.5%) initiated ART for PMTCT, 737 (72.5%) met the ART initiation criteria for non-pregnant adults. 767 (75.4%) were females and 307 (30.2%) had ever migrated out of the HDSS (Table 5.1).

Table 5.1: Baseline characteristics of patients lost to follow-up and those who transferred, and factors associated with transfer to another facility

	LTFU	Transfers				
	1017	315			n=902	
DEMOGRAPHIC AND CLINIC VARIABLES	N (%)	N (%)	HR (95% CI)	p-values	aHR (95% CI)	p-values
Sex						
Female	767 (75.4)	258 (81.9)	Reference	__	Reference	__
Male	250 (24.6)	57 (18.1)	0.64 (0.43, 0.94)	0.024	0.76 (0.56, 1.03)	0.078
Age[4]						
18-29	333 (32.7)	117 (37.1)	1.18 (1.02, 1.37)	0.027		
30-44	484 (47.6)	147 (46.7)	Reference	__		
45-59	141 (13.9)	38 (12.1)	0.89 (0.50, 1.58)	0.681		
60+	58 (5.7)	13 (4.1)	0.84 (0.52, 1.34)	0.457		
Missing	1 (0.1)	0 (0)	__	__		
ART reason						
Non-PMTCT	737 (72.5)	233 (74.0)	Reference	__		
PMTCT	280 (27.5)	82 (26.0)	0.79 (0.50, 1.26)	0.325		
ART start year						
2014	211 (20.8)	58 (18.4)	0.71 (0.46, 1.09)	0.122	0.80 (0.55, 1.15)	0.229
2015	414 (40.7)	149 (47.3)	Reference	__	Reference	__

[4] Age was assessed on August 15, 2017 the date that data was extracted from the PIRL database

2016	350 (34.4)	100 (31.7)	0.85 (0.72, 1.01)	0.072	1.02 (0.82, 1.28)	0.827
2017	42 (4.1)	8 (2.5)	0.47 (0.23, 0.97)	0.042	0.49 (0.22, 1.10)	0.083
Time on ART						
≤3 months	325 (32.0)	89 (28.2)	Reference	__	Reference	__
3-6 months	190 (18.7)	62 (19.7)	1.18 (0.84, 1.66)	0.337	1.25 (0.83, 1.89)	0.275
6-12 months	228 (22.4)	79 (25.1)	1.37 (1.11, 1.70)	0.004	1.31 (1.04, 1.66)	0.024
12-24 months	219 (21.5)	76 (24.1)	1.54 (1.26, 1.87)	<0.001	1.73 (1.46, 2.06)	<0.001
>24 months	55 (5.4)	9 (2.9)	0.83 (0.38, 1.79)	0.637	0.98 (0.46, 2.08)	0.96
Baseline CD4[5]						
<100	206 (20.2)	64 (20.3)	1.29 (1.07, 1.56)	0.008	1.43 (1.15, 1.77)	0.001
100-199	185 (18.2)	46 (14.6)	0.94 (0.74, 1.18)	0.581	1.02 (0.84, 1.24)	0.857
200-349	261 (25.7)	69 (21.9)	Reference	__	Reference	__
350-499	193 (19.0)	72 (22.9)	1.51 (1.04, 2.19)	0.03	1.52 (1.03, 2.24)	0.037
500+	145 (14.3)	53 (16.8)	1.55 (1.12, 2.13)	0.007	1.57 (1.23, 2.01)	<0.001
Missing	27 (2.6)	11 (3.5)	__	__		
Baseline WHO stage						
I	722 (71.9)	230 (73.0)	Reference	__		
II	143 (14.1)	42 (13.3)	0.94 (0.73, 1.22)	0.651		
III	129 (12.7)	39 (12.4)	1.02 (0.68, 1.52)	0.924		
IV	10 (1.0)	1 (0.3)	0.36 (0.37, 3.56)	0.386		
Missing	13 (1.3)	3 (0.9)	__	__		
Refill schedule						

[5] Blood for a baseline CD4 was drawn on the date of HIV diagnosis

1 month	672 (66.1)	210 (66.7)	Reference	__		
2 months	233 (22.9)	71 (22.5)	0.94 (0.78, 1.13)	0.49		
3 months	79 (7.8)	30 (9.5)	1.30 (0.88, 1.93)	0.185		
>3 months	33 (3.2)	4 (1.3)	0.46 (0.17, 1.22)	0.117		
Health Facility						
Agincourt	272 (26.7)	66 (20.9)	Reference	__	Reference	__
Belfast	186 (18.3)	52 (16.5)	1.01 (0.97, 1.05)	0.573	1.18 (1.03, 1.35)	0.015
Cunningmore	58 (5.7)	21 (6.7)	1.71 (1.66, 1.76)	<0.001	2.04 (1.75, 2.37)	<0.001
Justicia	120 (11.8)	30 (9.5)	0.86 (0.83, 0.89)	<0.001	1.06 (0.86, 1.30)	0.594
Kildare	117 (11.5)	50 (15.9)	1.80 (1.76, 1.84)	<0.001	2.14 (1.92, 2.38)	<0.001
Bhubezi	166 (16.3)	51 (16.2)	1.08 (1.05, 1.12)	<0.001	1.55 (1.40, 1.72)	<0.001
Thulamahashe	25 (2.5)	4 (1.3)	0.62 (0.60, 0.63)	<0.001	0.62 (0.54, 0.71)	<0.001
Xanthia	73 (7.2)	41 (13.0)	2.61 (2.53, 2.68)	<0.001	3.12 (2.96, 3.27)	<0.001
Time since last appointment						
≤1 year	526 (51.7)	146 (46.3)	Reference	__		
1-2 years	369 (36.3)	134 (42.5)	1.18 (1.00, 1.40)	0.051		
>2 years	122 (12.0)	35 (11.1)	0.70 (0.43, 1.14)	0.156		
Ever been late for a scheduled clinic visit						
No	603 (59.3)	184 (58.4)	Reference	__		
Yes	414 (40.7)	131 (41.6)	1.12 (0.88, 1.41)	0.348		
	Median (IQR)	**Median (IQR)**				
Distance to the clinic (KM)[6]	3.91 (1.06, 6.36)	4.16 (0.65, 7.78)	1.03 (0.99, 1.08)	0.169	1.04 (1.01, 1.08)	0.019

[6] Distance to the clinic is calculated using GPS coordinates for the clinic and GPS coordinates of the centre of the village of residence

SOCIO-ECONOMIC VARIABLES				
Ever migrated outside the HDSS				
Permanent resident	710 (69.8)	208 (66.0)	Reference	__
Migrant	307 (30.2)	107 (34.0)	1.17 (0.96, 1.43)	0.127
Education				
No formal education	47 (4.6)	13 (4.1)	1.19 (0.64, 2.22)	0.58
Some primary	240 (23.6)	76 (24.1)	Reference	__
Completed primary	79 (7.8)	29 (9.2)	1.26 (0.76, 2.09)	0.365
Some secondary	5 (0.5)	2 (0.6)	2.27 (0.44, 11.71)	0.329
Completed secondary	204 (20.1)	63 (20.0)	1.09 (0.89, 1.33)	0.397
Completed tertiary	19 (1.9)	6 (1.9)	0.88 (0.38, 2.06)	0.773
Missing	423 (41.6)	126 (40.0)	__	__
Marital status				
Single	385 (37.9)	132 (41.9)	Reference	__
Married	56 (5.5)	13 (4.1)	0.61 (0.46, 0.81)	0.001
Separated	75 (7.4)	19 (6.0)	0.64 (0.36, 1.13)	0.125
Informal union	83 (8.2)	27 (8.6)	0.85 (0.58, 1.26)	0.42
Divorced	29 (2.8)	11 (3.5)	1.28 (0.60, 2.71)	0.521
Widowed	46 (4.5)	11 (3.5)	0.85 (0.35, 2.04)	0.711
Missing	343 (33.7)	102 (32.4)	__	__
SES quintile[7]				
1	134 (13.2)	35 (11.1)	Reference	__

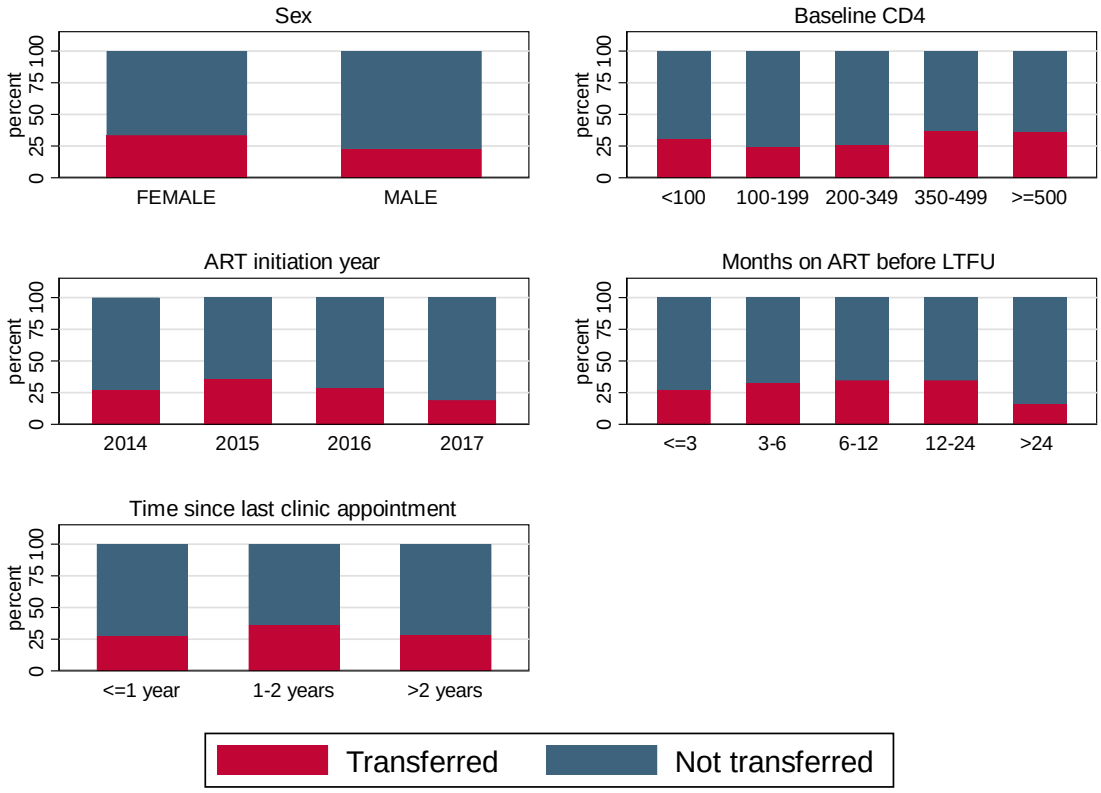
[7] SES quintile is an assets-based measure calculated at household level in the Agincourt HDSS

2	137 (13.5)	49 (15.6)	1.43 (0.97, 2.11)	0.068
3	129 (12.7)	39 (12.4)	1.28 (0.82, 2.02)	0.275
4	136 (13.4)	40 (12.7)	1.19 (0.82, 1.73)	0.358
5	103 (10.1)	33 (10.5)	1.31 (0.93, 1.85)	0.121
Missing	378 (37.2)	119 (37.8)	—	—

5.4.2. Transfer characteristics

Of 1017 patients LTFU, 315 (31.0%) had transferred to another facility. The proportion of transfers differed by sex (p=0.001), ART initiation year (p=0.02), time on ART (p=0.032), baseline CD4 (p=0.027), health facility (p<0.001), and time since last clinic appointment (p=0.021) (Figure 5.1).

Figure 5.1: Stacked bar graphs for variables for which the proportion of patients that transferred their care to another facility differs statistically

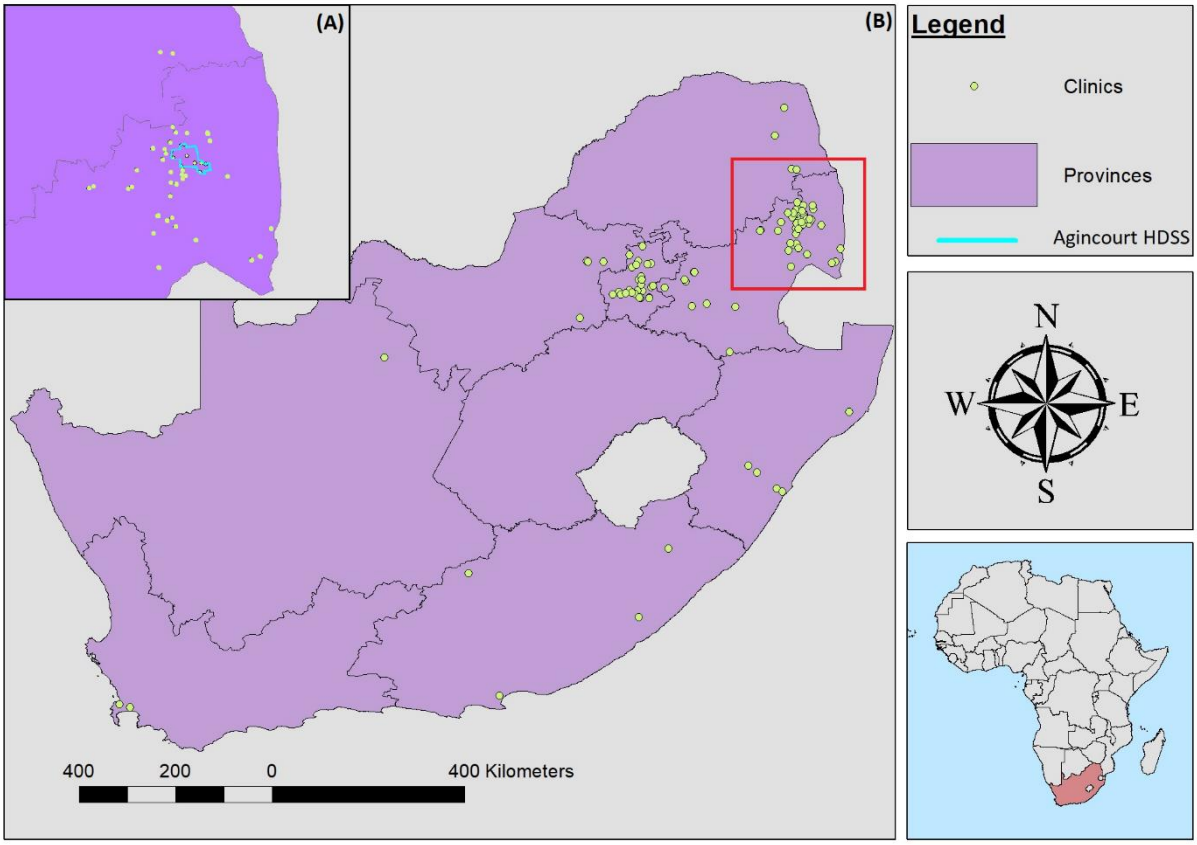


Of 315 transfers, 133 (42.2%) were documented at the sending health facility, 35 (11.1%) silent transfers were eventually reported to the sending health facility, and 147 (46.7%) remained undocumented at the sending health facility. Women were more likely to have transferred, with 82 of 280 (29%) women who initiated ART for PMTCT, and 176 of 487 (36%) non-pregnant women having transferred compared to 57of 250 (23%) men (p<0.001). Undocumented transfers were more common among women who initiated ART for PMTCT (69.5%, n=82), compared to (54.0%, n=176) for non-pregnant

women and (52.6%, n=57) for men (p=0.043). Undocumented transfers were more common among patients on shorter ART refill schedules (a proxy for care stability, p=0.043). One hundred forty-nine (47.3%) transfers occurred on or before the next scheduled clinical appointment, 43 (13.7%) occurred after the next scheduled appointment, but before the patient would have been considered LTFU, 111 (35.2%) happened after the patient would have been considered LTFU, and 12 (3.8%) were missing a transfer date.

One hundred thirty-one patients (41.6%) transferred to facilities within the HDSS, 89 (28.3%) to other health facilities in Mpumalanga province, 37 (11.8%) to Gauteng province, 25 (7.9%) to other provinces, 7 (2.2%) out of Mpumalanga province but with no new facility specified, 23 (7.3%) had transferred without any indication of their final destination, and 2 (0.6%) had transferred out of the country (1 to Mozambique and 1 to Zimbabwe). Transfers outside the HDSS were to economic hubs (Figure 5.2).

Figure 5.2: Maps of clinics attended for HIV care after transferring (A) near the HDSS and (B) within South Africa

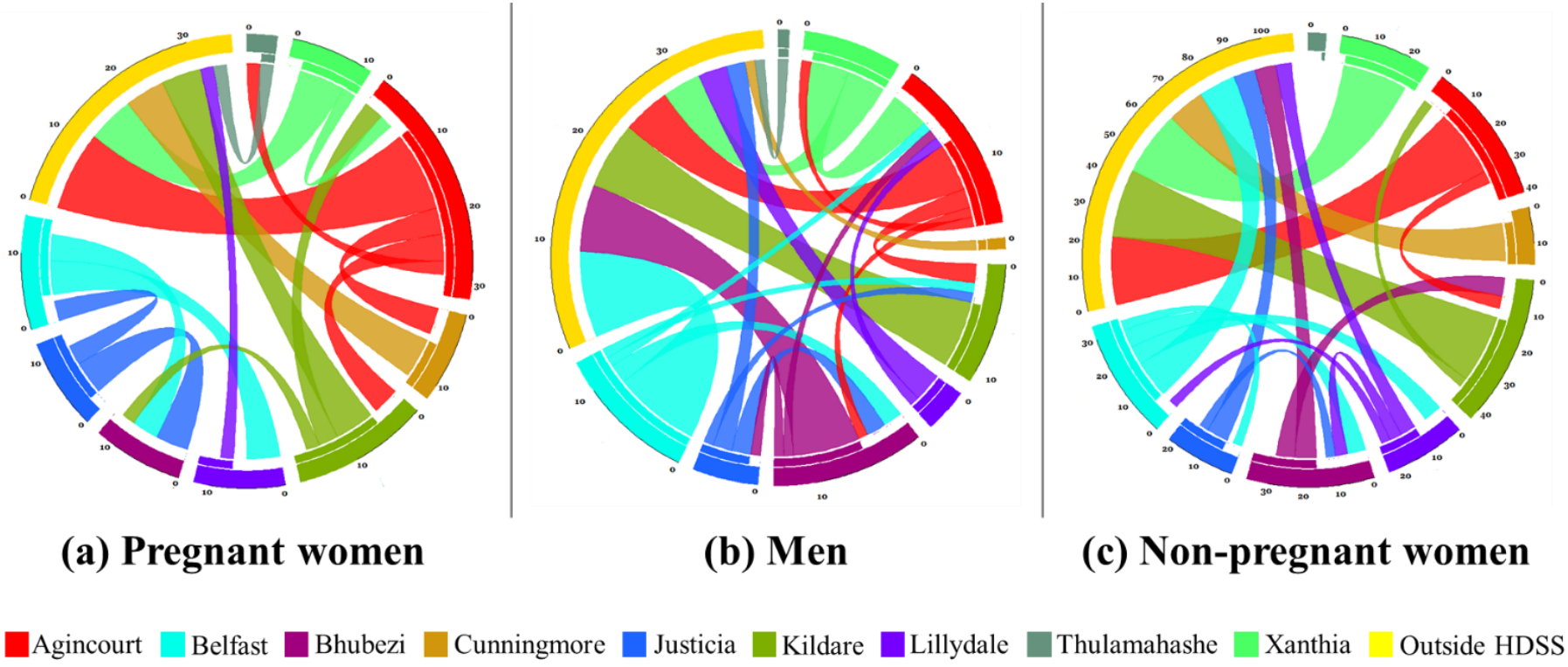


Men were most likely to transfer to facilities outside the HDSS with 39/57 (68.4%) transferring to an outside facility, compared to 109/176 (61.9%) non-pregnant women, and 36/82 (43.9%) women who initiated treatment for PMTCT (p=0.006) (Figure 5.3). Undocumented transfers were more common for transfers within the HDSS 105/131 (80.1%) compared to 77/184 (41.8%) transfers outside the HDSS (p<0.001) (Figure 5.4). The proportion of undocumented transfers reduced for transfers in provinces further away with transfers to the Eastern Cape, Western cape, Northern Cape, and North West provinces all being documented.

Patients were out of care for a median of 22.5 days (IQR: 1, 245). Women who initiated treatment for PMTCT were out of care for a median of 129 days (IQR: 1, 324), compared to 8 days (IQR: 1, 183) for non-pregnant women and 33 days (IQR: 1, 313) for men (p=0.0014). Patients who transferred to a health facility within the HDSS were out of care a median of 206 days (IQR: 8, 437) compared to 1 day (IQR: 1, 63.5) for those who transferred to health facilities outside the HDSS (p=0.0001). Undocumented transfers were out of care longer than documented transfers (p=0.0001).

The median transfer distance was 13.73 kilometres (IQR: 8.97, 88.29). This differed statistically by reason for ART initiation (p=0.0392), with women who initiated ART for PMTCT having a median transfer distance of 9.99 kilometres (IQR: 8.97, 59.47) compared to 17.02 kilometres (IQR: 9.22, 99.99) for non-PMTCT patients. Median transfer distance also differed by sex (p=0.0414) with men transferring further away, ART initiation year (p=0.0087), type of transfer (p=0.0001), and health facility (p=0.0001) (Figure 5.5). The transfer distance was weakly negatively correlated with health facility distance (between village of residence and origin health facility) (coefficient = -0.0718) and time spent out of care (coefficient=-0.2457). The median health facility distance was higher for transfers to health facilities within the HDSS compared to those outside the HDSS (p=0.0001). Distance to the origin and destination health facilities was weakly negatively correlated for all transfers (coefficient=-0.0803) and transfers to health facilities within the HDSS (coefficient=-0.1774).

Figure 5.3: Circle plots to visualise patient transfers in the Agincourt HDSS disaggregated by pregnancy status at ART initiation (largest 50% for each group)



*The origins and destinations of transfers are represented by the colour-coded circle segments. The length of each segment represents all the movements in and out of the particular health facility and therefore longer circle segments represent higher number of transfers to and from that clinic. The inner segment represents movements out of a clinic. Segments closer together represent clinics that are geographically close to each other (within reason). The volume of movements is indicated by the width of the flow and the direction of the flow is encoded by the sending facility colour.

Figure 5.4: Circle plots to visualise patient transfers in the Agincourt HDSS disaggregated by type of transfer (largest 50% for each group)

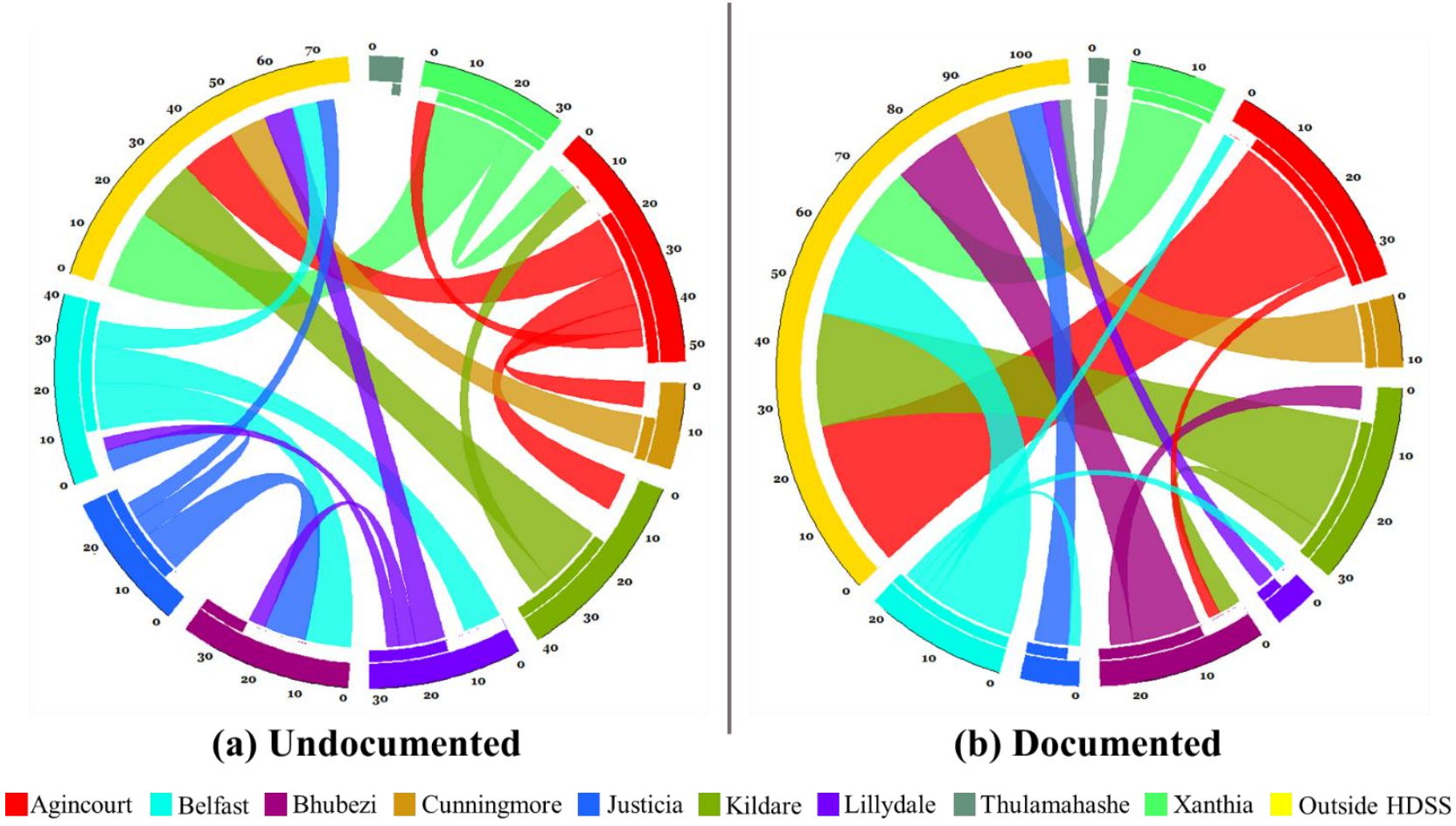
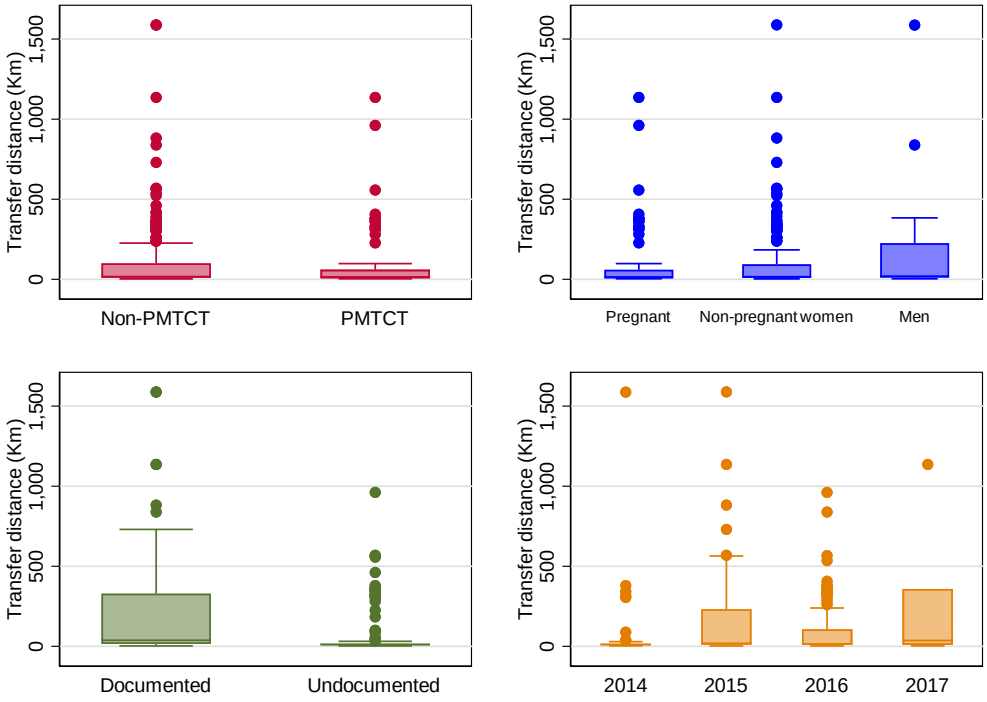


Figure 5.5: Box plots of transfer distances disaggregated by ART initiation reason, pregnancy status at ART initiation, type of transfer, and year of ART initiation



5.4.3. Factors associated with transfer to another clinic

In multivariable Cox regression, patients on ART for 12-24 months when they became LTFU (aHR: 1.73, 95% CI: 1.46-2.06), and patients with baseline CD4 (<100 cells/μL aHR: 1.43, 1.15, 1.77; 350-499 cells/μL aHR: 1.52, 1.03-2.24; ≥500 cells/μL aHR: 1.57, 1.23-2.01) were more likely to have transferred to another health facility. The hazard of transfer increased with increasing distance between a patient's village of residence and their health facility (aHR: 1.04, 1.01-1.08) (Table 5.1).

5.5. Discussion

Within a cohort of South African patients who had been categorised as LTFU, we found evidence of HIV care continuation, with 31% transferring their care to another facility. Similar to other studies (15,102), we found high levels of undocumented transfer. Women were more likely than men to transfer their care, with women who initiated treatment for PMTCT the least likely to have their transfer documented at the health facility where they initiated treatment, and the most likely to transfer to a health facility within the study area.

Mobility during pregnancy and after childbirth are high (102,443,444,456), and transfer patterns may reflect this. Longer time on ART, higher baseline CD4 and further distance to the health facility from patient residences were associated with higher risk of transferring to another facility.

Most transfers outside the HDSS study area were to economic hubs, including agricultural and mining towns, suggesting that these transfers were due to labour migration which is common in South Africa (472). As earlier studies suggested that PLHIV were moving back home to die (459,473), this migration is encouraging, suggesting that PLHIV feel healthy enough to work, and countering challenges early in the epidemic, when HIV mortality and morbidity disproportionately affected people of working-age (474). In our study, patients who initiated ART in later years transferred further away, suggesting programme expansion has led to healthier PLHIV initiating treatment, who may be more mobile. However, given that patients with CD4<100 cells/μL were more likely to transfer this might also show that there is still a substantial cohort of sicker patients moving back home to die.

The weak negative correlation between origin health facility distance and transfer distance may suggest "clinic shopping" (102), as patients who transferred to another health facility within the HDSS attended an origin health facility further from their village of residence. It might also reflect a rational decision to move to a closer facility as scale-up increases options. However, as patients who transferred to health facilities within the study area were more likely to be undocumented and were out of care longer than those who transferred outside the HDSS, other mechanisms such as stigma, fear of accidental disclosure, fear of healthcare worker reactions on reengaging at the same health facility, and a desire for anonymity may influence patients' decision to "shop" around local health facilities (102,245,283,285,289,329). Furthermore, as undocumented transfers were out of care longer, they may represent a loss of motivation to stay engaged in care. Women who initiated treatment for PMTCT were out of care longer, more likely to transfer to a health facility within the HDSS and healthier in terms of baseline CD4 and WHO staging, therefore "clinic shopping" might be more common for healthier, asymptomatic patients or women with young children may be less

inclined to migrate outside the HDSS. Longer time out of care could pose higher risks for mortality, vertical and horizontal transmission (187,456,457), suggesting the need for tailored interventions to address treatment interruptions among this population (475,476).

Undocumented transfers were common, especially for women who initiated treatment for PMTCT, less stable patients and transfers to health facilities within the HDSS. Undocumented transfers present several problems including the risk of amplification and transmission of HIV drug resistance when experienced patients are offered regimens with no therapeutic benefit (445). Furthermore, this can lead to over-estimation of the number of people newly initiated on ART and ever initiated on ART, biasing ART programme indicators. Finally, these undocumented outcomes affect estimations of retention in HIV care (15).

This study adds to extant evidence examining continued care among individuals considered LTFU after ART initiation in sub-Saharan Africa (14,17,54,477), and particularly transfer to other facilities (18,102). We provide detailed comparisons of transfers by reason for ART initiation, on types of transfers and factors associated with transferring to another facility. Our use of linked demographic surveillance and clinical data to ascertain outcomes for patients considered LTFU allowed us to utilise unique HDSS identifiers to follow patients between health facilities. However, not all clinic records were linked to a demographic surveillance record, which is a limitation to our analyses. Although unique identifiers are recommended by the World Health Organisation, these are not feasible in many settings (370). Facility-linked data improves the ability to follow patients and to monitor their long-term outcomes (18,371). Transfers to health facilities further away from the HDSS were more likely to be documented. However, we could only check the records of health facilities within the study area and might have missed undocumented transfers to health facilities outside the HDSS, potentially introducing bias. Undocumented transfers should become less prevalent with increased use of national IDs at health facilities and as TIER.Net becomes fully networked. The use of a centre point for each village to represent residence may introduce some bias to our findings. Furthermore, searching for patient outcomes

involved time consuming manual procedures and is more feasible as a research exercise than within routine clinical follow-up. Other data sources like the national reference lab database might improve ascertainment of transfers and has been shown to be feasible (102). Finally, given the small numbers, these results should be interpreted with caution.

5.6. Conclusions

Our findings suggest that an HIV diagnosis may no longer be viewed as a major impediment and people are getting on with their lives, with many transfers appearing linked to labour migration. We highlight the importance of ascertaining undocumented transfers as these individuals stay longer out of care, which has implications for onward transmission. As ART programmes continue to expand in sub-Saharan Africa, nationally linked treatment databases would improve the capture of transfers in highly mobile populations, to enable those who wish to transfer to do so, and to ensure continuity of care among migrants.

6. Paper C: Misreporting of patient outcomes in the South African national HIV treatment database: consequences for programme planning, monitoring and evaluation

Introduction to chapter:

This paper (C) uses data from the record review and tracing study described in chapter 3 to investigate objective 2. This paper was conceived as a means to appraise the performance of routine data sources (represented by electronic medical records) in accurately reporting patient treatment outcomes. The paper compares treatment outcomes ascertained through the record review and tracing study to outcomes reported in TIER.Net (South Africa's national HIV treatment database). The rationale for this exercise is to measure the bias of relying solely on one data source to measure retention in care. I also compare the magnitude of misclassification of treatment outcomes by sex and pregnancy status at ART initiation in order to explore whether misclassification differs significantly for pregnant and postpartum WLHIV compared to other adults on ART.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1603703	**Title**	Mr
First Name(s)	David		
Surname/Family Name	Etoori		
Thesis Title	A mixed methods study using linked demographic surveillance and health facility data to investigate and compare loss to follow-up among women living with HIV who initiated antiretroviral therapy during pregnancy under Option B+ in Agincourt, South Africa		
Primary Supervisor	Alison Wringe		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Frontiers in Public Health		
When was the work published?	2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	No		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the study, planned and executed the fieldwork. Supervised data collection in the field. I conducted all the pertinent analyses and interpreted the findings. I drafted the manuscript.

SECTION E

Student Signature	[redacted]
Date	14/07/2020

Supervisor Signature	[redacted]
Date	14/07/2020

6.1. Abstract

Background: Monitoring progress toward global treatment targets using HIV programme data in sub-Saharan Africa has proved challenging. Constraints in routine data collection and reporting can lead to biased estimates of treatment outcomes. In 2010, South Africa introduced an electronic patient monitoring system for HIV patient visits, TIER.Net. We compare treatment status and outcomes recorded in TIER.Net to outcomes ascertained through detailed record review and tracing in order to assess discrepancies and biases in retention and mortality rates.

Methods: The Agincourt Health and Demographic Surveillance System (HDSS) in north-eastern South Africa is served by eight public primary healthcare facilities. Since 2014, HIV patient visits are logged electronically at these clinics, with patient records individually linked to their HDSS record. These data were used to generate a list of patients >90 days late for their last scheduled clinic visit and deemed lost to follow-up (LTFU). Patient outcomes were ascertained through a review of the TIER.Net database, physical patient files, registers kept by two non-government organisations that assist with patient tracing, cross-referencing with the HDSS records and supplementary physical tracing. Descriptive statistics were used to compare patient outcomes reported in TIER.Net to their outcome ascertained in the study.

Results: Of 1074 patients that were eligible for this analysis, TIER.Net classified 533 (49.6%) as LTFU, 80 (7.4%) as deceased, and 186 (17.3%) as transferred out. TIER.Net misclassified 36% of patient outcomes, overestimating LTFU and underestimating mortality and transfers out. TIER.Net missed 40% of deaths and 43% of transfers out. Patients categorized as LTFU in TIER.Net were more likely to be misclassified than patients classified as deceased or transferred out.

Discussion: Misclassification of patient outcomes in TIER.Net has consequences for programme forecasting, monitoring and evaluation. Undocumented transfers accounted for the majority of misclassification, suggesting that the transfer process between clinics should be improved for more accurate reporting of patient outcomes. Processes that lead to correct classification of patient status including patient tracing should be

strengthened. Clinics could cross-check all available data sources before classifying patients as LTFU. Programme evaluators and modelers could consider using correction factors to improve estimates of outcomes from TIER.Net.

6.2. Introduction

At the end of 2017, it was estimated that there were 36.9 million people living with HIV (PLHIV) worldwide, with 70% of the disease burden situated in sub-Saharan Africa (24,448). The World Health Organisation's (WHO) revised HIV treatment guidelines in 2015 call for immediate provision of lifelong antiretroviral therapy (ART) to all people testing positive for HIV. By the end of 2017, 60% of PLHIV in sub-Saharan Africa were on ART (24,448). Whilst ART initiation rates have been increasing over time, in order to reduce HIV transmission rates and achieve 90-90-90 AIDS elimination goals, there is a need for accelerated increases in treatment adherence and retention in care (98,478,479). South Africa has the largest population of PLHIV worldwide, with an estimated 18.8% of the adult population aged 15-49 years old living with HIV, representing 7.2 million people (24,448). By the end of 2018, an estimated 68% of PLHIV in South Africa were on ART (24,448).

The rapid growth in access to ART has accentuated the need for an affordable and accurate way to monitor and evaluate treatment programmes (480–482), including documenting the number of people alive and on treatment, and programme impact on mortality. In the past, the progress of patients on ART was mainly monitored through patient cohorts (483) and tallying numbers of services rendered to inform resource allocation (482). However, evaluation of HIV programmes has proved challenging due to multiple data constraints. These include concerns about data reliability (482), and continued use of paper registers which often lack unique identifiers, suffer from incompleteness (99), and are cumbersome to use with increasing patient numbers and length of patient follow-up (100,101). Another major concern is "silent transfers" whereby patients change clinics informally and without accompanying documentation, a phenomenon which has become more prevalent with the expansion of ART programmes (15,484). As a result, there is concern that many high-burden countries are ill-equipped to report on the outcomes of patients in care and on treatment (480,481,485–487).

In order to address these concerns, many countries are scaling-up the use of electronic patient registers (100). However, challenges persist including insufficient linkages between clinics (99), insufficient training of staff who are

responsible for entering this information (99), and staff shortages (488–491), resulting in some staff responsible for data management being stretched across multiple roles (492). This sometimes leads to poor workflow, and staff resistance which results in poor change management. Privacy and security issues (492) are also a major concern.

In 2010, South Africa adopted TIER.Net, a three-tiered monitoring approach involving paper registers (TIER 1 – recommended for facilities with less than 500 patients), an offline electronic register (TIER 2 – recommended for facilities with 500-2000 patients) and networked electronic medical records (TIER 3 – recommended for facilities with more than 2000 patients) (100). This allowed for different tiers to be implemented in each facility based on the context and resources available at the time of implementation and typically involved a phased evolution, beginning with preparation for TIER.Net, installation and training, back capturing, live capturing and finally a live site able to produce monthly and quarterly reports with staff on-site to manage it. In 2014, an estimated 3000 out of 4000 public sector clinics in South Africa were using TIER.Net (493,494) in one of the three phases of implementation. As of 2017, TIER 3 was still in its pilot phase (495).

ART patient outcomes have evolved since the start of national HIV treatment programmes. In several cohort studies of ART programmes in sub-Saharan Africa, there have been reports of higher rates of LTFU among patients who initiated ART in later years compared to earlier years (114,450,451). This may be explained by patients increasingly initiating treatment while less severely ill (453), as well as a negative consequence of patient numbers increasing such as facility workloads (452), raising concerns about the sustainability of these programmes. Some systematic reviews have shown that the percentage of patients LTFU who have died has decreased in later years as eligibility criteria have evolved to include less immunologically compromised patients, and as the proportion of patients LTFU has increased (14,15). Furthermore, scale-up and decentralisation of these programmes means ART can be offered at clinics closer to patients' homes, which may serve as an incentive to self-transfer in order to continue treatment at more convenient locations (15,53).

Unpublished TIER.Net analyses from 2018 showed LTFU rates to range from 11%-15% in the first three months and from 27%-34% in the first year of ART (Y.Pillay, HIV Think-tank update, March 19, 2019). The high percentages of LTFU present many issues. Firstly, if these patients have really stopped ART then they have a higher mortality risk (56,455,496), and are more likely to transmit HIV (48,187,456,457). Given that patients that are LTFU have poorer outcomes, LTFU can also through misclassification bias event rates such as mortality downwards (497), leading to biased performance indicators for ART programmes. Accurate mortality rates are also important as they are used as parameters for projections such as in the UNAIDS spectrum package (498,499).

We compare patient outcomes recorded in TIER.Net to the outcomes ascertained through a record review and tracing study for patients deemed lost to follow-up in eight public sector health facilities in rural north-eastern South Africa. We aimed to assess misreporting in TIER.Net and potential biases in the national programme statistics reported from the TIER.Net database.

6.3. Methods

6.3.1. Setting

The Agincourt Health and Demographic Surveillance System (Agincourt HDSS) is located in rural north-eastern South Africa, in Mpumalanga province which has the second highest prevalence of HIV at 14.1% (468). HIV prevalence among people 15 years of age or older in the HDSS was estimated at 19.4% in 2010 (398). The Agincourt HDSS comprises of 31 villages covering an area of 475 square kilometres with an estimated population of 115,000 people (20,469).

There are five primary health facilities and three secondary community health centres located within the Agincourt HDSS. Every HIV-positive patient has a clinical file that is opened when they first register at an ART clinic and updated at each clinic visit. Following the clinic visit, visit-level information from the patient file is entered into the national electronic database, TIER.Net. All health facilities routinely trace patients that are late for a scheduled clinic appointment. This tracing is done in conjunction with two non-profit

organisations, Right to Care (RtC) and Home-Based Carers (HBC). Clinic staff must contact all patients first by phone and if this does not yield a satisfactory outcome, a home visit is organised. Patients are classified as lost to follow-up (LTFU) if they have not returned 90 days after their scheduled visit.

6.3.2. Demographic surveillance

Data collection aims to capture all demographic events for the Agincourt HDSS population. Fertility, mortality and migration data are based on a comprehensive household registration system that has been in operation since 1992. Following the baseline demographic surveillance survey in 1992 and three update rounds until 1998, the site has conducted annual surveys since 1999 (20,413,414,470). Trained fieldworkers visit each household and interview the most knowledgeable adult available. During the visit, individual-level information on all household members is checked and updated and any events that have occurred since the last census round are recorded. Starting in 2017, data have been collected utilising an electronic data collection system using tablets (471).

6.3.3. Point-of-contact interactive record linkage (PIRL)

A key element of the data infrastructure for this study consists of HIV patient visit logs collected by a study fieldworker in the health facilities that provide ART in the area. This work started in April 2014 at seven government facilities and was extended in 2016 to include one additional health facility. In addition to logging patient visits, these records are linked to the Agincourt HDSS using a procedure that we have previously described as Point-of-Contact Interactive Record Linkage (PIRL) (103,104). In brief, a fieldworker conducts a short uptake interview with patients in the waiting area of the clinic. Patients who consent are asked to declare a few personal identifiers that are used to search a local copy of the Agincourt HDSS database using a probabilistic algorithm. Matches are confirmed in interaction with the patients, and the names of other household members are used as a key attribute to adjudicate between possible matches.

6.3.4. Record review and tracing study

Through the PIRL database, we identified patients who were more than 90 days late for a scheduled clinic appointment from HIV services on August 15, 2017 (the date of data extraction) at any of the eight health facilities located in

the Agincourt HDSS area. These patients were recruited into a cohort and followed up to ascertain their treatment and vital status i.e. whether they were still alive.

All PLHIV aged 18 years or over, who had ever declared residency in Agincourt HDSS, and had enrolled in the HIV treatment and care programme since 2014 (after the Agincourt HDSS record linkage was established at the health facilities) were eligible for inclusion in the study.

Trained and supervised fieldworkers conducted a thorough record review, comparing the list of patients LTFU against (a) TIER.Net (b) patient clinic files, and (c) logbooks kept by the RtC and the HBC. The PIRL database was also reviewed for duplicate patients (different clinical records linking to the same individual in the Agincourt HDSS database, which was taken as evidence of silent transfers), and residency and vital status were extracted from the Agincourt HDSS database. This was done on a case-by-case basis.

HBC conducted a visit to the households of all patients for whom a definitive outcome (defined as death, transfer out, stopped ART, migrated, re-engaged in care, and alive with ART status unknown) could not be established, or for whom routine patient tracing was not done. Finally, all patients who remained LTFU after the HBC visit, were searched for in TIER.Net databases at clinics in close proximity to their home residence to capture any further silent transfers.

We also reviewed the records for a stratified random sample of 162 patient records who were not LTFU as of August 15, 2017, in order to assess whether TIER.Net misclassified any patients that were still in care. This sample was chosen to include 18 patients from every clinic (6 men, 6 non-pregnant women and 6 women who initiated ART while pregnant) with the exception of one clinic which had recently merged with another, and from which we sampled 18 patients who had enrolled whilst in each of the clinics prior to the merger.

Table 6. 1: Definitions of terms used

Term	Definition
The last appointment	The last scheduled appointment for each patient as of August 15, 2017, when we generated the list of patients deemed LTFU.
TIER.Net treatment status	The treatment status of the patient as recorded in TIER.Net during the comprehensive record review.
The final outcome	The outcome ascertained for each patient through the record review and tracing process.
Data error	A situation in which a patient was found still in care and <90 days late for their last appointment. Some data errors occurred because visit dates had not been properly entered in the PIRL database. Patients categorised as a data error were excluded from our analyses.
Re-engagement	A patient was considered to have re-engaged in care if they were found to be still in care at the same clinic where they initiated treatment but were >90 days late for their last appointment (had been LTFU).
Transfer out	A patient was considered to have transferred if they had either reported taking treatment at another clinic (for clinics outside the Agincourt HDSS), if their ART initiation clinic had communicated with and ascertained their transfer to another clinic, or if there was record of them collecting treatment at another clinic within the Agincourt HDSS.
Migration	A patient was classified as having migrated out of the study site if they were recorded as having migrated through the Agincourt HDSS demographic surveillance, this migration event happened after their last clinic visit date and there was no proof that they were taking treatment at another facility.

Alive and not on ART	A patient was considered alive and not on ART if they had been found and had said they had stopped ART, denied their HIV status or refused to return to the clinic.
Alive with ART status unknown	A patient was considered alive with ART status unknown if they were found to still be alive through the most recent Agincourt HDSS demographic surveillance, with a surveillance date after their last clinic visit and there was no proof that they were taking treatment at any facility.

6.3.5. Statistical analyses

For patients included in the record review and tracing study, we calculated counts and proportions for socio-demographic and baseline clinical characteristics, TIER.Net treatment status, the final outcome, and cross-tabulated TIER.Net status and the final outcome.

To assess the degree and direction of misreporting of patient outcomes in TIER.Net, we graphically present TIER.Net treatment status and the final outcome proportions by some selected patient characteristics. A Pearson's chi-square test was used to compare whether TIER.Net treatment status and the final outcome varied by all the categorical variables. We also present a cross-tabulation of patient outcomes from the two sources.

A binary outcome variable was created to indicate whether TIER.Net had misclassified a patient's treatment status, with a second outcome created to identify whether the patient was recorded as LTFU in TIER.Net. All cases where an electronic record could not be found were removed from further analysis.

To explore factors associated with misclassification in TIER.Net, we ran bi-variate analyses with patient-level treatment characteristics, demographic characteristics and facility-level characteristics. All variables with $p<0.1$ were included in the multivariable logistic regression model. A parsimonious model was achieved using Wald tests. This same procedure was followed in order to understand what factors were associated with being reported LTFU in

TIER.Net. All analyses were conducted in Stata 15 (418) and all data visualisation was done using R (419).

6.3.6. Ethics

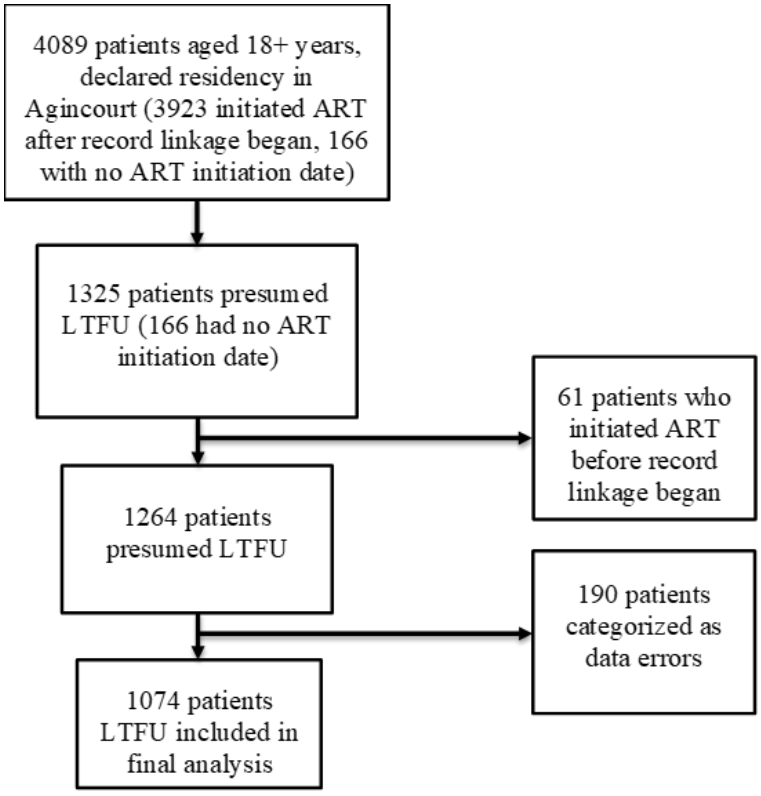
Ethical approval was obtained from the London School of Hygiene and Tropical Medicine, the University of Witwatersrand and the Mpumalanga Department of health.

6.4. Results

6.4.1. Database population characteristics

Over the study period, 4089 patients were added to the PIRL database and met the inclusion criteria. Of these 4089, 1325 (32.4%) met the LTFU criteria and were eligible for inclusion into the record review and tracing study. Of these 1325 patients, 166 (12.5%) did not have an ART initiation date and were assumed to be pre-ART. Further investigation of these 166 patients found 46 (27.7%) had initiated ART after record linkage, 59 (35.5%) were genuine pre-ART patients and 61(36.7%) had initiated ART before record linkage began. These 61 patients were excluded from further analyses. Of the remaining 1264 patients, 190 (15.0%) were found to have data errors (mostly due to missing clinic visits in the PIRL database) and were excluded from further analysis (Figure 6.1).

Figure 6.1: Numbers of patients that were eligible at each stage and the number of patients excluded at each stage



Of 1074 remaining patients, 280 (26.1%) initiated ART for prevention of mother-to-child transmission (PMTCT), 737 (68.6%) met the ART initiation criteria for non-pregnant adults, and 57 (5.3%) had not initiated ART yet (pre-ART).

Thirteen (8.0%) of the 162 patients still in care were excluded from the analysis because they had not declared residency in the HDSS. The remaining 149 from the random sample of patients still in care were also assessed to see if misclassification also occurred for those who remained engaged in care (Table 6.2).

Table 6.2: Database population characteristics

	Not in sample	Sample		
	Still in care	Still in care	LTFU	Data error
	2615	149	1074	190
	N (%)	N (%)	N (%)	N (%)
Sex				
Female	2016 (77.1)	94 (63.1)	807 (75.1)	147 (77.4)
Male	599 (22.9)	55 (36.9)	266 (24.8)	42 (22.1)
Missing	0 (0)	0 (0)	1 (0.1)	1 (0.5)
Age				
18-29	559 (21.4)	18 (12.1)	350 (32.6)	39 (20.5)
30-44	1298 (49.6)	76 (51.0)	509 (47.4)	102 (53.7)
45-59	544 (20.8)	36 (24.2)	152 (14.1)	38 (20.0)
60+	212 (8.1)	19 (12.7)	60 (5.6)	10 (5.3)
Missing	2 (0.1)	0 (0)	3 (0.3)	1 (0.5)
ART reason				
Non-PMTCT women	1533 (58.6)	54 (36.2)	487 (45.3)	101 (53.1)
PMTCT women	431 (16.5)	40 (26.9)	280 (26.1)	45 (23.7)
Men	598 (22.9)	55 (36.9)	250 (23.3)	42 (22.1)
Pre-ART	0 (0)	0 (0)	57 (5.3)	2 (1.1)
Missing	53 (2.0)	0 (0)	0 (0)	0 (0)
ART start year				
2014	320 (12.2)	62 (41.6)	211 (19.6)	41 (21.6)
2015	773 (29.6)	42 (28.2)	414 (38.6)	84 (44.2)
2016	951 (36.4)	32 (21.5)	350 (32.6)	54 (28.4)
2017	571 (21.8)	13 (8.7)	42 (3.9)	9 (4.7)
Missing	0 (0)	0 (0)	57 (5.3)	2 (1.1)
Time on ART				
<=3 months	190 (7.3)	10 (6.7)	325 (30.3)	15 (7.9)
3-6 months	260 (9.9)	2 (1.3)	190 (17.7)	9 (4.7)
6-12 months	560 (21.4)	23 (15.4)	228 (21.2)	41 (21.6)
12-24 months	842 (32.2)	40 (26.8)	219 (20.4)	75 (39.5)
>24 months	763 (29.2)	74 (49.7)	55 (5.1)	48 (25.3)
Missing	0 (0)	0 (0)	57 (5.3)	2 (1.1)
Baseline CD4				
<100	468 (17.9)	25 (16.8)	220 (20.5)	20 (10.5)
100-199	476 (18.2)	18 (12.1)	193 (18.0)	37 (19.5)
200-349	656 (25.1)	40 (26.9)	267 (24.9)	50 (26.3)
350-499	464 (17.7)	34 (22.8)	198 (18.4)	50 (26.3)
500+	455 (17.4)	30 920.1)	164 (15.3)	33 (17.4)
Missing	96 (3.7)	2 (1.3)	32 (3.0)	0 (0)
Refill schedule				
1 month	1056 (40.4)	38 (25.5)	714 (66.5)	72 (37.9)
2 months	1016 (38.8)	77 (33.7)	240 (22.3)	64 (33.7)

3 months	314 (12.0)	26 (17.4)	86 (8.0)	17 (8.9)
>3 months	229 (8.8)	8 (5.4)	34 (3.2)	37 (19.5)
Health Facility				
Agincourt	540 (20.6)	18 (12.1)	282 (26.3)	160 (84.2)
Belfast	379 (14.5)	16 (10.7)	191 (17.8)	2 (1.0)
Cunningmore	227 (8.7)	15 (10.1)	74 (6.9)	0 (0)
Justicia	284 (10.9)	18 (12.1)	122 (11.4)	3 (1.6)
Kildare	462 (17.7)	18 (12.1)	120 (11.1)	6 (3.2)
Lillydale/Bhubezi	487 (18.6)	35 (23.5)	181 (16.8)	11 (5.8)
Thulamahashe	89 (3.4)	14 (9.4)	27 (2.5)	8 (4.2)
Xanthia	147 (5.6)	15 (10.1)	77 (7.2)	0 (0)
Agincourt HDSS outcome				
Still in HDSS	1827 (69.9)	107 (71.8)	530 (49.3)	122 (64.2)
Deceased	2 (0.1)	0 (0)	83 (7.7)	1 (0.5)
Migrated	503 (19.2)	37 (24.8)	282 (26.3)	56 (29.5)
Not linked	283 (10.8)	5 (3.4)	179 (16.7)	11 (5.8)
Time since last appointment				
<=1 year	—	—	539 (50.2)	—
1-2 years	—	—	392 (36.5)	—
>2 years	—	—	143 (13.3)	—

Not in sample: All patients eligible for the study but not LTFU in the PIRL database and not included in the still in care sample; **Sample:** All patients included in the study (149 still in care, 1264 LTFU=1074 really LTFU + 190 data errors); **Data error:** Patients included as LTFU but found to be still in care and <90 days late for their last appointment; For ART start year data from 2017 reflects number of ART initiations up to mid-August when data extraction occurred

6.4.2. TIER.Net treatment status

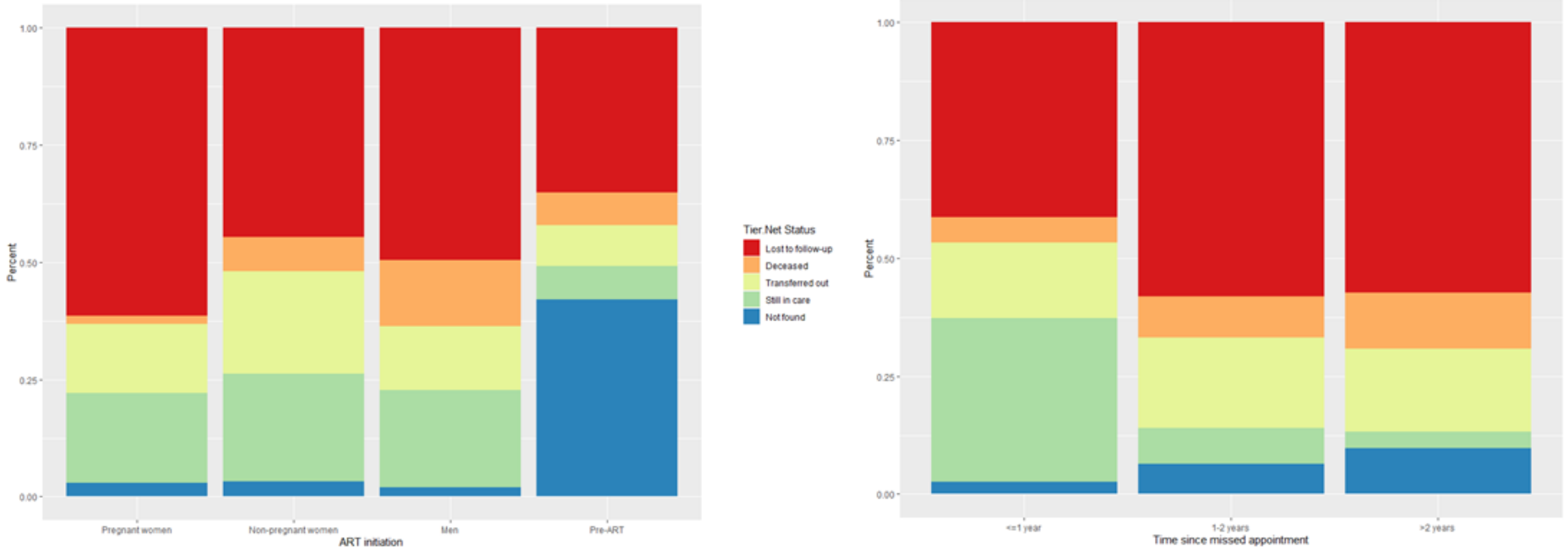
Of the 1074 patients who remained eligible for this analysis, 533 (49.6%) were categorized as LTFU, 222 (20.7%) as still in care, 186 (17.3%) as transferred out, 80 (7.5%) as deceased, and 53 (4.9%) could not be found in the TIER.Net database (Table 6.3).

There was a statistically significant difference (all $p<0.001$) in the TIER.Net treatment status by sex, age, ART initiation status and reason, year of ART initiation, baseline CD4 count, time on ART, clinic visit schedule, health facility, and time since a missed appointment (Figure 6.2). Women who initiated ART for PMTCT were less likely to be categorized as deceased and more likely to be LTFU. All 149 patients sampled as still in care were also reported as still in care in TIER.Net.

Table 6.3: Disaggregated TIER.Net treatment status

	TIER.Net status					
	LTFU	Deceased	Transferred	Still in care	Not found	Total
	533	80	186	222	53	1074
	n (%)	n (%)	n (%)	n (%)	n (%)	
Age						
18-29	191 (54.6)	8 (2.3)	60 (17.1)	74 (21.1)	17 (4.9)	350
30-44	253 (49.7)	41 (8.1)	88 (17.3)	103 (20.2)	24 (4.7)	509
45-59	66 (43.4)	18 (11.8)	28 (18.4)	32 (21.0)	8 (5.3)	152
60+	23 (38.3)	13 (21.7)	9 (15.0)	12 (20.0)	3 (5.0)	60
Missing	0 (0)	0 (0)	1 (33.3)	1 (33.3)	1 (33.3)	3
ART initiation						
Pregnant women	172 (61.4)	5 (1.8)	41 (14.6)	54 (19.3)	8 (2.9)	280
Non-pregnant women	217 (44.6)	36 (7.4)	106 (21.8)	112 (23.0)	16 (3.3)	487
Men	124 (49.6)	35 (14.0)	34 (13.6)	52 (20.8)	5 (2.0)	250
Pre-ART	20 (35.1)	4 (7.0)	5 (8.8)	4 (7.0)	24 (42.1)	57
ART start year						
2014	108 (51.2)	25 (11.8)	30 (14.2)	41 (19.4)	7 (3.3)	211
2015	213 (51.4)	27 (6.5)	85 (20.5)	76 (18.4)	13 (3.1)	414
2016	179 (51.1)	20 (5.7)	62 (17.7)	81 (23.1)	8 (2.3)	350
2017	13 (30.9)	4 (9.5)	4 (9.5)	20 (47.6)	1 (2.4)	42
Missing	20 (35.1)	4 (7.0)	5 (8.8)	4 (7.0)	24 (42.1)	57
Time on ART						
<=3 months	184 (56.6)	34 (10.5)	49 (15.1)	46 (14.1)	12 (3.7)	325
3-6 months	115 (60.5)	8 (4.2)	34 (17.9)	26 (13.7)	7 (3.7)	190
6-12 months	116 (50.9)	16 (7.0)	50 (21.9)	42 (18.4)	4 (1.7)	228
12-24 months	82 (37.4)	12 (5.5)	45 (20.5)	76 (34.7)	4 (1.8)	219
>24 months	16 (29.1)	6 (10.9)	3 (5.4)	28 (50.9)	2 (3.6)	55
Missing	20 (35.1)	4 (7.0)	5 (8.8)	4 (7.0)	24 (42.1)	57
Baseline CD4						
<100	92 (41.8)	42 (19.1)	43 (19.5)	33 (15.0)	10 (4.5)	220
100-199	108 (56.0)	15 (7.8)	28 (14.5)	37 (19.2)	5 (2.6)	193
200-349	147 (55.1)	11 (4.1)	42 (15.7)	58 (21.7)	9 (3.4)	267
350-499	96 (48.5)	6 (3.0)	43 (21.7)	45 (22.7)	8 (4.0)	198
500+	70 (42.7)	5 (3.0)	28 (17.1)	46 (28.0)	15 (9.1)	164
Missing	20 (62.5)	1 (3.1)	2 (6.2)	3 (9.4)	6 (18.7)	32
Time since last appointment						
<=1 year	223 (41.4)	29 (5.4)	86 (16.0)	187 (34.7)	14 (2.6)	539
1-2 years	228 (58.2)	34 (8.7)	75 (19.1)	30 (7.6)	25 (6.4)	392
>2 years	82 (57.3)	17 (11.9)	25 (17.5)	5 (3.5)	14 (9.8)	143

Figure 6.2: TIER.Net treatment status by (a) ART initiation status and (b) time since the last clinic appointment



(a)

PMTCT (pregnant women) less likely to have died and more likely to be LTFU. Men most likely to have died, second most likely to be LTFU. Pre-ART more likely not to have an electronic record. Not found is mostly pre-ART patients. Might be an electronic record was never started for them. It might also be that they got a new file number once they initiated ART.

(b)

Percentage deceased and LTFU increases the longer a patient has not been seen at the clinic.

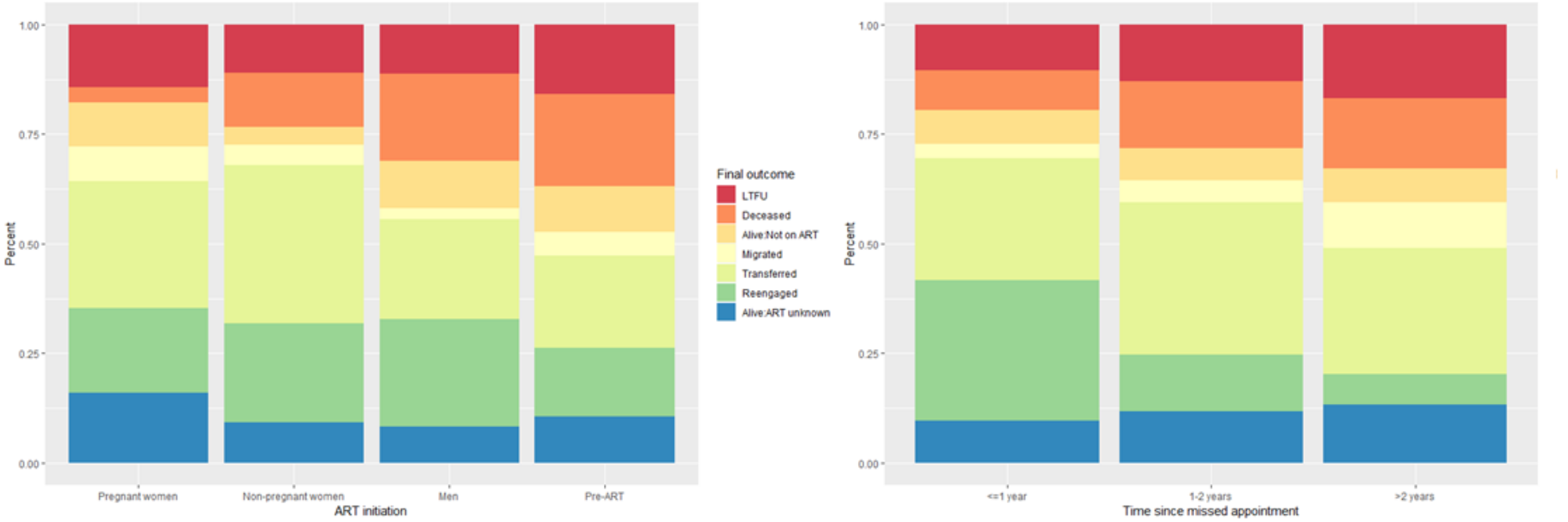
6.4.3. Outcomes after record review and tracing study

Of the 1074 patients who remained eligible for this analysis, 326 (30.3%) were found to have transferred to another clinic, 234 (21.8%) to have re-engaged in care, 132 (12.3%) were deceased, 117 (10.9%) were alive with ART status unknown, 81 (7.5%) were alive but not on treatment, 53 (4.9%) had migrated to another place of residence, and 131 (12.2%) were still LTFU (Table 6.4). These outcomes differed (all $p<0.001$) by sex, age, ART initiation status and reason, baseline CD4 count, time on ART, clinic visit schedule, health facility, whether the patient record was successfully linked to an Agincourt HDSS record, and time since a missed appointment (some selected variables illustrated in Figure 6.3).

Table 6.4: A cross-tabulation of TIER.Net treatment status and the final outcome

	TIER.Net status					
	Deceased	**Lost to follow-up**	**Not found**	**Still in care**	**Transferred out**	**Total**
Final Outcome	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
LTFU	0 (0)	112 (21.0)	9 (17.0)	10 (4.5)	0 (0)	131 (12.2)
Deceased	80 (100)	38 (7.1)	8 (15.1)	6 (2.7)	0 (0)	132 (12.3)
Alive/Not on ART	0 (0)	70 (13.1)	3 (5.7)	8 (3.6)	0 (0)	81 (7.5)
Migrated	0 (0)	47 (8.8)	5 (9.4)	1 (0.5)	0 (0)	53 (4.9)
Transferred	0 (0)	116 (21.8)	8 (15.1)	16 (7.2)	186 (100)	326 (30.4)
Re-engaged	0 (0)	56 (10.5)	9 (17.0)	169 (76.1)	0 (0)	234 (21.8)
Alive/ART unknown	0 (0)	94 (17.6)	11 (20.8)	12 (5.4)	0 (0)	117 (10.9)
Total	80	533	53	222	186	1074

Figure 6.3: Outcomes ascertained through record review and tracing stratified by (a) ART initiation status and (b) time since the last clinic appointment



(a)

PMTCT (pregnant women) less likely to be deceased but more likely to still be LTFU. Pre-ART and men more likely to have died.

(b)

Likelihood of death and remaining LTFU increases the longer someone has been disengaged.

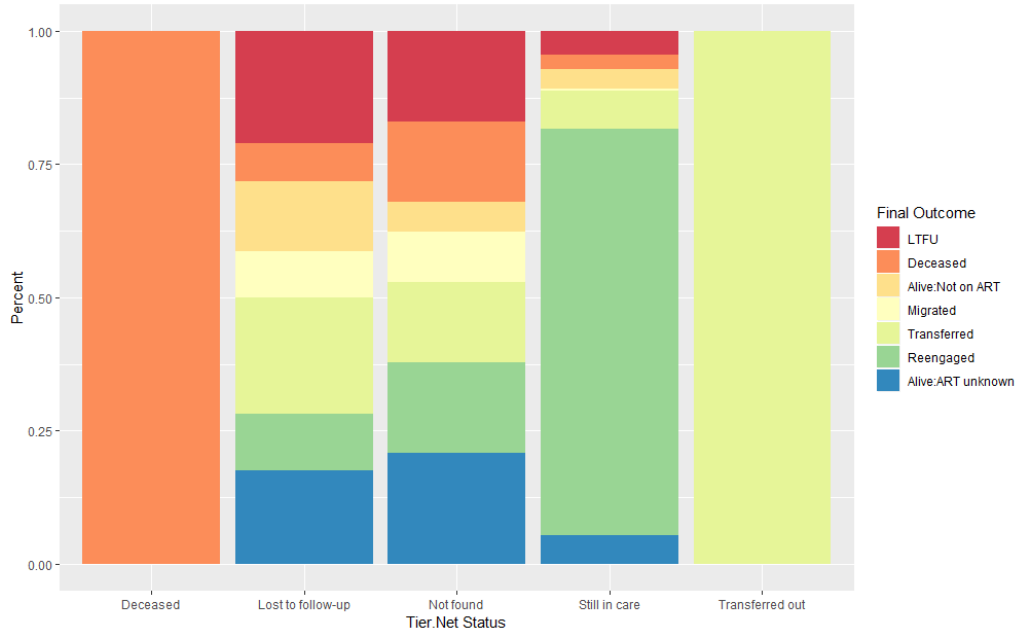
6.4.4. Differences between TIER.Net treatment status and Final outcomes

Records of patients who had died or transferred out documented in TIER.Net aligned with patients' final outcome (i.e. no inaccuracies found for these two statuses). However, TIER.Net misclassified 52 (39.4%) of 132 deaths. Of these 52, 38 (73.1%) were classified as LTFU, 6 (11.5%) as still in care, and 8 (15.4%) were not found in the system at all.

TIER.Net also misclassified 53 patients as still in care. Of these, 10 (18.9%) were found to be LTFU, 16 (30.2%) to have transferred, 12 (22.6%) as alive with unknown ART status, 8 (15.1%) alive but not on treatment, 6 (11.3%) to have died, and 1 (1.9%) to have migrated to another place of residence. TIER.Net correctly captured 186 (57.1%) of 326 transfers.

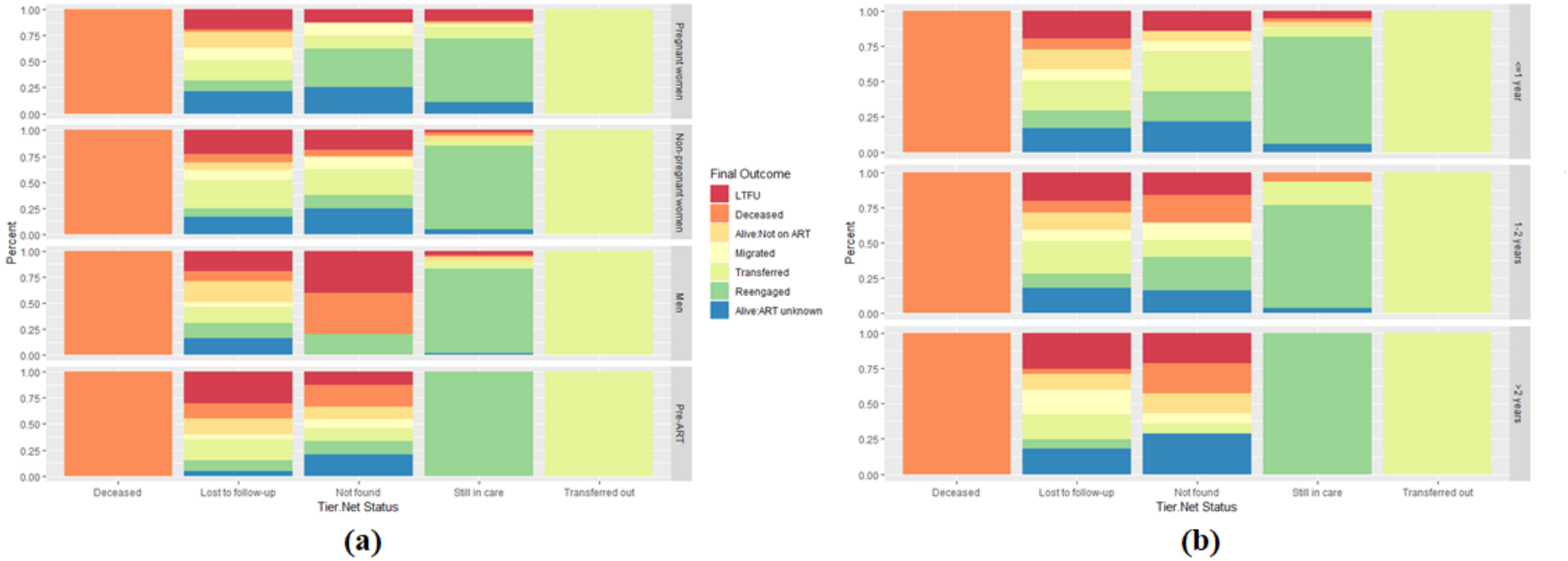
Of 533 patients classified as LTFU by TIER.Net, 116 (21.8%) were found to have transferred to another clinic, 70 (13.1%) to be alive but not on treatment, 47 (8.8%) to have migrated to another place of residence, 38 (7.1%) to have died, and 56 (10.5%) to have re-engaged in care (38 of whom were resolved by new visit data in the PIRL database and so it is possible that their TIER.Net status could have also changed back to still in care) (Figure 6.4 & Figure 6.5).

Figure 6.4: Outcomes ascertained through record review and tracing stratified by TIER.Net status



A deceased or transferred status in TIER.Net is accurate**.** There are inaccuracies in the LTFU and still in care categories. Some patients categorised as still in care are LTFU, not currently on treatment, transfers out or dead.

Figure 6.5: Final outcome by TIER.Net treatment status and (a) ART initiation status and (b) time since the last clinic appointment



As patients classified as LTFU in TIER.Net were more likely to be misclassified we report on the factors associated with being classified as LTFU in TIER.Net.

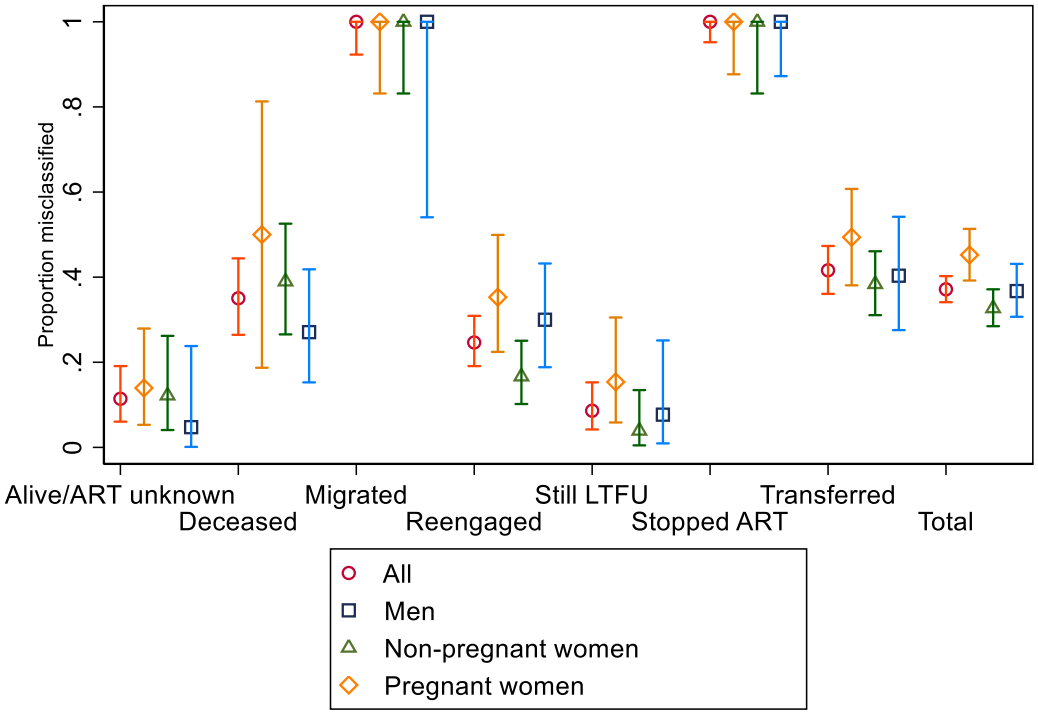
6.4.5. Factors associated with being categorised as LTFU in TIER.Net

In the multivariable model (Table 6.5), initiating ART for PMTCT (OR: 1.69, p=0.004) and baseline CD4 between 100-349 (CD4 100-199 OR: 1.76, p=0.012, CD4 200-349 OR: 1.72, p=0.01) were associated with higher odds of being categorised as LTFU in TIER.Net. Older age (age 30-44 OR; 0.71, p=0.042), later ART initiation date (2016 OR: 0.43, p<0.001, 2017 OR: 0.12, p<0.001), and longer time on ART (6-12 months OR: 0.61, p=0.015, 12-24 months OR:0.35, p<0.001, >24 months OR: 0.20, p<0.001) were associated with lower odds of being categorised as LTFU in TIER.Net. Likelihood of being categorised as LTFU also varied by health facility with Belfast (OR: 3.11, p<0.001), Justicia (OR: 2.54, p<0.001) and Bhubezi (OR: 3.82, p<0.001) more likely to classify patients as LTFU when compared to Agincourt clinic.

Table 6.5: Factors associated with being classified as LTFU in TIER.Net.

	cOR (95%CI)	p-value	aOR (95% CI) (n=963)	p-value
Sex				
Female	Reference			
Male	0.92 (0.69 to 1.22)	0.554		
Age				
18-29	Reference		Reference	
30-44	0.81 (0.61 to 1.07)	0.143	0.71 (0.51 to 0.99)	0.042
45-59	0.63 (0.42 to 0.93)	0.021	0.64 (0.39 to 1.03)	0.065
60+	0.50 (0.28 to 0.89)	0.019	0.53 (0.28 to 1.02)	0.059
ART reason				
Non-PMTCT women	Reference		Reference	
Pregnant women	2.01 (1.48 to 2.73)	<0.001	1.69 (1.18 to 2.43)	0.004
Men	1.20 (0.88 to 1.63)	0.249	1.24 (0.88 to 1.76)	0.219
Pre-ART	1.80 (0.88 to 3.70)	0.11	__	__
ART start year				
2014	Reference		Reference	
2015	1.01 (0.71 to 1.41)	0.967	0.77 (0.51 to 1.16)	0.209
2016	0.98 (0.69 to 1.38)	0.892	0.43 (0.27 to 0.68)	<0.001
2017	0.41 (0.20 to 0.84)	0.015	0.12 (0.05 to 0.31)	<0.001
Baseline CD4				
<100	Reference		Reference	
100-199	1.73 (1.16 to 2.58)	0.007	1.76 (1.13 to 2.73)	0.012
200-349	1.70 (1.17 to 2.45)	0.005	1.72 (1.14 to 2.59)	0.01
350-499	1.31 (0.88 to 1.94)	0.179	1.22 (0.77 to 1.93)	0.4
>=500	1.14 (0.74 to 1.73)	0.552	0.99 (0.60 to 1.64)	0.96
Health Facility				
Agincourt	Reference		Reference	
Belfast	3.28 (2.21 to 4.86)	<0.001	3.11 (2.02 to 4.79)	<0.001
Cunningmore	2.00 (1.17 to 3.43)	0.012	1.64 (0.89 to 3.05)	0.114
Justicia	2.90 (1.86 to 4.52)	<0.001	2.54 (1.56 to 4.13)	<0.001
Kildare	1.63 (1.05 to 2.53)	0.029	1.56 (0.97 to 2.50)	0.067
Lillydale/Bhubezi	3.79 (2.51 to 5.72)	<0.001	3.82 (2.40 to 6.06)	<0.001
Thulamahashe	1.11 (0.48 to 2.55)	0.805	0.90 (0.35 to 2.34)	0.83
Xanthia	1.06 (0.62 to 1.80)	0.834	1.00 (0.56 to 1.77)	0.987
PIRL linkage				
Not linked	Reference			
Linked	0.81 (0.58 to 1.13)	0.218		
Time since missed appointment				
< 1 year	Reference			
1-2 years	2.22 (1.69 to 2.92)	<0.001		
>2 years	2.36 (1.59 to 3.52)	<0.001		
Clinic visit schedule				
1 month	Reference			
2 months	1.14 (0.84 to 1.53)	0.394		
3 months	0.90 (0.57 to 1.44)	0.669		
>3 months	0.30 (0.13 to 0.68)	0.004		
Time on ART				
<=3 months	Reference		Reference	
3-6 months	1.19 (0.81 to 1.72)	0.373	0.91 (0.60 to 1.39)	0.661
6-12 months	0.75 (0.53 to 1.06)	0.108	0.61 (0.41 to 0.91)	0.015
12-24 months	0.43 (0.30 to 0.62)	<0.001	0.35 (0.22 to 0.54)	<0.001
>24 months	0.30 (0.16 to 0.57)	<0.001	0.20 (0.09 to 0.43)	<0.001

Figure 6.6: Proportion of patients misclassified by TIER.Net disaggregated by final outcome, sex, and pregnancy status at ART initiation



6.4.6. Factors associated with misclassification

In the multivariable model (Table 6.6), men (OR: 1.47, p=0.021) had higher odds of misclassification when compared to women who initiated ART for non-PMTCT reasons (CD4, WHO stage, tuberculosis coinfection). Higher baseline CD4 (CD4 100-199 OR: 1.95. p=0.002, CD4≥500 OR: 1.81, p=0.014) was also associated with higher odds of misclassification when compared to patients who initiated treatment with CD4<100. Health facility also remained statistically significant suggesting that facility level variability plays a role in misclassification. Patients who were linked to an Agincourt HDSS record in the PIRL database (OR: 2.09, p<0.001) were more likely to be misclassified. Finally, patients who were between 1 to 2 years late (OR: 1.62, p=0.001) were more likely to be misclassified. Older age (30-44 years OR: 0.73, p=0.046, 45-59 years OR: 0.63, p=0.046) was associated with lower odds of misclassification and patients on longer refill schedules (>3 months OR: 0.31, p=0.009) were less likely to be misclassified.

Table 6.6: Factors associated with TIER.Net misclassification

	cOR (95%CI)	p-value	aOR (95% CI) (n=1074)	p-value
Sex				
Female	Reference			
Male	1.08 (0.82 to 1.43)	0.584		
Age				
18-29	Reference			
30-44	0.81 (0.62 to 1.07)	0.141	0.73 (0.54 to 0.99)	0.046
45-59	0.62 (0.41 to 0.92)	0.017	0.63 (0.40 to 0.98)	0.041
60+	0.72 (0.40 to 1.27)	0.253	0.70 (0.37 to 1.33)	0.279
ART reason				
Non-PMTCT women	Reference		Reference	
Pregnant women	1.64 (1.22 to 2.20)	0.001	1.28 (0.92 to 1.78)	0.142
Men	1.34 (0.98 to 1.82)	0.063	1.47 (1.06 to 2.06)	0.021
Pre-ART	1.69 (0.83 to 3.47)	0.149	1.26 (0.57 to 2.78)	0.568
ART start year				
2014	Reference			
2015	1.11 (0.79 to 1.54)	0.556		
2016	1.08 (0.76 to 1.52)	0.671		
2017	0.92 (0.47 to 1.80)	0.8		
Baseline CD4				
<100	Reference		Reference	
100-199	1.83 (1.22 to 2.74)	0.003	1.95 (1.28 to 2.97)	0.002
200-349	1.29 (0.87 to 1.90)	0.201	1.45 (0.96 to 2.19)	0.074
350-499	1.32 (0.88 to 1.99)	0.183	1.52 (0.98 to 2.37)	0.063
>=500	1.62 (1.05 to 2.49)	0.029	1.81 (1.12 to 2.91)	0.014
Health Facility				
Agincourt	Reference		Reference	
Belfast	2.42 (1.66 to 3.52)	<0.001	1.97 (1.30 to 2.97)	0.001
Cunningmore	2.01 (1.16 to 3.49)	0.013	1.64 (0.91 to 2.96)	0.101
Justicia	2.25 (1.46 to 3.47)	<0.001	1.96 (1.21 to 3.17)	0.006
Kildare	1.74 (1.12 to 2.71)	0.015	1.42 (0.89 to 2.28)	0.14
Bhubezi	2.53 (1.73 to 3.71)	<0.001	2.26 (1.50 to 3.41)	<0.001
Thulamahashe	1.14 (0.50 to 2.60)	0.762	1.47 (0.64 to 3.36)	0.363
Xanthia	1.74 (1.01 to 2.98)	0.045	1.86 (1.07 to 3.24)	0.028
PIRL linkage				
Not linked	Reference		Reference	
Linked	1.59 (1.10 to 2.29)	0.014	2.09 (1.41 to 3.10)	<0.001
Time since missed appointment				
< 1 year	Reference		Reference	
1-2 years	1.89 (1.44 to 2.46)	<0.001	1.62 (1.21 to 2.17)	0.001
>2 years	1.58 (1.06 to 2.34)	0.025	1.34 (0.87 to 2.07)	0.181
Clinic visit schedule				

1 month	Reference		Reference	
2 months	0.96 (0.72 to 1.28)	0.793	0.97 (0.71 to 1.34)	0.872
3 months	1.00 (0.64 to 1.57)	0.99	0.95 (0.59 to 1.52)	0.832
>3 months	0.19 (0.08 to 0.44)	<0.001	0.31 (0.13 to 0.74)	0.009
Time on ART				
<=3 months	Reference			
3-6 months	0.83 (0.57 to 1.20)	0.314		
6-12 months	0.72 (0.51 to 1.01)	0.055		
12-24 months	0.59 (0.42 to 0.83)	0.003		
>24 months	0.32 (0.18 to 0.56)	<0.001		

6.5. Discussion

In this paper, we described the discrepancies between the treatment, vital and residency status of HIV patients enrolled in care between April 2014 and August 2017 in a rural South African setting as recorded in the national treatment database (TIER.Net) and their treatment outcome following a comprehensive record review and tracing study.

We found that TIER.Net misclassified 36% of the patient outcomes. ART initiation reason, baseline CD4, health facility attended, PIRL linkage, time since the last appointment, age, and ART refill schedule were all found to be significantly associated with misclassification. TIER.Net underestimated mortality and overestimated the number of patients who were LTFU. Seventy-nine percent of patients classified as LTFU in TIER.Net had a final outcome ascertained, mirroring findings from a systematic review of low and middle income country ART programmes which found that tracing generated higher estimates of mortality and lower estimates of LTFU (52). Our findings show that LTFU is still an important problem in ART programmes in this setting, even with routine patient tracing in place. TIER.Net also missed 43% of transfers with these silent transfers being the biggest contributor to misclassification among those documented as LTFU. We also found that 21.8% of patients had re-engaged in care, a phenomenon that was previously not well understood, but which is now increasingly recognised as becoming a common feature of ART programmes (52). Using our findings to revise LTFU figures to reflect re-engagement may help improve programme evaluation and forecasting.

In our study, we found that 40% of deaths were missed by TIER.Net, indicating that mortality of ART patients would be underestimated if relying on this data source. Given the role that national statistics play in HIV/AIDS projections (498–500), our findings suggest a need for correction factors for the estimates of the effect of ART on mortality. Although South Africa has a good vital registration system in place (501), these data are not currently linked to clinic-based information. However, with the move to registering patient national ID numbers, clinics should consider matching patients that are LTFU to the national death registry and other available databases such as the national health laboratory services database to ascertain vital status as this has proved useful in other studies in South Africa (102,446,447). Clinics in the Agincourt HDSS study area and other HDSS sites could also consider using vital status data from annual demographic surveillance to ascertain vital status for all patients.

The number of patient transfers to another clinic that were missed in TIER.Net suggests that communication between clinics is sub-optimal and that the current system for transferring patients between clinics can be improved. With studies reporting patient fear and concern about provider reactions if they return to care after a treatment interruption (367,502) it is possible that some patients considered it less stressful to self-transfer or restart treatment at another nearby clinic, rather than returning to the facility where they had initiated treatment. These silent transfers could lead to double counting of patients currently on treatment, the second of the 90-90-90 targets, potentially suggesting that the programme is performing better than it is. Furthermore, given that the national treatment programme relies on data from TIER.Net to plan and procure ART based on active patient numbers, misclassification in the database, and more specifically double-counting due to silent transfers may lead to inaccurate drug forecasts and misestimation of medicines and other commodities at the national level. This bias will only increase as the South African ART programme expands with more patients potentially moving into new clinics closer to their homes and more people initiate ART with the move to test and treat. Future work will consider how application of correction factors from this research would change programme statistics and drug forecasts.

It is also important to consider the risk that silent transfers pose with regards to drug resistance, as this misclassifies treatment experienced patients as treatment naïve and may lead to patients being offered regimens that have lost their optimal therapeutic benefit. This is particularly concerning because resistance testing is not commonly used in these settings, and can potentially lead to increases in levels of transmitted drug resistance (445). Better referral systems, patient education, regular information exchange between clinics, and provider training (364), could improve recording of transfers and clinic staff attitudes towards less adherent patients. The WHO also recommends enforcement of unique identifiers as paramount to improve patient safety, improve the efficient use of programme resources by reducing duplications, and to improve programme monitoring and evaluation (370). With national IDs becoming mandatory at clinic registration, information exchange could prove useful in identifying silent transfers. This should also become less of an issue when TIER.Net is upgraded to a fully networked database.

We found several factors to be associated with misclassification of outcome in TIER.Net, with older age and longer ART refill schedules found to be protective factors. Older patients were less likely to be classified as LTFU in TIER.Net which probably explains why they were subsequently less likely to be misclassified. Given that longer ART refill schedules are synonymous with previous good adherence (503), these patients accounted for 11% of the patients LTFU and were also more likely to have re-engaged in care, a category that contributed very little to misclassification. Patients whose clinic record was successfully linked to an Agincourt HDSS record in the PIRL database were more likely to be misclassified. They were also more likely to have been resolved which could explain this association. Health facilities were also positively associated with misclassification, with the facilities with the highest proportion of patients classified as LTFU in TIER.Net being more likely to misclassify patients. Two of these clinics also had issues with routine tracing, with one clinic not undertaking any physical tracing at all, emphasising an additional benefit of routine tracing. Finally, patients who had been LTFU for a longer duration were more likely to be classified as LTFU in TIER.Net, more likely to have transferred to another clinic, and less likely to have re-engaged in care which probably explains their higher likelihood of misclassification.

This analysis has several limitations. Firstly, TIER.Net was only consulted at a specific point in time. The cross-sectional nature of TIER.Net outcomes means that some may have changed, but we would have no way to ascertain this. We checked TIER.Net 12 months after the initial record review for all patients whose outcome after record review and tracing was still LTFU and 85% of the outcomes had not changed. However, for patients whose final outcome was resolved through new visit data in the PIRL database, it is likely that their TIER.Net outcome also changed. It is also possible that some of the patients categorised as LTFU in TIER.Net are due to the rigidity of the system as TIER.Net only allows for four possible outcomes; still in care, transferred out, LTFU and deceased (100,504,505). It is possible that for some patients, their outcomes were ascertained, but the rigidity meant that they could not be recorded in the database and may call for the inclusion of other possible outcomes in the database. The exclusion of patients for whom an electronic record could not be found from the multivariable analyses might bias our findings. However, given the relatively small number we expect that this bias is fairly small. Finally, we did not adjudicate causes of death, so it is possible that patients died from causes other than those related to HIV/AIDS. A strength of this study is that we attempted to trace all patients that were LTFU and not a sample. Therefore, the findings might be more generalisable to other settings. The multiple methods, data sources and levels of follow-up used to trace patients are also a strength.

6.6. Conclusions

Although TIER.Net misclassified 36% of patient outcomes, this reflects the various challenges with the processes and upstream factors that lead to this misclassification and calls for their improvement rather than the utility of the database itself, as patients classified as LTFU were most likely to be misclassified. Clinics should consider training staff about ascertaining patient outcomes, putting more emphasis into patient tracing and using other data sources such as the national death register to improve ascertainment of patient treatment outcomes. For policy and planning purposes, programme evaluators should consider using correction factors to improve the accuracy of estimates from TIER.Net.

7. Paper D: “If the results are negative, they motivate us.” Experiences of early infant diagnosis of HIV and engagement in Option B+.

Introduction to chapter:

This paper (D) utilises data collected through the in-depth interviews to explore objective 3. Many qualitative papers cited in the literature review have considered factors ranging from biomedical, to individual, and structural to explain maternal engagement in care. During the conception phase of this research, some published literature described the importance of pregnancy in fostering engagement in care by giving women a legitimate explanation for the need to take their medication and attend the clinic. However, no published literature had explored infant characteristics and outcomes and their association with engagement in care for the mother in the postpartum period. Given that protecting the child is a major motivating factor for ART initiation, this was an important literature gap that needed exploration.

Initial exploration of the data generated through the IDIs showed EID to be an important thematic area. This paper was conceived as a means to explore the interaction between postpartum women’s experiences of EID and their engagement in care. This paper also provides a way to conceptualise this interaction. The rationale for this paper is to encourage the inclusion of the pregnancy and its outcomes in the exploration of maternal outcomes as maternal engagement in care is additionally complicated by the needs of the infant. The mother and infant are a dyad. Failure to recognise this fact is detrimental to both the mother and the infant.

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SECTION A – Student Details

Student ID Number	1603703	**Title**	Mr
First Name(s)	David		
Surname/Family Name	Etoori		
Thesis Title	A mixed methods study using linked demographic surveillance and health facility data to investigate and compare loss to follow-up among women living with HIV who initiated antiretroviral therapy during pregnancy under Option B+ in Agincourt, South Africa		
Primary Supervisor	Alison Wringe		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Global Public Health		
When was the work published?	2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	No		
Have you retained the copyright for the work?*	Yes	Was the work subject to academic peer review?	Yes

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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the study, planned and executed the fieldwork. Supervised data collection in the field. I conducted all the pertinent analyses and interpreted the findings. I drafted the manuscript.

SECTION E

Student Signature	[redacted]
Date	14/07/2020

Supervisor Signature	[redacted]
Date	14/07/2020

7.1. Abstract

Few studies have explored the relationship between early infant diagnosis (EID) of HIV and mothers' engagement in care under Option B+. We conducted in-depth interviews with 20 women who initiated antiretroviral therapy (ART) under Option B+ in rural South Africa to explore the interactions between EID and maternal care engagement. Drawing on practice theory, we identified themes relating to Option B+ care engagement and EID.

Women's practice of engagement with HIV care shaped their decision-making around EID. Mothers who disengaged from care during pregnancy were less inclined to utilise EID as they lacked information about its availability and benefits. For some mothers, tensions between wanting to breastfeed and perceptions that it could facilitate transmission led to repeated utilisation of EID as reassurance that the child remained negative.

Some mothers used their child's negative result as a proxy for their status, subsequently disengaging from care. For some participants, an HIV diagnosis of their infant and the subsequent double burden of treatment visits for themselves and their infant, contributed to their disengagement.

Women's care-seeking practices for themselves and their infants work in a symbiotic ecosystem and should be viewed interdependently to tailor interventions to improve EID uptake and Option B+ care engagement.

7.2. Introduction

By 2015, Option B+, which involves initiating all HIV positive pregnant women on antiretroviral therapy (ART) regardless of immunological stage (9) and testing all exposed infants (183) had been adopted as national policy for prevention of mother-to-child transmission of HIV (PMTCT) programmes in the majority of sub-Saharan African countries, including South Africa (402). Option B+ has dramatically increased the number of pregnant women initiating ART, however retention has been challenging, particularly in the postnatal period and after breastfeeding cessation (69,241,305,318). Attrition from Option B+ programmes contributes to morbidity and mortality linked to ART cessation (56,455,496). Furthermore, if the women are not virally suppressed it increases their potential onward transmission both horizontally and vertically (in their current or subsequent pregnancies) (456,457,506). In addition, for PMTCT programmes to be effective, mothers need to attend services to receive prophylaxis for new-borns, test their infants (early infant diagnosis (EID)) and for those who test positive, initiate them onto lifelong ART.

Serological assays used for adult testing are not reliable for infants given that maternal HIV antibodies can persist in infants up to 18 months. EID seeks to establish the presence of HIV infection in children less than 18 months old through DNA polymerase chain reaction (PCR) testing. EID allows for HIV-infected infants to be linked to care and treatment early, which reduces infant morbidity and mortality (260,262,507). Ninety percent of HIV exposed infants (HEI) should be tested by eight weeks according to the World Health Organisation global targets, but EID uptake in many sub-Saharan African countries is suboptimal (110,227,264), with only half of HEI in 21 priority countries reported to have been tested in 2015 (26).

A growing body of qualitative research has explored underlying reasons for poor retention across the Option B+ cascade (237,241,245,249). Many of these reasons mirror those identified among the general population on ART, including stigma, grappling with the lifelong commitment of daily treatment-taking (255,339), denial of HIV status (240,245,319,355), and treatment side effects (251,289,353,508). Other reasons that are specific to Option B+

included still feeling healthy, and lack of readiness to start ART when still coming to terms with a recent positive diagnosis (237,286), especially in settings where same-day ART initiation is offered and expected (239). Disengagement from care following transfer from PMTCT programmes to routine care can occur if women have to attend different HIV clinics for themselves and their child (257), or if they have not yet disclosed to anyone, and post pregnancy they no longer have an easy explanation to attend HIV clinics or take daily medication (245), or they do not have anyone they can leave the baby with (289). Some post-partum women feel their babies are no longer at risk of HIV transmission and no longer feel the need to take medication (289), while others who experience post-partum depression may also struggle to remain engaged in care (366).

An infant's engagement in care is inextricably linked to that of the mother, however EID rates are lower than maternal care engagement (35,509), suggesting additional factors drive this poor uptake. Poor quality counselling, fear of stigma, fear of disclosure, costs of multiple clinic visits, and a lack of service integration have been highlighted as barriers to achieving optimal EID coverage (263,326,510–513). The stressfulness of EID for the mother, lack of knowledge regarding EID and infant ART, the perception of health care workers as authority figures, fear of disclosure of own and/or child's HIV status, lack of psychosocial support, and intent to shorten the life of the child have also been shown to be significant barriers and facilitators of EID (267,514). However, few studies have investigated how experiences with EID may influence a mother's engagement and retention in care. Given that one key motivation for mothers to start ART is to prevent transmission to their baby (237), a positive EID result for example could be a direct cause of disengagement.

Practice theory is increasingly being used to understand HIV engagement in sub-Saharan African settings (80–82). Practice theorists treat practices – the elements that shape our perceptions, interpretations and actions – as their primary units of enquiry and contend that people's practices can be explained by generic 'elements' which include materials or tools required to enact a practice, symbolic meanings associated with a practice, and competence and

know-how to enact a practice. Each individual has a constellation of practices that they engage in, with some of these practices interacting either harmoniously or in conflict. Consequently, the enactment of one practice is likely to affect other practices (83,85–87). Shove (87) and Schatki et al (86) speak of "bundles of practices" to describe such a grouping of inter-reliant practices and encourage the understanding of how these bundles evolve, share and compete for resources through their connections.

We draw on theories of practice in our analysis to explore how the practices of engaging in HIV care and utilising EID are socially situated, being shaped by the materials, competences and meanings in the lives of women offered Option B+ in a rural South African setting.

7.3. Methods

7.3.1. Study design and setting

Data for this analysis are part of a larger mixed methods study which aimed to ascertain patients' treatment outcomes after they become lost to follow-up and to explore experiences of HIV services, disengagement and re-engagement in care from the perspective of people living with HIV living in Agincourt in rural South Africa. The larger parent study (not included in these analyses) involved a comprehensive record review of clinic records of patients meeting the LTFU criteria, as well as supplementary tracing by community healthcare workers (HCWs) (116).As part of this larger parent study, we conducted thirty-two IDIs between January and February 2018 (20 Option B+ women, 7 non-Option B+ women, and 5 men).

The qualitative sub-study presented here includes the IDIs conducted with Option B+ women living with HIV (n=20, 7 not engaged in care) who had given birth since 2015 and who resided in the area covered by the Agincourt health and demographic surveillance system (AHDSS) in rural Bushbuckridge, Mpumalanga province, north-eastern South Africa in 2017 (20).

The AHDSS has been tracking demographic and health events in Tsonga or Shangaan people since 1992. The populace of approximately 115,000 people spread over 30 villages is served by eight government health facilities: five clinics and three community health centres. PMTCT services have been offered

in all facilities since 2004, with Option B+ starting in 2015. Participants in the AHDSS who attend health facilities in the study area give consent to have their clinic records linked to their demographic surveillance data.

7.3.2. Sampling and recruitment

We drew up a sampling frame using the linked AHDSS and clinic database of all patients who initiated ART during pregnancy since 2015. We then recruited participants purposively to ensure diversity in terms of age, parity, clinic attended, and current treatment status. We utilised home Global Positioning System (GPS) coordinates collected routinely by the AHDSS to locate potential participants including those currently disengaged from care, many of whom have been lost to the health system and as a result are under-represented in research (422). Avoiding recruitment through health services was also to help limit bias that may arise from refusals that might result from participants' perceptions that recruitment was an attempt to re-engage them in care.

Participants were approached and invited by a fieldworker who explained the study. This population is routinely studied through demographic surveillance and participants give permission to be contacted at home for further research, so contact with fieldworkers is not unusual and would not inadvertently breach their privacy. Participants received an information sheet with study details and contact information and were asked to give written informed consent prior to the interview.

The first author, a male PhD student, trained and supervised five female fieldworkers who conducted the interviews, four of whom had previous experience with conducting IDIs. The research team emphasised their role as researchers to participants to minimise the power dynamics that may be associated with patient provider interactions.

Trained fieldworkers that were previously unknown to the participants conducted IDIs in Shangaan language based on a topic guide. Interviews were conducted in a private location of the patient's choice. Interviews lasted approximately 60-90 minutes, and participants were encouraged to speak candidly as their accounts would only be reported anonymously. The topic guide covered experiences using HIV care and treatment services, including EID services, and episodes of engagement and dis-engagement from care.

Field notes were taken and all IDIs were audio-recorded and transcribed directly into English. Transcripts were anonymised, password-protected and stored on a non-networked password-protected hard-drive.

7.3.3. Data analysis

We analysed the data generated thematically drawing on the principles of inductive coding to construct themes. Three initial interviews were transcribed and manually open coded by the lead author to identify emerging themes, refine the topic guide and develop the coding framework. We held debriefing sessions with fieldworkers to provide an opportunity to reflect on the interviews, refine the topic guides and provide guidance on interviewing techniques. All the transcripts were then coded with the aid of Nvivo11. The coding framework was continually refined as more transcripts were analysed to capture new codes as they emerged. Codes were then grouped and conceptualised to identify themes and considered in relation to the main social practices of interest. Interpretations were built by exploring relationships between the social practices mentioned by the participants and considering the meanings they gave to these practices and the competences they described in relation to enacting them. We drew quotations from individuals that exemplify the findings to highlight certain thematic areas and to allow greater depth of exploration (participant quotations are presented in Figures 7.1 and 7.2 and numbered for easy reference, for example (Figure 7.1, 1) refers to quote 1 in Figure 7.1).

7.3.4. Ethics

This study received ethics clearance from the London School of Hygiene and Tropical Medicine, the University of Witwatersrand and the Mpumalanga department of health. All participants provided their written informed consent for the study in addition to the consent they had already provided as participants of the AHDSS. They were informed that their participation was voluntary and that their refusal would not affect the services they received through the healthcare system or result in any loss of benefits pertaining to medical treatment.

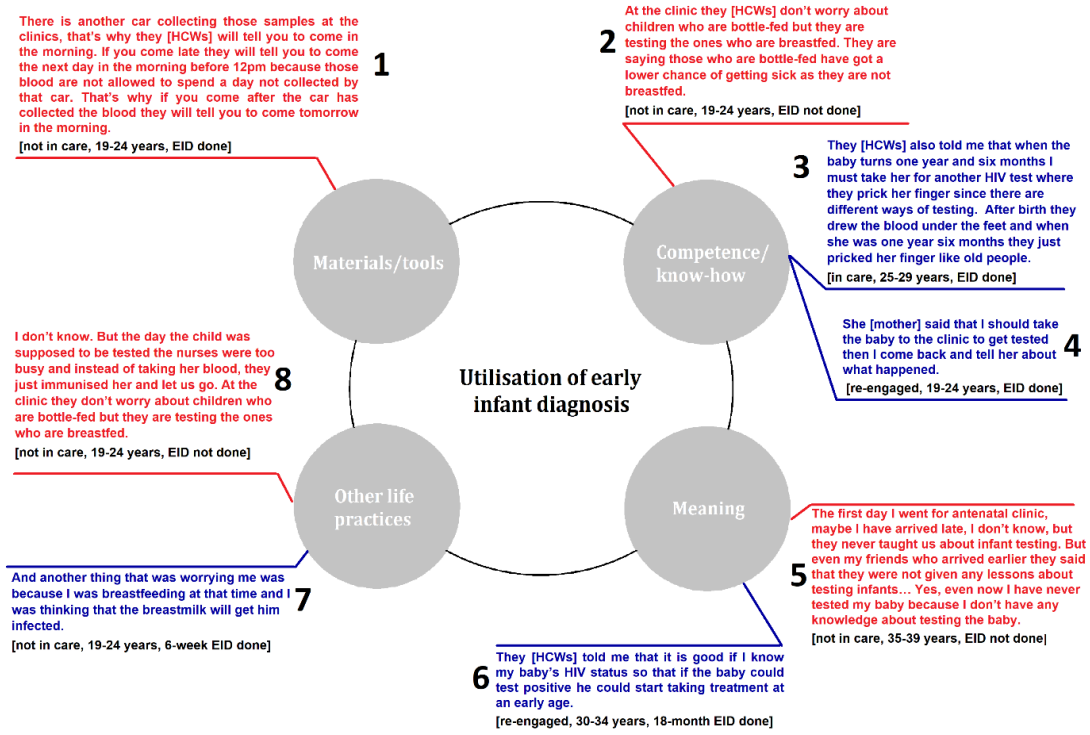
7.4. Results

Overall, 32 Option B+ women were sampled to participate and 20 were interviewed (three were not at home, five had migrated temporarily or

permanently, one could not be found, and three refused to participate). Participants' ages ranged from 19 to 37 years. Most participants were in informal relationships (12) and had some secondary school education (15) (Table 7.1). Participants came from 11 villages.

The focus of this analysis is the interrelatedness of the practices of undertaking EID and maternal engagement with HIV services. The different elements of practice theory were seen to underly the enactment or impediment of both EID and engagement in HIV care throughout participants' narratives and accounts.

Figure 7.1: Schematic illustration with quotations to show how practice theory can be applied to explore the utilisation of early infant diagnosis



*Blue quotes represent positive aspects of the elements of the practice which might facilitate its enactment while red quotes represent negative aspects which might impede its enactment

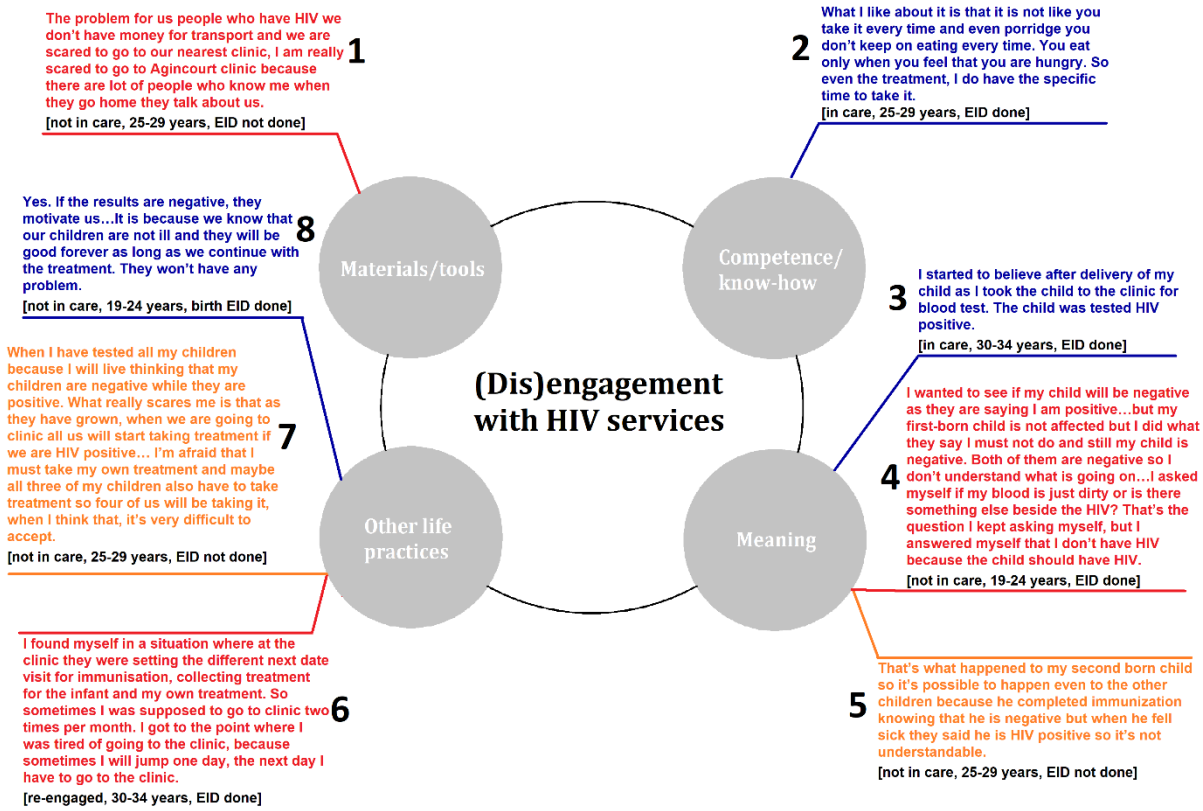
Table 7.1: Demographic and treatment characteristics of the participants and non-participants

	Age in years				
	19-24	25-29	30-34	35+	Total
Participants	7	6	5	2	20
Marital Status					
Single	1	1	1	0	3
Married	0	2	2	0	4
Informal	6	3	2	1	12
Separated	0	0	0	1	1
Education status					
Primary	0	2	1	0	3
Secondary	5	4	4	2	15
Tertiary	2	0	0	0	2
Parity					
1-2	7	5	4	1	17
3-4	0	1	1	1	3
Self-reported treatment status					
In care	4	4	4	1	13
Not in care	3	2	1	1	7
Clinic treatment status					
Re-engaged	3	4	3	1	11
Transferred	1	1	1	0	3
Not in care	3	1	1	1	6
Timing of HIV diagnosis					
Newly diagnosed	3	3	4	2	12
Previously diagnosed	4	3	1	0	8
EID done					
Yes	4	4	5	1	14
No	1	2	0	1	4
Incomplete (child<18 months old)	2	0	0	0	2
Infant's HIV status at the time of the interview					
Negative	6	4	4	1	15
Positive	0	0	1	0	1
Unknown	1	2	0	1	4
Non-participants	5	4	2	1	12
Clinic treatment status					
In care	2	3	1	1	7
Not in care	3	1	1	0	5

7.4.1. Theories of practice and early infant diagnosis of HIV

Materials and tools were necessary for EID often reflecting the level of HIV care infrastructure. For example, one participant mentioned that EID samples were collected at a specific time each day and if mothers brought their infants to test after this time, they would be asked to come back the next day (Figure 7.1, 1) which could have major implications for whether EID was performed. One advantage of dried blood spots is their stability at room temperature and might indicate a lack of understanding from the clinic staff which speaks to competence and know-how constellation of practice theory. Competence is further elucidated with some participants mentioning the HCWs' prioritisation of breastfed infants over those that were bottle-fed (Figure 7.1, 2). Competence could be gained through interactions with HCWs (Figure 7.1,3) or from other family members (Figure 7.1, 4). Furthermore, if mothers placed some meaning on EID, usually manifested as the need to diagnose their infants expeditiously, they appeared to be more likely to utilise EID (Figure 7.1, 6). Finally, maternal engagement in care and breastfeeding emerged as other practices that might help or hinder the utilisation of EID (Figure 7.1, 7 & 8).

Figure 7.2: Schematic illustration with quotations to show how practice theory can be applied to explore (dis)engagement with HIV services



*Orange quotes represent what could be interpreted as either positive or negative aspects of an element of a practice which might facilitate or impede its enactment

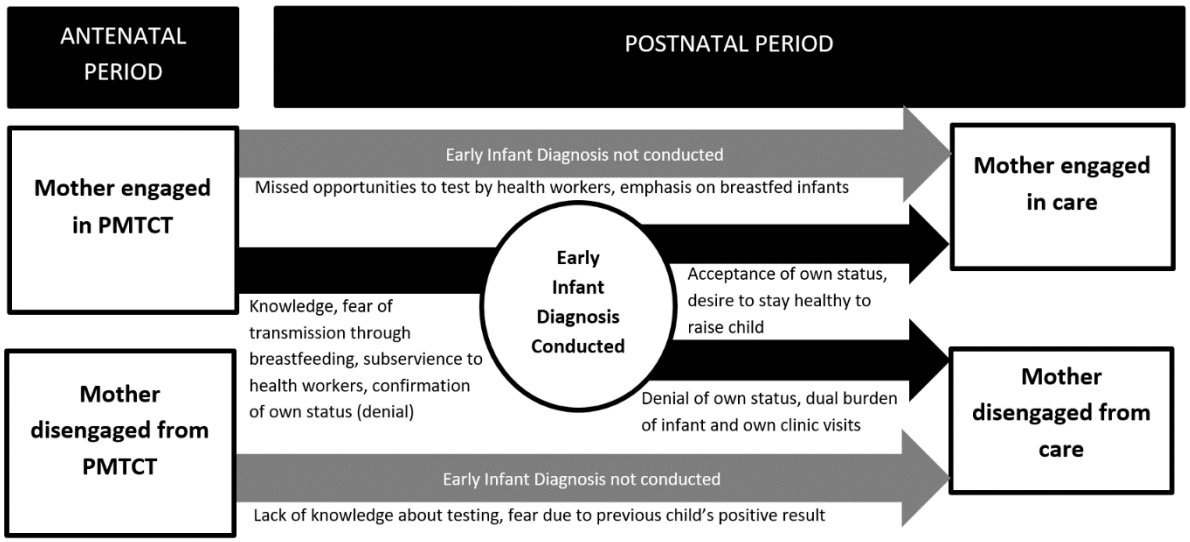
7.4.2. Theories of practice and engagement in HIV care

Materials and tools were equally important for engagement in HIV care. Lack of funds required for the logistics of remaining engaged in care for example to cover transports costs to the clinic were mentioned by some participants (Figure 7.2,1). Competence was acquired through HCWs and expert clients who helped with counselling patients and equipping them with the tools needed to navigate a life of daily treatment taking, regular clinic visits and stigma management. Where participants accepted this new normal, they were more likely to remain engaged in care (Figure 7.2,2). The meaning participants placed on remaining engaged in care could also help or hinder their continued engagement in care and this meaning could be derived from other practices

that were enacted (Figure 7.2, 5). Early infant diagnosis emerged as another practice that could affect engagement in care (Figure 7.2, 8).

We found that mothers' continued engagement in care could be undermined by EID especially in instances where the EID experience fostered denial or complicated clinic visits (usually due to scheduling conflicts regarding their infant and their own clinic visits). It could also foster engagement in care by facilitating the acceptance process. Continued engagement in care was of paramount significance in the utilisation of EID (Figure 7.3).

Figure 7.3: Schematic representation of the complex relationship between EID and mothers' engagement in care



7.4.3. Maternal engagement in HIV care and its influence on EID uptake

Engagement with HIV services encouraged uptake of EID by giving it meaning and improving women's competence and know-how regarding EID. The need for EID was not common knowledge to all the participants at their first antenatal care (ANC) visit, particularly those who were newly diagnosed, younger, or primigravida. However, information and counselling sessions throughout the ANC period ensured that most participants were aware of infant testing by the time of delivery. Consequently, women who disengaged from care early on in their pregnancy missed opportunities to learn about the procedures and benefits of EID (Figure 7.1,5).

Interactions with HCWs (an element associated with engagement in care) provided opportunities to learn about EID and HCWs influenced mothers'

decision to test their infants with some mothers expressing subservience or suggesting they did not have a choice in the matter. In other cases, HCWs were, according to patients, too busy and mothers missed opportunities to undergo EID (Figure 7.1,8). Some mothers felt that priority for EID was given to mothers who breastfed their babies reinforcing their perception that this mode of feeding was riskier than bottle-feeding (Figure 7.1,7), subsequently driving EID uptake.

7.4.4. Infant testing and its influence on maternal engagement in care

The practice of undergoing EID for their babies, and mothers' responses to the results of the tests, had consequences for their own engagement with HIV care. In most cases, mothers expressed an initial fear of testing their infant, which they had overcome through the desire to know their infant's HIV status so that they could decide the next appropriate steps to sustain their child's health. However, a positive infant HIV test result was often met with fear, with little knowledge about the next steps and fear that the child would die if they did not receive proper treatment. Conversely, many women reported that a negative result for their child encouraged them to adhere to their own ART, because they wanted to live long lives to see their children grow up (Figure 7.2,8).

For some mothers who had not fully accepted their own HIV status, the infant test could be seen as proxy for their own HIV status (Figure 7.2,3). However, discordant results for the mother and child often caused confusion and could hinder the acceptance process, or even reinforce denial (Figure 7.2,4). In this example in Figure 2 the participant's confusion was exacerbated by the fact that the negative HIV status of her child did not correspond with her expectations of it being positive because she had not adhered to HCWs' advice about taking ART. The use of the child's status as evidence for the necessity of ART was also seen among some other mothers, for whom the negative HIV status of their child was proof of their own regular treatment-taking. One participant who suggested that she had problems with proving to HCWs that she was taking treatment as prescribed mentioned that the negative result for her infant proved once and for all that she was taking treatment properly.

For some mothers, a confluence of issues relating to EID and the subsequent practice of linking their child to care worked together to undermine their own engagement in care. One participant described how her second born fell ill, was hospitalised, and tested positive while she was in Gauteng province. She moved back to Agincourt and twice attempted to initiate her child on treatment but was unsuccessful because she did not have the child's paperwork. She also anticipated stigma and maltreatment by the clinic staff at her nearest clinic, but she did not have the finances to travel to a further clinic (Figure 7.2,1). She only wanted to start treatment after she had *"sorted"* herself out but suggested that she felt far from achieving this. The confusing and difficult time she had with initiating her second born child on ART undermined her trust in the HCWs and undergoing EID this time around (Figure 7.2,5). This late seroconversion undermined her own engagement in care and was reinforced by her fear that her other children might also have HIV and the double burden this would entail (Figure 7.2,7).

Subsequent uptake of infant treatment, for those who tested positive, could interfere with engagement in care for some mothers, especially if they were expected to visit the clinic on separate occasions for their own treatment and that of their infant. Some mothers expressed fatigue at this dual burden of appointments for themselves and their child, which resulted in them prioritising their infant's treatment over their own, and in some of these cases, the mother stopped going to the clinic all together (Figure 7.2,6).

7.5. Discussion

In this study with mothers living with HIV in north-eastern South Africa, we explored the interplay between mothers' engagement in HIV care and EID, highlighting its complexity and bi-directional nature (Figure 7.3).

Our findings build on those from previous studies which have shown that mothers who remained engaged in HIV care were more likely to access EID (263,511), by describing the aetiology of this relationship. Mothers' practice of continued engagement in care facilitated EID uptake through improved knowledge about the availability of EID and risk factors for transmission like breastfeeding, and also increased the influence of HCWs over mothers regarding their decision to undergo EID. However, a lack of understanding of

vertical transmission for some mothers could also reflect a failing of the HCWs who might either not understand it themselves or might not have taken the appropriate time to communicate effectively with the mothers for a myriad reasons and could reflect an over-burdened system. This highlights the need to consider more innovative solutions to deliver the multiple facets of care like ongoing counselling using lay HCWs (515).

Other studies suggest that HCWs are often perceived as authority figures by mothers, leading to mothers' subservience towards them in the clinic setting (267). Whilst mothers who were engaged in care benefited from multiple interactions with HCWs, which often included encouragement to undergo EID, others may have felt pressured to test their infants. Other researchers have noted that the hierarchies of power that are implicitly present in patient-provider relationships can enable potentially coercive practices to increase HIV testing rates among pregnant women (288,310–312), with unintended consequences for women's disengagement from care in the longer term (516), and similar risks of disengagement should be considered for mothers who feel pressured to test their infants before they feel ready to receive the results. Health workers' apparent prioritisation of EID for breastfed babies shows that this practice was not solely dependent on the competence of mothers but also that of HCWs. The consequences of this may include missed opportunities for infant testing, as well as driving concern among breastfeeding mothers about HIV transmission risks.

Blue et al (85) suggest that the requisite elements necessary for a practice to be enacted are not evenly distributed within society. This coupled with how these practices are reproduced, synchronised, and coordinated in daily life and become more deeply embedded than others, helps to explain why some women utilised EID while others did not. Our findings suggest that the practice of EID is linked to other practices such as breastfeeding and immunisation. Conversely, engagement in care is linked to EID and other practices such as maternal testing, with counselling playing a role in how the two practices interact by providing meaning and supporting competencies among women who are enrolled in Option B+. We found that for some mothers who had not accepted their HIV status, the practice of EID could prove detrimental to

continued engagement in care especially in the case of a discordant result with the infant. This suggests the need for a better understanding of the ecosystem of practices in which EID and engagement in care are enacted, and how they interact, in order to effectively intervene to improve both the utilisation of EID and engagement with HIV services.

Women responded to EID results in different ways. The process of acceptance of an HIV status is influenced by various events and experiences that are unique to each individual (338). Our findings suggest that receiving EID results can feed into this process by either helping to confirm or challenge mothers' beliefs about their own HIV status. Similarly, other studies have also shown how denial of HIV status can manifest itself in repeat testing (516) or use of a partner's results as a confirmatory test (517), highlighting the fluid and protracted nature of the acceptance process for some persons living with HIV and the need for ongoing counselling to help some mothers to accept their own status, particularly if it differs from that of their child.

EID facilitated mothers' engagement in care in many ways. Mothers desired to stay healthy and raise their children, expressing an innate maternal desire to protect their children and mirroring findings around women's motivation to initiate ART in PMTCT programmes (237,245). When an infant's HIV results were concordant with their own, EID could also act as an important aid in the mothers' acceptance process of her own HIV status.

Conversely, for other mothers, a negative result for her infant was seen as proof of their own adherence to treatment, recalling Vale's notion of the blood "panopticon" whereby blood test results can be a powerful disciplining tool to ensure patients' continued compliance to health provider rules and expectations, but may also serve to reinforce the patient's version of their adherence history (518).

Our findings also highlight the importance of testing mothers throughout the MTCT risk period including breastfeeding, given the additional challenges that mothers may face in accepting their own and their child's seroconversion after earlier HIV negative results. Country policies regarding postnatal testing for negative mothers vary (519,520) and are linked to the infant immunisation

schedule, although challenges with implementation include other caregivers bringing the infant for immunisation. Nevertheless, given the significant HIV incidence in the postnatal period and the high vertical transmission risk linked to this (521), more emphasis should be placed on testing during the breastfeeding period.

Conflicting scheduling of clinic visits for mothers and HIV-infected babies led to disengagement from care with mothers prioritising their infant's visits over their own, in line with results from studies in Malawi and Mozambique (326,510), highlighting an urgent need for longer-term integrated and coordinated maternal and infant HIV services beyond 6-10 weeks postpartum as one strategy to keep more HIV-infected mothers engaged in care.

Our findings highlighted some important areas for further research. As HIV programmes expand, and more pregnant women living with HIV have initiated ART prior to pregnancy or during past pregnancies, it will be important to explore how experiences and responses to EID utilisation vary between newly diagnosed and experienced ART patients with a view to optimising the timing and frequency of EID counselling for different patients. Future research should also consider adolescent mothers, who often have poorer engagement in HIV care, as their experiences may differ from those of women represented here.

A strength of this study was our ability to include women that were not currently in care, a group that has been underrepresented in previous studies. Nevertheless, their response rate was lower, and it is plausible that some of the women who chose not to be interviewed could have had deferring views from the included participants. Other limitations include the fact that we interviewed participants once, making it difficult to get a sense of the fluidity of their views regarding EID or their engagement in care over time. One-time interviews also meant less time to develop rapport with these women which may have resulted in them speaking less candidly about their experiences in relation to EID and care engagement.

Furthermore, although they did not emerge as findings in our study, other factors have been shown to affect women's engagement in care which might

also influence EID utilisation in other settings, including clinic factors such as stock-outs and disclosure status (235,284). This is perhaps because these were not important issues in this setting or because we did not probe about them. Finally, while the women interviewed for this research share similarities with other sub-Saharan settings, they represent a specific population and findings and conclusions drawn from this research should be interpreted with this in mind.

7.6. Conclusions

We found that practice of engagement with HIV care under Option B+ shaped their decision-making around EID. Engagement in care, EID and other practices that patients enact need to be viewed and researched as an interdependent system. A failure to recognise this interconnectedness may lead to outcomes that are counter to expectations. Furthermore, since one size does not fit all with regards to HIV care and treatment, a more practice-centred, differentiated care approach might enable HIV programmes to better serve women living with HIV and their children in the future.

8. Paper E: Challenges with tracing patients on antiretroviral therapy who are late for clinic appointments in rural South Africa and recommendations for future practice.

Introduction to chapter

This paper (E) uses data from the record review and tracing study, observations of health facility procedures and tools during the data collection process, and conversations with health facility staff to investigate objectives 2 and 4. Most HIV programmes in sub-Saharan Africa implement some form of routine tracing for patients who do not return for scheduled clinic visits. However, this is inconsistently done and fraught with issues resulting in many patients becoming lost to the system. This paper was conceived as a means to evaluate and critique the implementation of patient tracing procedures in the health facilities that serve the Agincourt HDSS. I report on gaps identified as well as offer recommendations to improve routine tracing in South Africa and similar settings.

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SECTION A – Student Details

Student ID Number	1603703	**Title**	Mr
First Name(s)	David		
Surname/Family Name	Etoori		
Thesis Title	A mixed methods study using linked demographic surveillance and health facility data to investigate and compare loss to follow-up among women living with HIV who initiated antiretroviral therapy during pregnancy under Option B+ in Agincourt, South Africa		
Primary Supervisor	Alison Wringe		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Global Health Action		
When was the work published?	2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	No		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the study, planned and executed the fieldwork. Supervised data collection in the field. I conducted all the pertinent analyses and interpreted the findings. I drafted the manuscript.

SECTION E

Student Signature	[redacted]
Date	14/07/2020

Supervisor Signature	[redacted]
Date	14/07/2020

8.1. Abstract

Background: It is common practice for HIV programmes to routinely trace patients who are late for a scheduled clinic visit to ensure continued care engagement. In South Africa, patients who are late for a scheduled visit are identified from clinic registers and called by telephone up to three times by designated clinic staff, with home visits conducted for those who are unreachable by phone. It is important to understand outcomes among late patients in order to have accurate mortality data, identify defaulters to attempt to re-engage them into care, and have accurate estimates of patients still in care for planning purposes.

Objective: We conducted a study to assess whether tracing of HIV patients in clinics in rural north-eastern South Africa was implemented in line with national policies.

Methods: Thirty-three person-day of observations took place during multiple visits to eight facilities between October 2017 and January 2018 during which clinic tracing processes were captured. The facility level implementation processes were compared to the intended tracing process and gaps and challenges were identified.

Results: Challenges to implementing effective tracing procedures fell into three broad categories: i) facility-level barriers, ii) issues relating to data, documentation and record-keeping, and iii) challenges relating to the roles and responsibilities of the different actors in the tracing cascade.

We recommend improving linkages between clinics, improving record-keeping systems, and regular training of community health workers involved in tracing activities. Improved links between clinics would reduce the chance of patients being lost between clinics. Record-keeping systems could be improved through motivating health workers to take ownership of their data and training them on the importance of complete data. Finally, training of community health workers may improve sustained motivation, and improve their ability to respond appropriately to their clients' needs.

Conclusions: Substantial investment in data infrastructure and healthcare staff training is needed to improve routine tracing.

8.2. Introduction

At the end of 2017, it was estimated that 34.6 million adults aged 15 years and older were infected with HIV worldwide, 70% of whom resided in sub-Saharan Africa (24). New treatment guidelines calling for immediate lifelong treatment for everybody testing positive for HIV (known as "Test and Treat") resulted in 15.4 million individuals initiating antiretroviral therapy (ART) by the end of 2017, representing 60% of all people living with HIV (PLHIV) in sub-Saharan Africa (24). By the end of 2015, South Africa had the largest ART programme in the world (21,107). In 2016 South Africa adopted the "Test and Treat" policy which translated to even more people being eligible for treatment (93,95). By the end of 2018, an estimated 68% of the 7.2 million PLHIV in South Africa were on ART (24,448).

PLHIV who are taking lifelong ART who are late for scheduled clinic appointments are labelled as lost to follow-up (LTFU), a general term that amalgamates several possible outcomes including death, default, and self-transfer to another clinic (14,15,55). Failure to account for the true outcomes of patients deemed LTFU leads to as much as five-fold underestimation of retention because silent (undocumented) transfers are not taken into account (425). Similarly, default rates are over estimated as all patients that are LTFU are assumed to have stopped taking treatment (52,425). Furthermore, if only deaths reported to the clinic are included in mortality estimates this results in them being underestimated. Inaccuracies in calculating the actual number of people alive and on ART has implications in the estimation of national ART coverage and corresponding ART programme budgets. Silent transfers can lead to double counting of the number of people who have ever initiated ART which could lead to overestimates of ART supplies needed, and over-estimates of ART programme coverage in national evaluations which could result in a reduced focus on reaching coverage targets (367). Finally, misclassification of patients who are alive and on ART elsewhere as LTFU underestimates the impact of ART on mortality (52,522) which is an important statistic for programme monitoring as well as for informing HIV modelling and projections by UNAIDS (498,499,523).

Effective tracing programmes are likely to become increasingly important in the context of "Test and Treat" strategy as more asymptomatic patients are initiating ART and may have higher rates of LTFU (524). Tracing is effective at improving engagement with studies showing that as many as 86% of patients who had defaulted from care reengage in care following tracing (55,525,526) and that active tracing significantly reduces attrition (52,527). Moreover, continued retention is crucial to mitigate the risk of development of resistance in patients who do not adhere correctly to ART (78,79,528,529)

Previous studies have documented some challenges related to tracing patients in HIV programmes in sub-Saharan Africa including organisational challenges, health worker shortages, and high costs which continue to limit the ability of HIV programmes to trace patients who are missing or LTFU (361,368), but few recommendations are made to mitigate these challenges.

This paper describes the challenges that were observed with routine tracing in the primary health care system in north-eastern South Africa, comparing policy to actual implementation. The observations were made whilst undertaking a study to consolidate routine tracing information and conduct supplementary tracing for PLHIV who were LTFU in a decentralised HIV treatment programme in the same setting. Recommendations to address these challenges are made to improve the implementation of tracing systems in this setting and beyond.

8.3. Methods

8.3.1. Setting

The clinics included in the broader tracing outcomes study were those serving the population of the Agincourt Health and Demographic Surveillance System (HDSS). The HDSS study area covers 475 km^2 in Bushbuckridge, Mpumalanga province, north-eastern South Africa. Agincourt HDSS has been tracking demographic and health events (i.e. births, deaths and migration) in Tsonga or Shangaan people since 1992 (20,414). By 2014, the population was approximately 115,000 people living in 17,000 households spread over 30 villages (20). The study site is run under the auspices of the Medical Research Council (MRC)/Wits Rural Public Health and Health Transitions research

unit, administrated by the School of Public Health at the University of Witwatersrand (WITS). Agincourt HDSS population is served by six primary health clinics and three secondary community health centres. Every HIV-positive patient has a clinical file that is established when they first register at the ART clinic and updated at each clinic visit. Following the clinic visit, visit-level information from the patient file is entered into the national electronic database, TIER.Net. Since 2014, Agincourt HDSS has undertaken an exercise called Point-of-contact Interactive Record Linkage (PIRL) (104) where chronic care patient visits in the clinics have been recorded and linked to the patient's HDSS record, provided that they ever lived in the HDSS.

8.3.2. Study design

The challenges and recommendations presented in this paper are based on 33 person days of observations in eight primary healthcare facilities (Table 8.1) in the Bushbuckridge sub-district between October 2017 and January 2018. Clinics were chosen because they were located within the HDSS. Each clinic was visited at least three times over this period to ascertain tracing outcomes for patients that were believed to be LTFU (more than 90 days late for a schedule clinic appointment). Briefly, this mixed methods study involved a comprehensive review of available clinic records documented through TIER.Net (the national electronic HIV patient monitoring database) and paper-based patient clinic files. We also consulted logbooks from Right-to-Care (RtC) and Home-Based Carers (HBC), two non-profit organisations that assist with tracing HIV patients LTFU through telephone calls and household visits respectively (Box 1).

Box 1: Description of the organisations that assist with tracing in Agincourt

Right-to-care:

- Founded in 2001
- Non-profit organisation who provide prevention, care and treatment for HIV and associated diseases (tuberculosis, cervical cancer, and other STIs)
- Work with government and communities to find solutions to build and strengthen public health care
- In Agincourt, this constitutes assistance with tracing usually through assistance with telephone tracing

Home-Based Carers:

- Started in the late 1980s in rural villages of the Limpopo region
- Introduced as a way of improving healthcare practices to promote health through population sensitisation around aspects including child care, nutrition, and personal hygiene
- In recent years they have become more structured and are at the forefront of healthcare service delivery including delivery of treatment, care and support for people living with HIV
- In Agincourt they assist with healthcare promotion and physical tracing of people living with HIV who are late for their scheduled clinic visits

We then worked with these organisations to conduct a further home visit for all patients for whom routine tracing had not previously been undertaken, or for those without a definitive outcome after record review. Observations of how the tracing systems operated were captured in logbooks. Primary healthcare facility managers usually a sister-in-charge (nurse) were informally consulted for further clarification of how the implementation took place in practice. In cases where the sister-in-charge was unavailable, RtC officers, clinic data typists or other nurses were consulted. We also visited ten HBC organisations to document how their work intersected with that of the clinics' tracing system. Additionally we reviewed one national policy document(412), which detailed how tracing should take place and had further conversations with other stakeholders and key actors.

Table 8.1: Selected characteristics of the eight clinics that serve the study area

Clinic	Type	Number of HDSS residents 18+ years that initiated ART between 2014-2017	Right to care presence	Personnel consulted	Number of days of observations
Agincourt community health centre	Public	975	Yes	Ward Based Outreach Team (WBOT) nurse, Facility manager (Sister-in-charge), Home Based Carers, Right-to-Care linkage officer, community health worker	6
Belfast clinic	Public	582	Yes (started July 2017)	Data typist, Right-to-Care linkage officer, Home Based Carers	4
Bhubezi community health centre	Public (originally private, merged with Lillydale clinic a public facility, in 2016)	689	Yes	Home Based Carers, 2 Data typists, Right-to-Care linkage officer, Right-to-Care supervisor	5
Cunningmore clinic	Public	300	No (Linkage officer resigned in 2016)	Data typist, 2 staff nurses, Home Based Carers, Right-to-Care supervisor	3

Justicia clinic	Public	423	No	Data typist, Home Based Carers, staff nurse	4
Kildare clinic	Public	586	Yes	Facility manager, data typist, Right-to-Care linkage officer, Home Based Carers	5
Thulamahashe community health centre	Public	133	Attached (same linkage officer works in Belfast and Bhubezi)	Data typist, Right-to-Care linkage officer	3
Xanthia clinic	Public	235	Attached (same linkage officer works in Agincourt)	Data typist, Home Based Carers, Right-to-Care linkage officer	3

8.3.3. Data collection

As part of the comprehensive clinic record review, we collected data from TIER.Net and patient files for 1325 patients that met the LTFU criteria on August 15, 2017. Data included information on the patient's treatment status (i.e. still in care, deceased, transferred out) and whether they had received a tracing intervention (typically a comment in their record about telephone or physical tracing). From RtC and HBC, we asked to view their tracing logs and collected data on any telephone or physical tracing interventions for each LTFU patient and the outcome of this tracing. Data were entered into a Microsoft access database. Discussions with HBCs centred around how physical tracing was performed in practice, and their interactions with clinic staff and patients.

In each clinic, through discussions with the staff, we identified the most knowledgeable person regarding each step and where possible asked for an explanation of how tracing typically occurred. We also asked to view all data collection instruments used in the tracing process including late patient lists and the tracing registers. Data were entered into an Excel spreadsheet.

8.3.4. Definitions

Implementation of tracing was defined as being optimal if lists of late patients, tracing registers, telephone and physical tracing were used as intended in policy and well documented with clinic staff able to produce these instruments when requested. Tracing implementation was defined as "inconsistent" if it did not align with policy or was not well documented. In the case of telephone and physical tracing inconsistency could also mean that these steps were not well documented, but we found evidence of telephone and physical tracing in patient files or TIER.Net. Tracing implementation was classified as "not observed" where clinic staff could not produce these instruments when requested and we could not find evidence of any intervention in patient files, TIER.Net, or any documentation kept by RtC and HBC and was classified as "not done" where clinic staff admitted that an intervention was not performed.

8.3.5. Data analysis

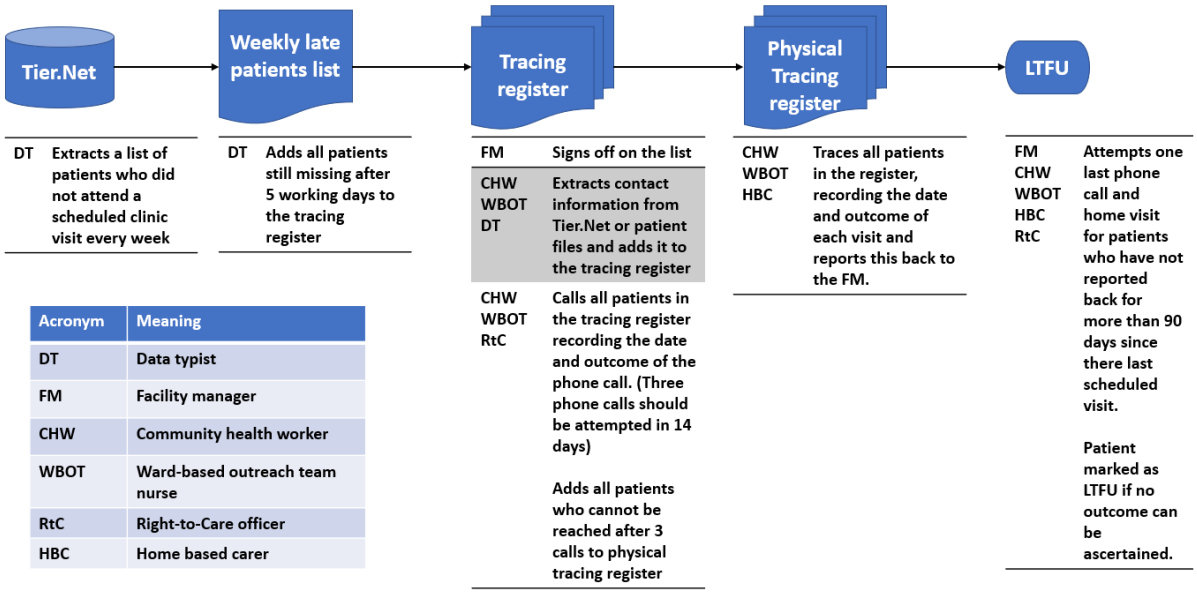
Data from the clinic record review was exported to Stata 14 for analysis. We produced a checklist for each clinic to determine whether each tracing step was optimally used, inconsistent, not observed or not done. Data were then summarised using proportions and frequencies.

8.4. Results

8.4.1. Expected implementation of the routine tracing system

In all of the clinics in this study setting LTFU was defined as being more than 90 days late for a scheduled appointment in accordance with national policy (412). All health facilities routinely traced HIV patients who were LTFU (Figure 8.1). Each health facility manager is responsible for ensuring that there is a functioning paper-based or electronic appointment system such that clinical files for patients who are expected the following day are retrieved from the filing room. Files for patients who do not attend a scheduled visit should be kept aside for further action. A list of patients who did not attend a scheduled appointment should be generated every week, either through the facility's appointment register or through querying the facility-level electronic database (TIER.Net). If a patient has not attended the facility within five working days to follow-up on a missed scheduled appointment, the patient's name should be registered in the facility tracing register to be traced.

Figure 8.1: Tracing steps and personnel in charge of each step



Acronym	Meaning
DT	Data typist
FM	Facility manager
CHW	Community health worker
WBOT	Ward-based outreach team nurse
RtC	Right-to-Care officer
HBC	Home based carer

This list should be signed off by the facility manager and transferred to the person responsible for tracing patients, usually a designated nurse, community health worker (CHW) or the ward-based outreach team (WBOT) lead. The delegated nominee should extract contact information including addresses and telephone numbers (which should be updated at every clinic visit) of the individuals on the list (and their treatment supporter where available) from the patient files and enter this information into the facility tracing register. The facility telephone should then be used to contact all the individuals who were added to the tracing register that week, with the date the phone call was attempted and the outcome of the phone call, and patient outcomes recorded in the register when obtained. Three calls should be attempted within 14 days after each patient's missed visit. Patients found to be alive, and who have not transferred to another clinic should be encouraged to return to treatment. Self-transfers should be further investigated usually through a phone call to the facility they have transferred to (Six facilities receive assistance with telephone tracing from RtC). The names of patients who cannot be reached after three attempts by phone should be transferred to a list of those to be traced through outreach and home visits. Patient consent for a home visit should be verified in the patient file before HBC attempt household visits.

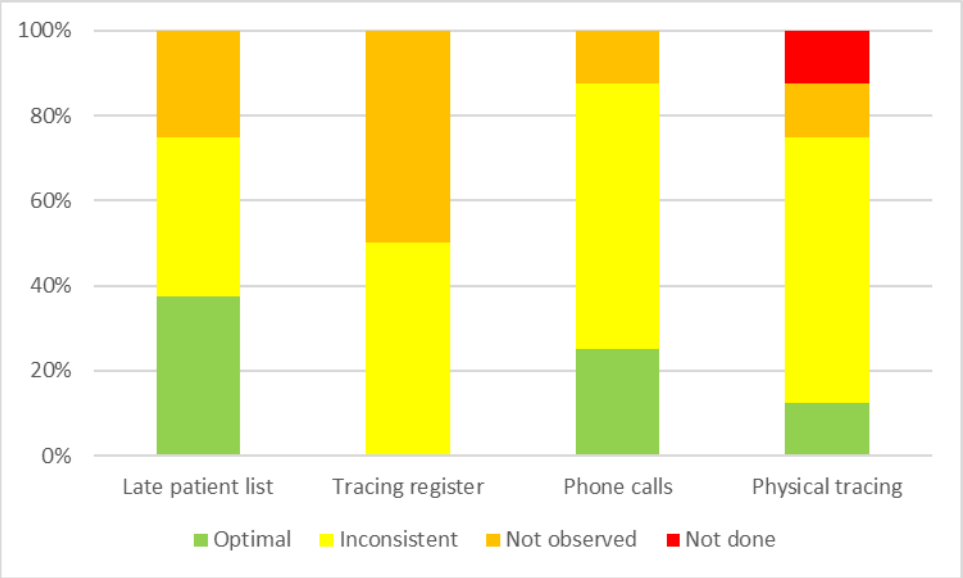
WBOTs, CHWs and HBC linked to the facility should be involved to physically trace defaulters. Details of each home visit, including the outcome of the visit, should be reported to the facility manager. Each outreach tracing effort should be marked in the facility tracing register, indicating the date and outcome of the tracing visit.

Patients who have not reported back to the clinic for 90 days since their last scheduled visit and do not have a tracing outcome e.g. transferred out, died, or stopped treatment are then in principle registered as LTFU. Before this entry is made, one more attempt at phoning or visiting the patient should be made. Information from this entire exercise should then be documented into the patients' electronic record.

8.4.2. Actual observed performance of the routine tracing system in the eight health facilities

Overall, none of the eight clinics had optimal performance with regards to all of the indicators (Figure 8.2). Optimal use of late patient lists was observed in 3 (37.5%) clinics, was inconsistent in 3 (37.5%) clinics and was not observed in 2 (25.0%) clinics. Similarly, tracing registers were inconsistently used in 4 (50.0%) clinics and not observed in 4 (50.0%) clinics. Phone calls were optimally used and consistently documented in 2 (25.0%) clinics, inconsistent in 5 (62.5%) clinics and not observed in 1 (12.5%) clinic. Finally, physical tracing was optimally used and documented in 1 (12.5%) clinic, inconsistent (usually due to poor documentation) in 5 (62.5%) clinics, not observed in 1 (12.5%) clinic, and was not done in 1 (12.5%) clinic. In both clinics, HBC and other community health workers were not engaged in the tracing procedures.

Figure 8.2: Performance on specific indicators from the tracing cascade for eight health facilities



8.4.3. Challenges identified in implementing the routine tracing system

Through the data collected, conversations with stakeholders and observations, we identified three major types of challenges to the optimal implementation of tracing in the eight facilities: facility-level barriers; challenges relating to data, documentation and record-keeping; and challenges relating to the roles of tracing personnel.

Diversity in clinic procedures

Whilst all the clinics drew guidance on patient tracing procedures from the same national guidelines and documents, in practice, their implementation of these guidelines varied. For example, each clinic that conducted routine tracing employed a different filing system and process for generating patient identification (ID) numbers. In some cases, these were based on patient characteristics such as birth dates, whereas in others, they were generated using sequential numbers. In one clinic, two different patient ID systems had been implemented, and while one had been discontinued in favour of another, both types of patient IDs remained in operation. The way in which files were stored was also different across the clinics, with some of them cataloguing and indexing files while others did not have any discernible filing system. Tracing procedures were also not consistent between clinics with different actors involved, and in some cases, certain tracing steps were not performed.

Furthermore, each clinic used TIER.Net independently with no links between the different clinic databases. This meant that if patients chose to move between clinics there was no clear way of identifying them as patients who were already in care elsewhere and a new file was opened in the receiving clinic. Moreover, the limited communication between clinics affected the efficiency and coverage of tracing activities. For example, if patients resided outside the catchment area of the HBC organisations attached to the clinic they were using, they would not be physically traced, as this would need the involvement of HBC from another clinic.

Data, documentation, and record-keeping challenges

Weekly lists of patients late for a scheduled clinic visit were always manually generated from TIER.Net by data managers. We observed that this was prone to human error with some patients who should have been categorised as late for a scheduled appointment being missed completely and not receiving any tracing interventions. In five clinics, a total of fifty-three patients who had not visited the clinic for more than 90 days were recorded as being still in care and had been missed by the data manager when the LTFU lists were generated. Additionally, whilst national tracing guidelines indicate that every clinic must keep a facility tracing register for planning, monitoring and research purposes, in most clinics, these registers could not be found and appeared not to be part of routine tracing practice. Furthermore, both TIER.Net and patient files did not have a dedicated space or module for capturing tracing outcomes. In some clinics, these outcomes were sometimes entered into the comments section, but this was not consistently done. Patients in some differentiated care models, including adherence groups and fast-track treatment collection appointments visited their clinic less frequently and, in some cases, do not have to interact with clinic staff when they pick up refills. However, TIER.Net and patient files did not always reflect this information about patients. This meant that some patients were erroneously categorised as LTFU, whereas they were still in care through differentiated models.

Whilst both RtC and HBC organisations were active patient tracing partners, they did not always keep records of their work. In one clinic, an HBC volunteer admitted that they traced patients, but did not document the tracing, likely due

to a myriad of reasons including a lack of training, a lack of understanding of the importance of documenting their work, and stationery shortages. Also, standardised tracing forms were often unavailable, or unused in practice, and some HBC being apparently unaware of them. In some clinics, supplies of tracing forms were expected to be generated by photocopying an existing form, but the equipment to do this was not always available or functioning. This led to staff utilising logbooks or exercise books for record keeping, or in the worst case, not documenting their work at all. Impromptu logbooks often had incomplete data and, in some cases, had been lost. HCWs struggled to capture quality data accurately and consistently as they prioritised their clinical work.

Additionally, tracing could only be performed if correct patient telephone numbers and addresses were available in their file. Also, for some patients the telephone number used by the clinic was only effective the first time as once patients recognised the clinic telephone number, they would not respond to any further calls received from it.

Challenges relating to roles and responsibilities of personnel involved in the tracing system

The number of actors involved in routine tracing varied between clinics, and we observed duplication of work or transfer of tasks and responsibilities from one actor to another. For example, as the list of patients who are LTFU is generated from TIER.Net, it is the responsibility of the data manager to crosscheck the LTFU list with physical files to confirm that no patient visit was missed and not entered into the database. However, in one of the clinics, this duty had been shifted to the WBOT nurse, meaning she dedicated less time to her clinical work. In some clinics, the different actors were not aware of each other's roles, meaning that work was duplicated, or that in other cases some patients did not receive all the tracing interventions because some actors did not receive their information. In one clinic, the HBC and RtC personnel had never communicated, culminating in some patients never being discussed nor physically traced. Also, whereas tracing organisations said they informed data managers about tracing done, this was not always reflected in TIER.Net.

Finally, we heard of various challenges within the different home-based care organisations. Many of the HBC felt that they were under-funded, and that

because of this HBC staff worked on a voluntary basis, only receiving a small stipend from the health department and some non-monetary incentives. Some expressed a loss of motivation to do their work which was fostered by their dissatisfaction with this system. Furthermore, HBC had not received formal training which could in some way explain the patients concerns over conduct, particularly in terms of maintaining confidentiality when they attempted to trace them. Further issues included cases whereby the HBC asked family members or friends of the patient why they had not attended the clinic, thereby inadvertently disclosing their HIV status. However, where HBC were active and motivated, they were more likely to become aware of a patient missing an appointment before they were contacted by the clinic. In one clinic, HBCs routinely visited patients ranking them by a colour system as stable (green – seen every 1-2 months) or volatile (yellow – seen fortnightly or red – seen weekly). If they suspected that a patient was LTFU they then confirmed this at the clinic, later going back to try to reengage the patient into care. This was a more practical system, relying less on communication between actors and less prone to errors due to miscommunication.

8.5. Recommendations for future practice

We found that most clinics had a system in place to identify and trace patients that had missed a scheduled clinic appointment. However, in practice, these procedures were heterogeneous and often led to gaps, leakages and missed opportunities within the tracing system. Ultimately this meant that tracing efforts were inconsistent and probably inefficient. We identified three main areas of challenges with routine tracing activities related to facility-level barriers; data, documentation, and record-keeping challenges; and the roles and responsibilities of the different actors.

8.5.1. Improved linkages between clinics

Each clinic in Agincourt HDSS has a catchment area that includes one or more villages within its vicinity. Home-based carers from the villages in this catchment area are attached to the clinic. However, many patients choose to initiate treatment at a clinic that does not correspond to their home village (530–532). In such instances, the current tracing strategy is significantly constrained due to a lack of linkages between clinics. Such challenges are further perpetuated by the way in which clinics are driven to achieve national

targets. National clinic evaluation meetings often present clinic targets in a way that fosters competition amongst clinics, putting unnecessary pressure on HCW to meet these targets (314). This competition might improve some targets (e.g. number of patients tested or initiated on ART) but undermine the general effectiveness of tracing endeavours.

Clinics should be encouraged to coordinate efforts working together to trace patients. In cases where a patient is under the jurisdiction of HBC not attached to a given clinic, there should be procedures that allow for the clinic to communicate with the HBCs to facilitate tracing. This would have to be coupled with significant patient education and sensitisation about the system to make sure they do not feel that their confidentiality has been breached. Patients should also be sensitised on the importance of declaring prior medical history when presenting at a new facility. Long term, linkages between the different clinic electronic recording systems and better implementation of unique patient identification numbers would also help to identify silent transfers.

8.5.2. Enhancements of recording systems

Data quality issues including incompleteness have been reported as a problem for tracing in other HIV treatment programmes (15). Studies suggest that data quality issues can be attributed to limited engagement of HCWs with the data for their own planning, research, and monitoring and evaluation purposes (99) as well as a lack of resources (e.g. logbooks). Insufficient training of HCWs responsible for recording information and inadequate auditing procedures to ensure that incomplete records are identified and rectified in a timely manner further exacerbates this issue (99). Healthcare workers need to balance different priorities with data entry often seen as less important.

Large investments have been made in establishing electronic medical records at all the clinics and each clinic has a dedicated data typist for TIER.Net, solely responsible for electronic data entry. However, the system still exists in an ad-hoc fashion (the data typist copying information from paper records) and is not fully integrated into medical practice (i.e. healthcare providers directly entering information into the system). Efforts are needed to fully integrate data entry into good clinical practice and clinic staff should be trained on the

importance of recording all patients' outcomes. Furthermore, efforts should be made to motivate HCWs to take ownership of and utilise their data for monitoring and evaluation. Whilst a dedicated module for tracing might be unrealistic in the near future, additional training on basic data analysis, provision of mentorship opportunities, as well as training on auditing records could lead to improvements in data completeness. Development of standard operating procedures for data entry and training on these could further improve data completeness.

8.5.3. Training for lay community healthcare workers

The inadequate healthcare workforce in sub-Saharan Africa has been well documented (533,534), and task shifting has been widely recommended and implemented as an efficient and sustainable strategy to expand HIV treatment programmes in this setting (535,536). However, we observed that the voluntary nature of HBCs, and the non-transparent recruitment strategies (537) can be problematic. These cadres are expected to be part of the health system, but not necessarily part of its organisation. They have shorter training than professional healthcare workers, and they require minimal qualifications (536). We observed concerns around their ability to handle confidential information. Over thirty years ago, Walt (538) identified several challenges to the success of HBC including lack of remuneration, insufficient training, poor management, and lack of supervision and logistical support which we found to still be prevalent in this setting.

HBCs should receive specific training in conducting tracing activities as this has been associated with sustained motivation, as well as with improving their ability to respond appropriately to their clients' needs (539) and could reduce issues related to breaches of confidentiality which undermine tracing efforts. Training could also contribute to furthering the legitimacy of HBC among patients and formal health workers (540,541). Future research should take a more in-depth consideration of the patient perspective with regards to routine tracing and its challenges.

8.6. Conclusions

Strengthening the recording and routine use of tracing data will capitalise on this source of information for patient monitoring at the facility level and

improve the accuracy of estimates of true outcomes for patients who become LTFU. This will necessitate significant investments in the health system, in the training of healthcare workers, and enhancements in data infrastructure. It is important that tracing systems and the data they generate keep abreast with evolving guidelines and rapidly shifting health service delivery.

9. Discussion

9.1. Introduction

This chapter collates the main findings from each paper presented within this thesis. Rather than repeating the detailed findings and conclusions from each paper, this chapter will serve as an opportunity to highlight the "big picture", drawing from the different analyses undertaken and discussing any contradictions or findings that might seem counterintuitive. Programme and policy recommendations will be given, followed by a discussion of the strengths and limitations of the methods and data sources used. I also reflect on dilemmas and challenges encountered while conducting this research, how I addressed them, and how my choices might have influenced my findings, especially with regards to the qualitative research. I will also summarise efforts to disseminate findings from the research, and finally, I will present the overarching conclusions of this PhD thesis.

9.2. Synthesis of findings

Table 9.1 gives a summary of the main findings from each paper. This section will synthesise these findings in relation to the overall aim of this thesis: 'to investigate women's treatment outcomes after they become lost to follow-up following uptake of PMTCT services and compare their outcomes to the general treatment cohort in a rural community in north-eastern South Africa'.

The overall aim led to the following objectives

1. To investigate loss to follow-up among patients who initiated ART under Option B+
    a. To understand the outcomes of these patients once they become LTFU in South Africa (Agincourt)
    b. To compare their outcomes to the general HIV patient treatment cohort
    c. To explore factors associated with different outcomes following loss to follow-up
2. To review and critique data sources and methods used to investigate retention in care following uptake of PMTCT services

a. To critique routine tracing procedures and methods used to investigate attrition from HIV treatment in South Africa (Agincourt)
b. To investigate discrepancies and biases in the official HIV-patient treatment statistics on retention rates, LTFU and mortality produced by TIER.Net the South African HIV-patient electronic monitoring system.

3. To explore the link between maternal engagement in care and early infant diagnosis of HIV
4. To identify and recommend strategies to improve women's retention in PMTCT services

The format will be guided by the specific objectives of the thesis and findings will be structured as they relate to these objectives.

Table 9.1: Summary of the main findings from the papers included in this thesis

Paper	Paper title	Publication	Methods	Thesis Objective	Main findings
A (Chapter 4)	Outcomes after being lost to follow-up differ for pregnant and postpartum women when compared to the general HIV treatment population in rural South Africa.	Published JAIDS, 2020(115)	Quantitative longitudinal analysis	1	Using multiple data sources and methods, we managed to ascertain the outcomes of 88% of the patients LTFU. I found that 31% of patients LTFU had transferred to another facility, 22% had re-engaged in care at the same facility, and 12% of patients had died. Outcomes for Option B+ women differed significantly from those of the general ART population, with these women less likely to have died and more likely to have stopped treatment or migrated. Age, pregnancy status at ART initiation, baseline CD4, and duration on ART predict mortality.
B (Chapter 5)	Getting on with their lives: Understanding clinic transfers among HIV patients considered lost to follow-up in rural South Africa.	Submitted, AIDS care, 2020	Quantitative analysis	1	Transfers to another facility accounted for 31% of patients LTFU. Women are more likely to transfer with Option B+ women the least likely to have a transfer documented. Option B+ women mostly transfer between clinics in the study area, while transfers out of the study area appear to be driven by labour migration.
C (Chapter 6)	Misreporting of patient outcomes in the South African national HIV treatment database: Consequences for programme planning, monitoring, and evaluation.	Published Frontiers in public health, 2020(116)	Quantitative analysis	1&2	Seventy-nine percent of patients classified as LTFU in TIER.Net had an outcome ascertained. TIER.Net misclassified 36% of the patient outcomes, with reason for ART initiation, baseline CD4, health facility attended, PIRL linkage, time since the last appointment, age, and ART refill schedule significantly associated with misclassification. TIER.Net underestimated mortality by 39% and overestimated LTFU by 62%. TIER.Net also missed 43% of transfers with silent transfers being the biggest contributor to misclassification
D (Chapter 7)	"If the results are negative, they motivate us." Experiences of early infant diagnosis of HIV and engagement in Option B+.	Published Global Public Health, 2020(117)	Qualitative analysis	3	Use and experiences of EID and maternal engagement in HIV care are inextricably intertwined. Engagement in care facilitated EID through increased HCW influence, improved knowledge about the availability of EID and risk factors for transmission. EID can either facilitate or hinder continued engagement for mothers by affecting the process of acceptance of HIV status.
E (Chapter 8)	Challenges with tracing patients on antiretroviral therapy who are late for clinic appointments in rural South Africa and recommendations for future practice.	Published Global Health Action, 2020(118)	Reflection on quantitative data collection	2&4	Challenges identified included facility-level barriers such as heterogeneity in procedures; challenges relating to data, documentation and record-keeping; and challenges relating to the roles of tracing personnel. These must be overcome in order to improve routine patient tracing and capitalise on this source of information for patient monitoring.

9.2.1. Objective 1: To investigate loss to follow-up among patients who initiate ART under Option B+

Loss to follow-up among pregnant and postpartum women living with HIV who enrol in Option B+ has not been widely researched in sub-Saharan African settings (17,18,102). There is a wealth of information on ART initiation rates and outcomes for women who remain retained in care, as well as on discontinuation rates and barriers and facilitators to engagement in care (both retention and adherence) (241,283). However, there is little information on those women who become lost to follow-up from the facility at which they initiated treatment. This is in part due to the relative novelty of the Option B+ approach which was first recommended by WHO in 2013. However, this is not the only reason; in-depth investigation into LTFU of pregnant women is hindered by weak healthcare infrastructure like data systems and personnel (99), as well as factors related to the population of pregnant and postpartum women such as their higher mobility which makes locating them after they stop attending their clinic visits significantly more difficult (18,102). Before 2015, most Option B+ programmes existed as implementation research projects, with the major aim of demonstrating the feasibility of this approach. As such, most early research focused on acceptability of the approach as well as uptake, specifically in terms of ART initiation (31,189). There has been a relatively high coverage of research and intervention in the antenatal period(241), which often coincides with high motivation to remain on treatment and therefore fewer problems with retention in care (542).

Objective 1 aimed to address this knowledge gap, and was further split into three sub-objectives namely, (i) to understand the true outcomes of PMTCT patients once they become LTFU in Agincourt, South Africa, (ii), to explore factors associated with different outcomes following loss to follow-up, and (iii) to compare the outcomes of PMTCT patients to the general HIV patient treatment cohort. The rationale for the comparisons with the general treatment cohort was that differences in outcomes could potentially explain why pregnant and postpartum women disengaged from HIV care and treatment at higher rates than other adults on treatment (89,543).

Paper A showed that women who initiated ART while pregnant or breastfeeding had statistically significant different outcomes than the general

ART treatment cohort once they became LTFU. Firstly, Option B+ women were 4 times less likely to have died. As many other researchers have speculated previously, this may be explained by the fact that they often initiate treatment while less immunosuppressed (mirrored by baseline CD4 counts in this study), and often before they have experienced any symptoms of infection (240,252,283). This was further supported by the fact that Option B+ women were more likely to be alive with ART status unknown even though they were less likely to have their clinic record linked to an HDSS record. Risk of death overall in the cohort appeared to be highest immediately following a final visit and reduced temporally as has previously been reported by other studies (447,544). However, when this was stratified by reason for ART initiation, this pattern was not observed for Option B+ women, with deaths distributed almost evenly between the time immediately following a last visit, after the next scheduled visit, and after becoming LTFU, giving further evidence that mortality is not a major driver of LTFU for this group. We attempted to ascertain the cause of each death, however, 51.7% of 120 total deaths had no verbal autopsy data. Nonetheless, of the causes ascertained for Option B+ women (6 out of 10 deaths), no deaths were attributable to HIV.

This paper also showed that Option B+ women were as likely as other adults on ART to have transferred to another health facility. Option B+ women were 1.5 times more likely to have transferred to a clinic within the HDSS, but their transfers were 1.3 times more likely to be undocumented. The findings suggest that postpartum women's mobility may not be over distances as long as other women or men. However, given that we could only investigate transfers using data from the clinics within the study area, the transfer data is one-sided, as we could not check data from clinics outside the HDSS. Consequently, it is likely that we missed many undocumented transfers to clinics outside the Agincourt HDSS. This is supported by comparisons between the transfer distances for documented and silent transfers. The distances for silent transfers (median (IQR): 9.99km (8.97,18.32)) were significantly shorter than those for documented transfers (median (IQR): 38.03km (14.66, 329.16)). Nonetheless, the geographic spread of transfer facilities indicated PLHIV in the HDSS are very mobile. South Africa's Apartheid history, where the black populace had to migrate to economic hubs for work while still being expected

to reside in rural areas likely still contributes to this phenomenon. Following the end of Apartheid, people move around freely but still maintain links to the area they grew up. Other studies have documented that mobility can have a detrimental impact on engagement in care (349,545), and that patients considered LTFU may be receiving care at another ART facility by utilising national reference lab databases (18,102). This mobility may also be detrimental for PMTCT as it is associated with higher risk of vertical transmission (546). Furthermore, this mobility may indicate changing priorities and preferences for Option B+ women who may choose a clinic for ANC based on convenience and proximity but may prioritise confidentiality or anonymity following delivery and hence choose to switch clinics (285,547).

Estimates of ART stoppage and migration were also higher among Option B+ women. The estimated rate of re-engagement in care was lower for Option B+ women, however, given that it was second only to transfers, it appears that reengagement in care contributes significantly to outcomes following LTFU, further supporting calls to stop conceptualising engagement in care as a linear phenomenon (45). However, while re-engagement in care may be viewed as a positive outcome given that people are returning to care, it means that these patients had at least three months where they were not taking ART. Transfers also potentially mean patients have gaps in treatment if they transfer their care well after a final visit to an initiating facility. These lapses in treatment are associated with higher risk of mortality and onward transmission, and the development of drug resistance (38,48,56,456,457,506). These gaps in treatment are particularly worrying for women who may still be within the risk period of vertical transmission as it puts their infant at risk of HIV acquisition. Secondly, these gaps have a negative effect on maternal health which has a domino effect on infant survival independent of HIV transmission (274–276). With the substantial success of ART for PMTCT, vertical transmission has dropped dramatically (21,548), however, the majority of infant transmission is now occurring in the postpartum period through breastfeeding (198,253).

These results begin to explain the disparity between retention in care for Option B+ women when compared to the general ART treatment cohort. Considering that most programmes report facility specific retention and that

individuals with a documented transfer are often treated as retained in care, right-censored at the time of the transfer, or excluded from analyses (199,305), the higher propensity to transfer without documentation for pregnant and postpartum women reported in paper B explains some of the higher LTFU rates. Furthermore, paper C evaluated the national HIV treatment database, showing that it misclassified 36% of outcomes following LTFU. Option B+ women's outcomes were more likely to be misclassified in TIER.Net.

The high proportion of LTFU attributable to transfers is encouraging as it shows that these women are not completely stopping ART and therefore are still accruing the benefits of treatment. However, it suggests that ascertaining patient outcomes using data from a single facility may not be prudent.

Universal ART had just started being implemented in Agincourt when this research was conducted, and the clinical profile of patients on ART will evolve over time such that it might start to resemble pregnant women in terms of baseline CD4, WHO staging, and having no history of HIV symptoms. Given that higher baseline CD4 has been shown to be associated with higher risk of LTFU (549), the outcomes of the general ART cohort may start to resemble those of pregnant women. As such, in future cohorts, mortality might account for a lower proportion of LTFU and outcomes such as ART stoppage and silent transfers may become more prevalent. However, there are still some important differences between pregnant women and the general population cohorts pertaining to pregnancy, childbirth, and child rearing which may influence retention in care. I conducted the qualitative component of my research as a preliminary enquiry to tackle some of these differences and report on the findings from this exercise as part of objective three.

9.2.2. Objective 2: To critique data sources and methods used to investigate retention in care following uptake of PMTCT services

Given that the results from paper A cast doubt on the utility of measuring retention in care using only the data from the facility where ART was initiated, this objective aimed to critically evaluate the data sources from the initiating facility. The research questions were (i) how do we know whether a patient is retained in care or LTFU? and (ii) how reliable is the method we use to ascertain this? My interests were in first of all measuring the size and direction

of bias in utilising just one data source from the initiating clinic (in this case TIER.Net) versus relying on multiple data sources to measure retention in care with the aim of providing correction factors for similar ART programmes. Secondly, having measured this error, I hoped to identify practices that could reduce the occurrence of LTFU, whilst also improving the measurement of retention in care at a single facility. I hoped to achieve this by making the data on patient outcomes more accurate through reducing the instances of patients being recorded as LTFU in TIER.Net.

Paper C showed that LTFU contributed the most to misclassification of patient outcomes in TIER.Net. Conservative estimates showed that 39.4% of patients classified as LTFU in TIER.Net were misclassified, a number that could rise as high as 87%. Consequently, the methods and procedures used to determine patient outcomes needed to be scrutinised. The results from Paper A showed that many patients had transferred to clinics within the region emphasising the need for some form of linkage and communication between clinics and a data infrastructure that can catch these silent transfers. The PIRL database provided a unique method to collate data from different facilities in order to track movements between facilities. Even though data aggregation was not in real-time, there was still utility to this method. It allowed me to resolve multiple patient outcomes retrospectively using data from other clinics.

The availability of unique identifiers in the PIRL database also allowed me to follow individual patients and identify multiple patterns of engagement in care. For example, some patients collected treatment from multiple health facilities simultaneously (possibly to accumulate a cache of medication), often in preparation for travel. This suggests multiple barriers to optimal engagement, for example this patient might feel that the system is too rigid to cater to their specific need or may not be aware of the availability of longer pill refills as an option for travel. In a case where this patient stopped attending their visits, they would be assumed to have disengaged at both clinics but would still in theory have enough medication available to them. As such, this also raises questions about how we define and conceptualise optimal engagement. While an exception and not a rule, we may have to consider that patients can be adherent, but not retained in care. It also means that assessing

retention in care solely using the initial/initiation facility might not be very informative. Furthermore, it shows that LTFU is a complex phenomenon which will require better data to advance investigations into understanding it. For example, while individual clinics export a copy of TIER.Net and send it to the Ministry of Health where it is aggregated in order to produce reports on specific indicators for the national treatment programme, unique identifiers are not consistently entered into TIER.Net. This makes it hard to replicate an exercise similar to the one I was able conduct using the PIRL database. Consequently, an intervention that makes unique identifiers like a national identification number a mandatory field in TIER.Net would go a long way to helping improve retention estimates generated from this source.

The PIRL database was not perfect either as 190 (15%) of 1264 patients classified as LTFU were in fact not LTFU and shows how relying on one data source could give inaccurate outcomes for patients. The PIRL database erroneously categorised 97 (9.5%) patients with documented transfers as LTFU. Furthermore, many patients in differentiated care models (65 (34.2%) of 190 misclassifications) were also misclassified as LTFU as well. By triangulating facility data with the PIRL data I managed to arrive at more accurate estimates for the various outcomes.

Mothers may have different priorities when choosing which clinic to attend in the prenatal versus the postnatal period. Some clinics may have better child health services or conversely better antenatal care than others. While the clinics in this research catered to both pregnant women, children and non-pregnant adults, specialised maternal and child health facilities necessitate a change in facility, given that postpartum women are expected to transfer to the general treatment cohort (South African guidelines call for this transfer 6-10 weeks postpartum). Therefore, transfers are to be expected in the treatment life cycle. However, by only reporting facility-specific retention rates, retention estimates will inevitably be underestimated. This further illustrates the need for exploration of outcomes beyond a single facility in order to report less biased estimates.

If the most important goal in measuring retention is to know which patients are still in care regardless of what facility they are attending, then every

treatment programme will have to adapt some context-specific hybrid data system in order to improve the measurement of retention. The possibilities will be dictated by financial and human resources, existing data systems, as well as available infrastructure such as telecommunication and reliable power supply. The system I adapted shows that data update and aggregation does not have to happen in real-time in order for it to be useful. Patient outcomes can be retrospectively resolved in order to reduce the number of patients that get reported as LTFU and consequently improve the accuracy of retention statistics.

9.2.3. Objective 3: To explore the link between maternal engagement in care and infant outcomes

The results of this thesis also give additional insight into the factors that affect pregnant and postpartum women's engagement in care. Previous research has considered individual, biological and medical, health system, and structural barriers and facilitators of engagement in care (48,241,283). However, the relationship between engagement and infant outcomes has not been extensively studied.

Paper D qualitatively explored the intersection between women's experiences of EID and their engagement in Option B+. The finding that experiences of EID can either foster or hinder continued engagement in care further illustrates the complexity of engagement in care for women who initiate ART for PMTCT. Previous studies have shown that some women initiate treatment for the sole reason to protect their unborn child (237,319,340,508). It should therefore follow that the outcome for their infant might affect their engagement. Studies have also shown that a positive result for an infant can affect maternal engagement when maternal and infant clinic visits are not integrated or better streamlined. However, to my knowledge, this is the first study to show how an EID result can either foster or hinder acceptance of an HIV diagnosis and therefore have an impact on continued engagement in care. Paper D showed that engagement in care cannot be viewed as a standalone issue, other social practices can modify the effect of an EID result. For example, women who have received extensive and effective counselling and understand that their infant might still seroconvert even though they are taking treatment might be able to rationalise a seroconversion and

consequently remain engaged in care compared to those that have not. Mothers who have not received counselling might still be in denial about their diagnosis and may therefore use their infant's negative result as confirmation of their own negative status.

This research further illustrates the many differences and may further explain the discrepancies in retention for pregnant and postpartum women when compared to the general ART treatment cohort. Unlike the general treatment population, for pregnant women, HIV care is not just a mother's endeavour but rather one that she must embrace for her child as well. The mother and her infant's care and treatment can become diametrically opposed, for example, if her child seroconverts, which may be exacerbated by a case of separately scheduled mother and infant clinic visits. Consequently, future conceptual frameworks on women's engagement in care should include their infant's outcomes as potentially contributing to continued engagement in the postpartum period. Practice theory offers such a framework as it encourages us to look at engagement in care as part of a constellation of practices that women must navigate, practices which either help or hinder each other. Programmes should endeavour to rollout interventions that take into account these interactions and aim to mitigate any negative interactions.

Reflection on the approaches taken within the qualitative research

It is important to reflect on the methods used to come to these conclusions including fieldwork to identify and interview participants and analysis of the data generated.

Data collection

The recruitment process raised some ethical dilemmas. Given the scope of the research, many of the people in the sampling frame had disengaged from care, as such approaching potential participants to recruit them into the study came with some potential pitfalls. These are often harder to reach people, but it is important to understand their experiences as they are under-represented in research. This meant I had to be a bit more flexible and adaptable to give them the opportunity to share their voice and opinion. For these specific cases an approach from the clinic could be seen as an attempt to reengage them in care

and inadvertently cause them to refuse to participate (550) or in some cases HCWs might choose to only engage certain patients who meet some desirable criteria. I also did not wish to cause any disruption to HCWs which made utilising HCWs difficult. Therefore, I decided to approach participants through a fieldworker who could explain the study to them and ask if they were willing to participate. Even though it was explicitly mentioned that we were researchers who had no connection to the clinic and therefore could not influence their interactions with the treatment programme, some participants voiced concerns over how we knew they had been taking treatment at a given clinic, fieldworkers were trained to explain the study as well as confidentiality in research and how they were bound by this principle with a penalty of the loss of their job and prosecution if it was deemed necessary. Some participants did not feel this was sufficient and declined to participate as a result. Fieldworkers were also instructed not to frame their approach of participants along the lines of HIV or the presupposition of HIV status to mitigate this. As part of the approach process, I drove a marked WITS car to participants' households to look for them. Interviews happened around the time of annual demographic surveillance so a marked car would not have been out of the ordinary. In order to locate participants' households, I used GPS coordinates that are routinely collected by the HDSS for the purpose of demographic surveillance. Without the linked data, it would have been impossible to locate any of the participants. This also illustrates the challenges that CHWs must face in trying to track patients down in a rural area without an organised address system. Ideally, I would have preferred to be able to approach participants myself but given that I do not speak Shangaan this was not possible. The use of a fieldworker as an interpreter was also decided against as participants were female and there was a desire to minimise any unequal power dynamics given the cultural context. For the interviews, there was also the consideration of potential pitfalls from discussing topics that female participants might not feel comfortable discussing with a man. For this reason, I also did not observe interviews and left the fieldworkers to conduct them with the hope that their training would be sufficient to help them navigate any issues during the interview. I therefore cannot speak for the dynamics of this part of the data production process. However, I took other steps to remain

close to the data generation process including debriefing fieldworkers immediately after the interview.

With regards to the consent form and information sheet, it was decided that they should not contain any information specifically mentioning HIV treatment and care. This was to minimise the potential for inadvertently disclosing participants status if their consent form was read by someone else. Whilst I ultimately felt comfortable with this approach, I would consider it as an ethical "grey zone", with both potential advantages and disadvantages in terms of being transparent with participants about the nature of the research, whilst minimising risks of inadvertent disclosure.

With regards to benevolence in research, there were instances where, based on transcripts, patients appeared to be experiencing mental health challenges which raised some concerns for me regarding what procedures to follow under these circumstances. All these instances were several months removed from the actual fieldwork. Given how data collection was structured, most of the interviews were transcribed after I had already left the study area. Even with debriefing sessions during the fieldwork, some of these issues were not flagged early. I had discussions with more qualified qualitative researchers to figure out the best way to deal with situations where I thought a participant might require help without breaking confidentiality. One participant who had tried to reengage in care mentioned that she had been called by the clinic and counselled to return to care. However, when she decided to return to the clinic, the HCW she spoke to was not on duty that day and this made her apprehensive and ultimately, she did not re-engage in care. She had recently given birth and in her interview, she mentioned having suicidal thoughts and described having little motivation to wake every day. She was flagged and referred to the Home-Based Carers organisation that worked in her village, but this intervention felt insufficient given all she was struggling with. There was also no way to determine whether the HBCs had followed up on her. Given the distressing nature of some of the topics discussed, a lesson I take away from this experience is to plan ahead for psychosocial support interventions for participants that might be in emotional distress or at risk of self-harm. Quantitative research often means that you are removed from the lived

experiences of the subjects you are researching and consequently we may forget that real people contribute the numbers. My experience with qualitative research has made me a more conscientious and empathetic researcher attuned to the importance of thinking of the well-being of the subjects of the research first before thinking of the data they can contribute.

Data analysis

With regards to data analysis, my limited prior experience with qualitative research meant that notions of positionality and reflexivity were completely foreign topics to me. My default during analysis was not to be reflexive or to consider my position and it was something that I had to inculcate into my approach. I have gained a lot of experience by undertaking this research and I believe I am a much better researcher as a result of this. However, given that qualitative research is co-produced and influenced by my beliefs and biases, these must have shaped the conclusions drawn from the data collected. For example, in formulating the topic guide, one of the motivating factors for my line of questioning with regards to infant outcomes and their effect on maternal outcomes was my own childhood experiences of maternal and infant outcomes with regards to HIV and their interdependence. Furthermore, throughout my research career I was always baffled by the fact that the infant and its outcomes were seldom considered in trying to understand the outcomes of the mother. These experiences also permeated the analysis process. Whereas IDIs were conducted for a diverse group of participants, I started off by coding IDIs conducted with women who had recently given birth and ultimately ran out of time to analyse transcripts from other participants. Furthermore, the theoretical framework used to frame the findings was chosen because it offered a succinct way to situate infant outcomes particularly EID within the concept of maternal engagement in care.

9.2.4. Objective 4: To identify and recommend strategies to improve retention in PMTCT services

Objective 4 is partially covered in paper E and expounded on in the following section on programme and policy recommendations.

9.3. Programme and policy recommendations

Some of the policy implications from this research call for strengthening already existing interventions and are therefore immediately actionable. Some call for implementation of new interventions which may have to be enacted over the long term, and some like the call for a shift in the paradigm of ART provision may be a contribution to a much needed broader recognition of the need for more ambitious approaches in the future. However, I firmly believe that it is our role as researchers to pioneer. After all, the national treatment programmes in sub-Saharan Africa are proof and an important reminder of what can be achieved when we refuse to settle for the status quo. Illustrated by the jump in numbers of people on ART since treatment was rolled out, with an estimated 18 million people on ART in sub-Saharan Africa in 2019 (24).

Furthermore, the increased vertical transmission in the postpartum period coincides with the period where LTFU increases significantly. Women who experience any gaps in their treatment including transfers, those who re-engage and those who stop ART will therefore be an important population in which to intervene to further reduce the rate of new HIV infections in children. Programmes should therefore strive to identify the major causes of these gaps and implement interventions to mitigate the identified causes with the ultimate goal of eliminating or reducing the duration of gaps in treatment taking. It will be important to shift the focus away from the immediate outcomes of the pregnancy, such as vertical transmission, towards more sustained engagement in care as this will protect future pregnancies, improve maternal health and reduce the risk of transmission to partners as well.

9.3.1. Policies to reduce patient drop out

Whereas the key challenges of early ART programmes were to provide and scale-up access to ART, the challenges have now evolved to encompass not just ART coverage but retaining patients in care (Figure 9.1). Consequently, ART programmes must evolve to meet these new challenges. This evolution will include a move away from the "one-size-fits-all" model of service delivery towards a patient-centred one that caters to specific patients (551). This is not a radical suggestion as women in PMTCT routinely receive differentiated care that includes integration of ANC services. However, the fact that they must still transfer their care to the general treatment population in the postpartum

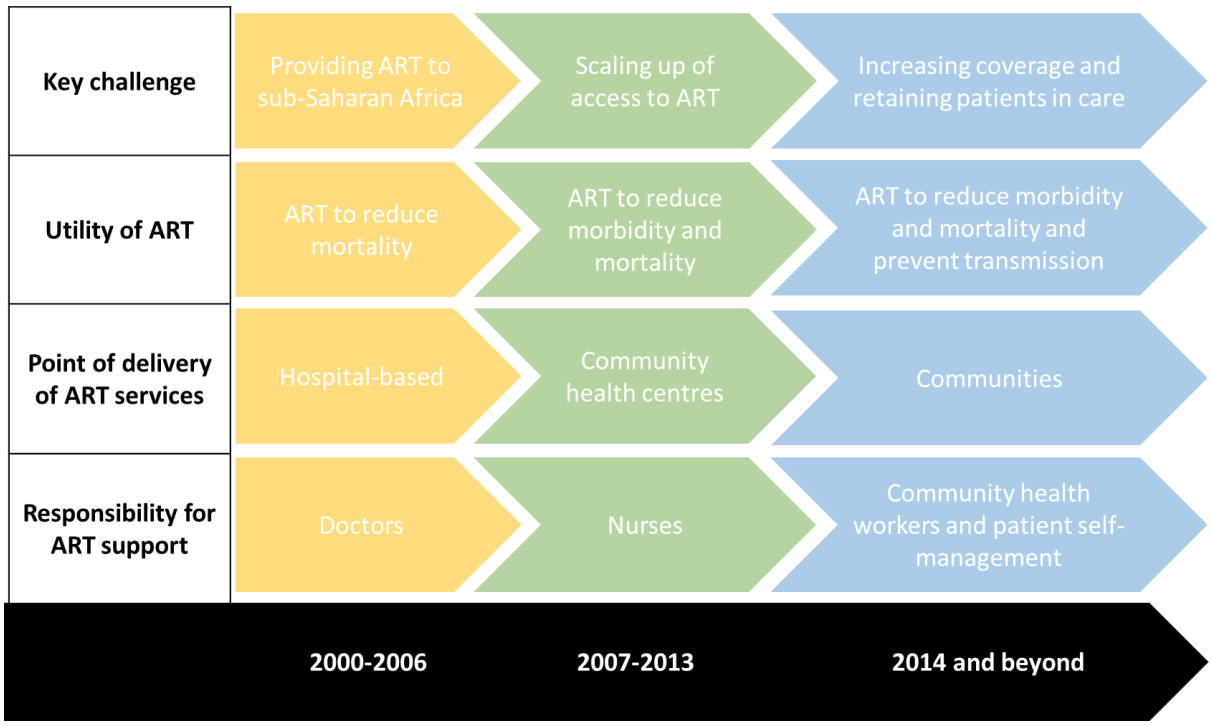
period is still a major factor contributing to their disengagement from care (18). As such one immediately actionable policy change would be to extend integrated and synchronised maternal and infant HIV services beyond 6-10 weeks postpartum in South Africa (296). This would have the added advantage of improving infant retention as has been reported in Kenya (552), and is supported by findings from paper D which showed conflicting scheduling of mother and infant clinic appointments contributed to disengagement from care.

Interventions to reduce the occurrence of LTFU due to administrative errors will also be crucial. Increasing numbers of patients initiating ART will necessitate the use of new monitoring and evaluation approaches, as patient volume may contribute to data quality issues that lead to administrative LTFU (e.g. where patient outcomes do not get recorded). In paper C, we found instances of LTFU patients recorded as still in care. Instances like this could be reduced by implementing an automated alert system within the database which might have flagged this error. We also found instances of patient outcomes available in a clinic register but not reflected in TIER.Net. The amounts of data that data clerks are expected to enter might be responsible for these occurrences and therefore a system that requires less data could be a solution. Choosing quality over quantity in terms of variables collected and streamlining this across the entire treatment programme would be one way to mitigate this. On the topic of important variables and biomarkers, it appears that CD4 is being phased out but given how important a predictor it is for outcomes such as mortality, programmes would be naïve to do so (553–555). To do this would be to undo the astronomical work it took to make CD4 a regularly and consistently collected metric.

To reduce LTFU through silent transfers, some potential interventions to improve the transfer process include; increased patient awareness and understanding of the transfer process (556), strengthening referral systems (364), simplifying the transfer process (557), and removal of preconditions for transfer (558). Finally, ascertaining outcomes beyond a single facility will need to become the norm to ensure that silent transfers are captured.

Ubiquity of mobile phones means that interventions through them will reach more people. Interventions such as automated reminder messages about upcoming appointments have shown mixed results with regards to keeping patients engaged in care (109,332,559).

Figure 9.1: The evolution of ART provision in sub-Saharan Africa
(Adapted from Grimsrud et al (61))



Healthier patients including pregnant women may need to be treated differently given that higher CD4 is associated with LTFU (61). There are myriad reasons for this including exposure to the clinic experience which includes long queues and interactions with much sicker patients which may be detrimental to motivation to stay in care especially given they may have never experienced any sickness (240). Furthermore, some authors argue that the care delivery model is outdated and paternalistic, and that expecting patients to report to the clinic monthly might be unrealistic (61,560). We have managed to bring testing to people's doorstep, and we must endeavour to make treatment as convenient. As patients with higher CD4 were more likely to have transferred their care, paper B shows that healthier patients will also have other priorities with regards to treatment provision which will need to fit into a more mobile life. More specifically, with regards to pregnant and postpartum women, paper D showed that each woman will have competing

practices unique to her that need to be accounted for when formulating the best way to deliver treatment to her and her infant.

Consequently, these patients may need different specialised counselling to cater to their particular hurdles and challenges. For example, given the ART stoppage significantly contributed to LTFU, another immediately actionable recommendation would be to continue emphasising the importance of ART beyond preventing vertical transmission and rebranding ART as not just for sick people but as a way to maintain health, especially because feeling healthy and doubts about the effectiveness of ART contribute to disengagement (240,281,354).

Additionally, recognising pregnant and postpartum women's different needs and perhaps moving them out of the clinics or putting them on longer refill schedules earlier will free-up these resources for sicker patients who may benefit more from them. The argument that patients need to be incentivised and monitored through monthly clinic visits is double-edged as a major cause of attrition is the time and monetary investment in monthly visits (561).

Consider also for example that while for a clinician or a researcher, it is their job to be at the clinic, for a patient, clinic attendance while vital to their survival, also eats into time they could spend working, something some patients might see as a greater priority. Therefore, work might take precedence for women who initiate ART while asymptomatic because they perceive deleterious effects of their infection as still far off in the future, but hunger, rent, and other obligations may be more immediate and pressing needs. In designing treatment schedules, clinics should prioritise the clientele and it underlines the need for ART models that fit each person's needs.

Furthermore, daily treatment can be an alienating experience and a constant reminder of HIV even in the absence of symptoms. Therefore, innovations in treatment such as long-acting subdermal medical implants and injections will also be critical to improving retention for these types of patients.

The current global COVID-19 pandemic shows us that now more than ever it is important to consider differentiated models of care. The pandemic has laid bare the fragility of a model where patients' treatment is dependent on regular

clinic visits. Consequently, radical new approaches to ART provision for pregnant and postpartum women will need to be considered. What these new approaches would look like is an important debate to be had and these approaches will have to be evaluated to determine their efficacy.

What might an ideal PMTCT programme look like?

Given the disproportionate number of women affected by HIV and also given the high fertility intentions among women in SSA, most HIV-positive women of child-bearing age will go through a PMTCT programme at some point provided that the health system emphasises the importance of ANC. Therefore, making PMTCT programmes as patient-centred as possible, as integrated as possible and as streamlined as possible will reach the largest number of people living with HIV. For example, longer-term integrated maternal and child healthcare (MCH) where all women of child-bearing age attend a specialised clinic with those who seroconvert automatically entering into the MCH programme in preparation for a possible future pregnancy and childbirth and only transferring once they have fulfilled their fertility intention or are no longer fecund. These clinics would have to include all women as other studies have found that such integrated clinics may not be effective if only HIV-infected women attend them as they potentially increase stigma (332,562). Contraception and other needs can be integrated including HIV care meaning that women get a one-stop shop. This means that their children are also covered and reduces the workload for HCW as it removes the need to probe for things like eligibility but will necessitate more broadly skilled HCWs (563).

There can also be further differentiated care models for mother-infant pairs (198) as the best interventions to improve EID treat the mother-baby dyad as a single entity. This makes sense given that for the first few years of life the infant is completely dependent on its mother. As such, interventions to reach infants should include some incentivisation for the mothers such as the afore-mentioned one-stop shop where they can access other services.

The time immediately following delivery can also be a cause of dropout as women have a new-born to worry about and might still be recovering from delivery. They might therefore be unable to consistently keep clinic

appointments. Treatment and care delivery should be tailored to make sure it causes the least disruptions. Longer refills around this time have been proposed to mitigate this (367,564), as treatment interruptions can be disastrous for mothers (37,496,565,566). Community-based models of care can further improve retention in care. For example, dispensing treatment at distribution points in the community could be offered to Option B+ women at this stage. They can then move back into the clinic once the child needs to receive immunisation and EID.

Immunisation coverage and maternal postnatal retention are higher than EID coverage indicating missed opportunities for infant testing during immunisation visits or ART follow-up for their mothers (198,567). Integration of HIV services with MCH services including immunisation programmes provides a critical opportunity for elimination of vertical transmission.

Non-pregnant women can be put on differentiated care models such as longer refill schedules or community-based care. For older women who transfer to the general population after they have fulfilled their fertility intentions, their needs will be different such as other chronic co-morbidities so other services such as chronic disease care can be emphasised. This system will necessitate decentralisation of ART provision with most of the responsibility designated to CHWs. This in turn will free up the limited professional medical corps to concentrate on more severe cases that would benefit most from their attention. Decentralised treatment can improve programme effectiveness and efficiency (568).

Retention promoting activities are necessary both within the facility and in the community. In the facility these could include adherence support and counselling, and defaulter tracing managed by facility staff. Outreach services and retention promoting activities in the community could be managed by community-based organisations, with coordination of all these activities by case manager (WBOT), and the coordination of patient information systems by data clerks.

Through this all, a supportive/collective approach to treatment delivery should be emphasised as a sense of connectedness to the clinic in conjunction

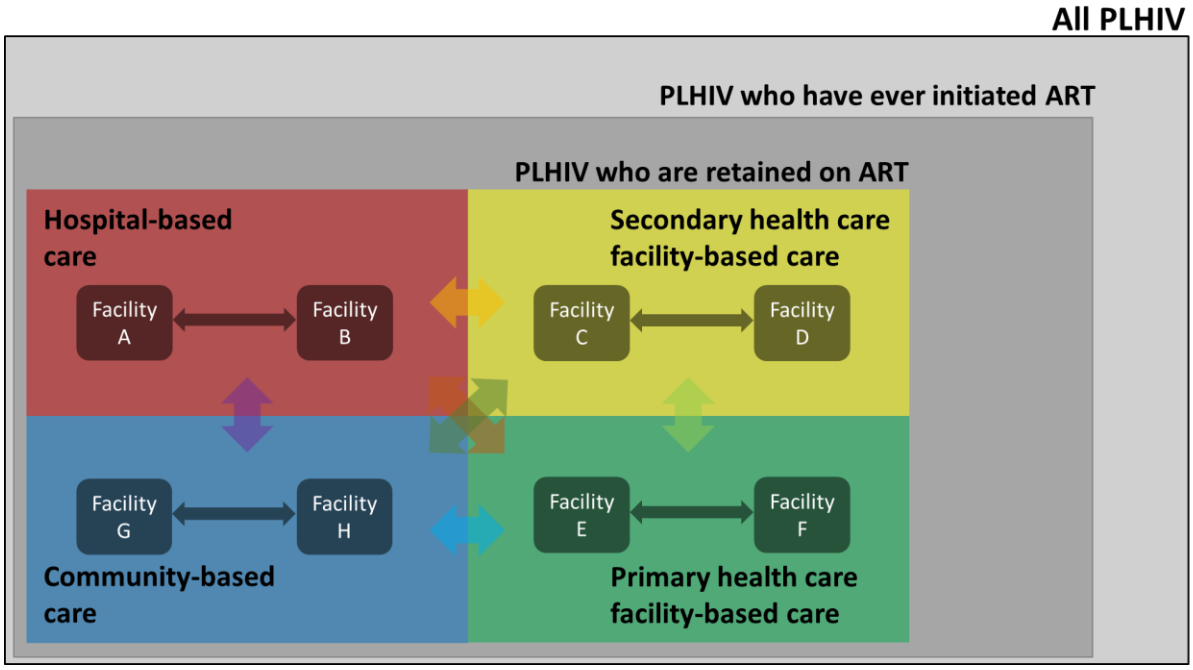
with family support have been shown to fuel patients' motivation to consistently overcome myriad obstacles to keep up clinic appointments (502).

An HIV diagnosis can be an ostracising experience that frays social cohesion. The Western context is one characterised by individualism while the African setting is still predominantly social and collective, as such a treatment programme that mirrors this stands to gain from this approach (358,547). Efforts to create a sense of connectedness such as music and drama groups, and income generating activities (e.g. community farms) recognise that patients who feel disconnected from their community will have poor outcomes which ultimately affect them, their families, and their community. While this might sound utopian and un-scientific, research has shown that interventions that emphasise connectedness and community within the treatment experience consistently have better retention estimates than those that do not (201,342,358,569).

9.3.2. Policies to improve tracking of patients who miss clinic appointments

With the expansion of ART programmes in sub-Saharan Africa, PLHIV can access HIV care at myriad locations. While advantageous to the people in care as it increases the options of facilities to attend for treatment, this expansion has made it much more difficult to track patients' movements within the treatment programme. Figure 9.2 shows what a treatment programme might look like and how patients might move between different facilities and different models of care. Knowing which patients are in care, regardless of which clinic they are attending will reduce LTFU substantially and ensure that appropriate resources are directed to patients that have truly disengaged from care. In order for a system of this nature to be effectively monitored and evaluated, it requires checks and balances that allow for the ascertainment of treatment outcomes independent of the initiating facility.

Figure 9.2: Models of care delivery and movements of patients



A robust surveillance system is recognised by the WHO as essential for elimination programmes (370). A case-based surveillance approach where measurement and monitoring of programmatic outcomes is accomplished by collecting individual patient-level data for key events is recognised as the best practice and serves as the backbone of HIV surveillance in developed countries. While such a system would be ideal, in South Africa, myriad hurdles exist that are hampering its implementation.

With regards to the phenomenon of self-transfer, it may be a patient's attempt at achieving some anonymity (102,285), and this anonymity might increase the likelihood of patients remaining in care and adherent (251,286,319,340). The onus to report their movements must be removed from the patients, especially considering that patients often move because of the same people (HCWs) to whom they are supposed to report their transfer (237,245,340). Data layers that allow for those responsible for monitoring and evaluation to do case surveillance (to flag silent transfers), that automate patient alerts (such as missed appointments) and allow for monitoring of clinic procedures offer a way for facilities to improve their operations and correct their estimates and statistics without breaking patient confidentiality.

One immediately actionable policy that would have the greatest effect on programmes' ability to track patients would be to institute a unique identification system (570–572). As mentioned previously, the availability of unique identifiers through the PIRL database significantly improved my ability to find patients at different clinics. Given how much LTFU is attributable to mobility in the form of migration and transfers to other facilities (which are sometimes "silent"), unique identifiers would help to monitor this mobility. This will ensure that patient outcomes are ascertained beyond the initiating facility.

In addition to the unique identifiers, the ability to link the different clinic databases through the PIRL database also helped to improve ascertainment of patient outcomes. The WHO also recommends data linkage, as unique identifiers on their own would be less effective without an overarching data infrastructure that links facility data (370). Linked data allows for measuring care continuity, for patient tracing beyond the facility of ART initiation, and for interventions as needed. The architects of TIER.Net recognise this and it is intended for the disparate facility databases to be linked at some point in the future. This by necessity is a more long-term objective but there are some short-term interventions that could improve patient tracking before a linked facility database becomes a reality.

Firstly, ensuring regular exchange of information between facilities (364). Given that TIER.Net data clerks have regular regional meetings, these could be restructured to include data consolidation exercises where review and comparison of patient lists is done using National IDs in the best-case scenario, and names and dates of birth in the worst case to catch silent transfers.

Innovation will also be required to develop better methods to track patients. Tracking down patients is notoriously hard in an environment with no functioning address system, or poor infrastructure that means that some places are cut off in rainy seasons. Some policies are already recommended but are not consistently implemented, for example, asking if the patient's contact information is accurate or if it has changed at every visit. This would ensure

that contact information remains up to date for the purpose of telephone tracing.

Programmes also need to develop services that are more adapted to harder to find patients. For the qualitative component of my research, I managed to use household GPS coordinates routinely collected by the HDSS to locate LTFU patients for IDIs. Readily available data like this could be utilised to try and locate lost patients. In a situation of a public health emergency, is it ethical to share this information with clinics? Clinics typically collect location data by asking for important landmarks near patients' homes. This more accurate location data would significantly improve patient tracing efforts. I think the clinics need all the help they can get, provided the data can be utilised in a manner that does not breach confidentiality, it would be of added benefit to the treatment programme. As other countries utilise all data available to them to track patients who go off the grid[8], it makes sense to do the same in this setting if we are going to achieve 90-90-90 and then 95-95-95 goals.

9.3.3. Policies to improve EID uptake and infant outcomes

The major objective which is elimination of vertical transmission should not be forgotten. Mothers' outcomes are important, and children's long-term outcomes are worse if their mother dies. Equally, an unfavourable outcome for the infant such as seroconversion is similarly detrimental. This is the balance that PMTCT programmes must strike.

Healthcare workers' understanding of EID and the logistics of its implementation are an important consideration. For example, through the IDIs one participant mentioned that if they arrived after sample collection, they were instructed to come back the next day. However, one of the reasons for the use of dried blood spots (DBS) is because they are quite stable, provided they are protected from humidity and moisture, and can be stored at room temperature (573). This perhaps indicates a need for better training of HCWs regarding the logistics of EID. It might also point to a lack of understanding on the part of the mother. It is possible that HCWs were referring to other blood tests which the mother misconstrued to mean EID. Furthermore, it

[8] See for example https://www.gov.uk/guidance/hiv-surveillance-systems "UK HIV surveillance systems" [accessed 28 August 2020]

might speak to a breakdown in communication where a mother was requesting for EID for her infant but the HCW mistook her request to be one for another blood test.

In South Africa infant mortality remains high, estimated at 28.5 deaths per 1000 live births in 2019[9]. Historically HIV exposed infants had even higher risk of mortality (274). Perhaps, because of this expectation, less focus was placed on EID, especially before the rollout of effective PMTCT programmes. It may be that for HEI where deaths are a more common occurrence independent of HIV transmission (275,276), the risk of infant mortality might not be a big enough incentive to encourage EID. In fact, death might be seen as respite or relief from a complicated life for their infant especially if mothers have faced challenges like stigma and ostracism due to their own diagnosis (267). Therefore, interventions to reduce stigma as well as interventions that weaken the links between a positive EID result and disengagement from care such as specialised counselling might mitigate fear of completing EID.

Late antenatal clinic attendance, incident maternal HIV infections during late pregnancy or the postpartum period, loss to follow-up from ART, and persistent viremia among HIV-infected women are among reasons for ongoing new paediatric HIV infections (244,574). As such, interventions tailored to these specific barriers will also improve HEI outcomes.

Studies have also shown that point-of-care EID testing improves uptake of EID (270,575,576). As such, point-of-care EID testing should be considered in PMTCT programmes to complement laboratory testing. Other interventions that may improve EID uptake include opt-out rather than opt-in testing policies where all infants receive an HIV test as part of their immunisation schedule. This may reduce the stigma of infant testing and also cast a wide net to capture any infant seroconversions from maternal seroconversion late in the pregnancy or breastfeeding period. This policy has been shown to improve uptake in other settings (577–579). Programmes should also consider improved links between mother-baby pairs in order to identify HIV-exposed infants. Some recent research is looking into the effects of this measure.

[9] See https://childmortality.org/ "UN Inter-agency Group for Child Mortality Estimation" [accessed 28 August 2020]

However, given that one of the major reasons infants do not get tested is because the system may not be aware of their HIV exposure (198,580), any intervention that makes it easier to identify HEI may improve the uptake of EID. Given that this research showed some mothers disengaged from care due to the dual burden of theirs and their infant's clinic visits, in the unfortunate event that a child tests positive, at worst, their clinic visits should be arranged to coincide with those of the mother, or better yet their clinic visits should be integrated. Women should not have to decide between their infant and their own health.

As these all become more prevalent as ART programmes mature, it is important to study if they really influence LTFU. Ascertainment of infant outcomes is inextricably linked with their mothers staying in care, maternal LTFU often means infant outcomes do not get fully and accurately reported (198,580). Any interventions for the mothers will influence the outcomes of the infants as well.

Box 2: Recommendations for policy and practice

Interventions to mitigate gaps in treatment and engagement in care

- Differentiated care including integrated mother-baby clinics past 6-10 weeks postpartum for Option B+
- Better data entry procedures and automated alerts for late patients
- Improve patient awareness of transfer procedure, strengthen the patient referral system, and simplify the transfer process
- Community distribution of treatment for pregnant women or longer refills around time of delivery
- Specialised counselling for new mothers to reduce the risk of drop-out due to a positive infant test

Improve tracking of patients who miss a clinic appointment

- Make sure to enter national ID numbers and updated telephone numbers for all patients
- Clinics should be encouraged to regularly exchange information on missing patients
- Form partnerships with the research community e.g. Agincourt HDSS routinely collects data on deaths and migration events

Interventions to improve uptake of early infant diagnosis

- Opt-out vs opt-in infant testing
- Point-of-care infant testing
- Better linkage of mother-baby pairs within clinic data

9.4. Recommendations for future research

Some of the findings of this research warrant further investigation. Some future research directions include:

Investigation of re-engagement in care. Re-engagement in care was the second most prevalent outcome for patients that had been recorded as LTFU. More research needs to be done to understand the factors associated with re-engagement in care. One factor that warrants further investigation is whether new pregnancies are associated with re-engagement in care. Furthermore, research testing and monitoring interventions to improve retention and reengagement in PMTCT such as text messaging needs some investigation.

Repeat testing for women who test negative during pregnancy. Late seroconversion emerged as a reason for one mother's disengagement from care in the IDIs. The timeline of this mother's seroconversion was probably after the 18-month EID test, but before the end of the breastfeeding period. The confusion of receiving a positive result for an infant that late was detrimental to her engagement in care. As such, more research is needed to ascertain the frequency of testing for mothers who initially test negative at ANC. The gap between the end of breastfeeding and the 18-month EID test will also need further research to make sure that infant testing is continuing past the end of the breastfeeding period.

Infant outcomes. While I was able to ascertain the outcomes for women who had been LTFU, this was not possible for their infants for many reasons. For example, uptake and results of EID for infants of the women interviewed as part of the IDIs were all self-reported and could not be corroborated. One of the major reasons infant outcomes could not be ascertained was a lack of identifiers that paired mothers and their infants. Future research should investigate infant outcomes to see how different outcomes for mothers influence the outcomes of their infants.

More research on LTFU is needed in other settings. While these findings are important and add to the available research on LTFU in sub-Saharan Africa, it might not be possible to extrapolate some of the findings to other settings such as those within the same region where labour migration is not a common phenomenon as migration probably plays a pivotal role in

patients' decision to transfer their care to another facility. Future research should also consider LTFU for teenage mothers (<18 years). Younger mothers have been shown to be different from older mothers in many ways (69,305,331,332,581). Consequently, it is possible that their outcomes following LTFU will differ significantly from those of the women represented in this body of work. Furthermore, patients who are lost before ART initiation will differ significantly from the group represented in this research. As such, further investigation of this group is an important consideration for future research. Additionally, how we operationalise or define LTFU especially in the presence of differentiated models of care will be important work to consider as treatment programmes continue to expand. Similarly, more research is needed on how we operationalise LTFU and retention in care where several facilities and changes in engagement e.g. treatment gaps, re-engagement, and transfers are also incorporated. If future research considers overall patterns and corrects for them, we may get a more accurate picture of retention in care and engagement in care more generally.

With regards to the mechanisms that drive retention, future research could compare retention rates in settings where integrated PMTCT and ANC services are offered up to 6-10 weeks like South Africa, and those where it goes up to 24 months (296). This might introduce challenges to retention especially if this transfer entails moving to a geographically separate clinic rather than between departments at the same clinic and involves accessing treatment from further away. The WHO has called for further research to determine the optimal time of transfer back to general population ART clinics and therefore more research on this may be needed before an official recommendation can be made (582,583).

Finally, the current COVID-19 pandemic shows how volatile my findings might be. The pandemic and the interventions implemented to mitigate its effects have caused interruptions to every aspect of the PMTCT cascade both with regards to the demand and supply of health services (584). In some places, healthcare workers have either gone on strike or refused to go to clinics for fear of either contracting COVID-19 or being shunned by their family members (585–587). This has the knock-on effect that services such as ANC, HIV

testing, and ART initiation may be severely hampered by lack of staff. Fears around COVID-19 and the need for protective equipment to visit clinics (which they may not be able to afford) may have also led to patients foregoing attending ANC, or routine ART clinic visits. These will all impact LTFU statistics as well as the outcomes following LTFU, with some mathematical models making some sobering conclusions (588,589). As such, research to consider how the pandemic might have affected these results is warranted.

Given that we were unable to resolve all the instances of LTFU and that migration was an outcome reported in the research findings, this identifies a new challenge in measuring retention. How best can we measure and incorporate mobility and migration of patients into the measurement of retention in care? Answering this question will be imperative to reducing instances of LTFU, especially for pregnant and postpartum women who may be more mobile (18,102). Some studies have used aggregated mobile phone network data retrospectively to study population mobility in relation to health issues such as natural disasters and disease transmission (590,591). Whether similar analyses could be utilised to study HIV retention especially in highly mobile populations might warrant some research.

The sheer amount of data generated through the IDIs and the limited time to complete my research meant that many topics of interest beyond what I have currently presented were identified, but I was not able to analyse all the data collected through the IDIs. Consequently, I have only scratched the surface, and this is data that I will revisit in the future as further analyses are required to explore and unpack many of the themes that were emerging from preliminary analyses. I chose to present themes that aligned with my research and this choice frames the findings presented. Themes like seroconversion late in pregnancy or in the breastfeeding period and its influences on engagement in care, the concept of engagement in care from patients' perspective and how this differs from our definition as researchers for example patients saw nothing wrong with say temporarily collecting treatment from another clinic where they worked, or collecting treatment from multiple clinics simultaneously in order to build up a cache before taking a short hiatus from visiting the clinic or travelling for work will be interesting topics to explore in

the future. I would also like to further explore the differences in themes that emerge around engagement in care comparing Option B+ women and adults that initiated ART for their own health.

9.5. Strengths and limitations

The overall strengths and limitations of this body of research are presented in this section with a focus on the key issues of this work with the different study components incorporated.

9.5.1. Strengths

Data used in this thesis come from a well-established cohort study. The availability of demographic data for 88% of the patients that were LTFU was invaluable in ascertaining patients' outcomes.

A major strength of this thesis is the mixed methods approach I adopted which involved both qualitative and quantitative components conducted in the same community around the same time. The quantitative component was essential to building the sampling frame for the qualitative component. Additionally, the methods used for the quantitative component identified new and important avenues for future research. Research using clinic data linked to a community cohort has only recently began to be undertaken in Africa. The analysis in this thesis provides community level statistics and estimates of outcomes following LTFU. The quantitative component also provided methodological contributions for measuring retention, and for linkage strategies to build a linked facility database.

The use of routine clinic data allowed the monitoring of a health system in real life, many of the cohorts providing data for previous estimates of outcomes were large, established research intervention and clinical trial cohorts supported by academic and non-governmental partners and not likely to be representative of the national cohorts. The inclusion of participants from all government facilities that serve the HDSS community was an advantage as it provided a more complete picture of LTFU in this community. Additionally, the recruitment of participants for the IDIs through a sampling frame built from various data sources meant that we were able to include patients that were currently not in care, a group that is usually underrepresented in research.

9.5.2. Limitations

The use of observational data for the quantitative component of this research is associated with potential bias and confounding. While I attempted to account for survivorship bias by only including patients who had initiated ART after record linkage began, it may be that some of these patients were in fact just re-initiating treatment at a different clinic. Restricting the analyses to patients who initiated ART after record linkage began means that the results of this research might only be generalisable to cohorts situated in similar time period especially since the advent of "test and treat" may change the composition of ART cohorts. Additionally, there are several private treatment facilities within the study area as well as government facilities just outside the periphery the study area. The exclusion of these facilities means that it is possible that some PLHIV receiving treatment in these facilities were not captured by this exercise.

There were several drawbacks with regards to data quality issues both within the clinic and HDSS databases. Socioeconomic factors could not be assessed for their association with the various outcomes as variables such as education status, marital status, and SES had varying levels of completeness. As such, confounding due to unmeasured variables is a possibility.

With regards to ascertainment of causes of death, verbal autopsy data was missing for 52% of the deaths we identified through this research. As such, we were unable to ascertain the causes for the majority of deaths reported in this research. These deaths could be due to other causes such as external trauma due to road accidents which is prevalent in South Africa (394,592) and would warrant different considerations if so. For example, interventions at the clinic level or with regards to treatment service delivery might have very little effect on these sorts of deaths.

Additionally, limitations on the linkage algorithm meant that 12% of the participants in this study did not have an HDSS record attached to their clinic record. The probabilistic algorithm for finding matches is not perfect and unfortunately in some cases, even in the presence of the patient, the records of those reporting residence in the HDSS could not be linked to the HDSS dataset. This could mean that patients misunderstood the question regarding

their residency, or that they thought that there might be some incentives for answering in the affirmative. It could also mean that they were genuine residents whose record could not be retrieved for a myriad of reasons including differently spelled names, or that they had moved into the HDSS after the most recent census round meaning their record had yet to be entered into the database. It was impossible to differentiate the different groups, so to minimise selection bias, all of them were kept for the analyses.

With the exception of paper C, this thesis only addresses losses after ART initiation. About 5% of patients investigated had not yet initiated treatment when they became LTFU. However, these were not included in papers A and B. This was done intentionally as the changes in treatment eligibility mean that the pre-ART phase has now been phased out and LTFU following ART initiation is a greater challenge for a myriad of reasons including risks of developing drug resistance. However, loss to follow-up occurs at multiple points on the treatment cascade and research shows that many patients (especially pregnant women) are lost following a positive HIV diagnosis but before they initiate ART (212,241,593,594). Patients who become LTFU before ART initiation will differ significantly from patients who might have accrued some benefits from ART and as such their exclusion from the research is a limitation.

There was a missed opportunity in failing to synthesise and triangulate the qualitative and quantitative data which would have helped to bolster the results from each component. Whereas quantitative analyses are important for measuring the extent of the issue, qualitative analyses would have helped to understand why. It was originally planned for the qualitative component to be used to complement the findings from the quantitative component. This approach would have helped to contextualise the findings by placing them within the narrative of individual participants. However, because the production of this body of work is time-bound, some plans had to be postponed for future enquiry (I go into further detail on this in the section 9.6.3).

Furthermore, the short time frame for qualitative data collection which lasted just over a month meant that I was unable to conduct repeat interviews to see

how participant experiences might have changed temporally. However, the qualitative findings are still important in giving detailed descriptions of participants' experiences and giving meaning to their actions (595). Furthermore, all infant testing outcomes were self-reported by the mother reflecting data quality and availability issues with no links between maternal and infant records.

The participants for the IDIs came from the HDSS population, which might be considered an over researched group. This could be a problem for the qualitative component of the research as participant fatigue can influence the findings of qualitative research (596–598). Furthermore, there were people approached who chose not to participate. These non-participants might differ significantly from participants and their experiences might differ from those discussed or described by participants within this research. Finally, the qualitative component does not document the experiences of health care workers and therefore missed the opportunity to juxtapose their position with that of patients in this setting.

9.6. Dissemination

The findings of this research have already been, or will shortly be shared with healthcare workers, researchers and Right-to-Care officials who work in the Agincourt HDSS. While the plan was to travel to South Africa later this year to disseminate the findings locally, given the current travel restrictions due to COVID-19 these plans have been replaced in favour of electronic communications.

9.6.1. Health workers, researchers, and community members in Agincourt

As part of their routine operations, the Agincourt HDSS has a public engagement office responsible for the dissemination of findings from research conducted within the HDSS. I plan to prepare a short report to share with them for this purpose. The public engagement office will share these findings with individual health facility managers and staff as well as health officials charged with the management and operations of all the Home-Based Carers organisations that operate within the HDSS. All my papers were co-authored by researchers who work primarily in the HDSS, so they are already aware of some of the recommendations emanating from this research.

9.6.2. Right-to-Care

I was in conversation with the RtC programme manager over email, in order to get permission to access their data. Data sharing was agreed on condition that findings from the research would be shared with them in order to improve their operating procedures. The same report distributed to the Agincourt public engagement office will be made available to the Right-to-Care organisation via email.

9.6.3. Researchers – Academic conferences and publications

Some of the papers contained within this thesis have already been published in peer-reviewed journals with broad international readership in the fields of HIV and other public health research. Additionally, the following presentations were made at conferences in 2018-2019 (posters or slide sets are included in the appendix):

Appendix 11.1.5: Etoori D, Wringe A, Reniers G, Renju J, Ndhlovu V, Ndubana S, Sihlangu E and Gomez-Olive FX. "Mothers' experiences of early infant diagnosis for HIV in Option B+ programmes and the implications for their engagement in care: Qualitative evidence from South Africa" Poster presented at the International AIDS Conference (AIDS), Amsterdam, Netherlands; July 2018.

- A precursor to the qualitative paper on EID and maternal engagement (paper D) presented in this thesis.

Appendix 11.1.4: Etoori D, Wringe A, Kabudula C, Gomez-Olive FX, Reniers G "Re-engagement in care following loss to follow-up from HIV treatment and care: findings from a cohort study in rural South Africa" Poster presented at the International Workshop on HIV and Hepatitis Observational Databases (IWHOD), Athens, Greece; March 2019.

- A quantitative analysis of the factors associated with re-engagement in care for women, non-pregnant and Option B+ following loss to follow-up.

Appendix 11.1.3: Etoori D, Wringe A, Kabudula C, Gomez-Olive FX, Reniers G "Use of linked clinic and demographic surveillance data to improve estimates of outcomes of HIV patient tracing in Agincourt Health and Demographic

Surveillance System (AHDSS)" Poster presented at the International Workshop on HIV and Hepatitis Observational Databases (IWHOD), Athens, Greece; March 2019.

- Preliminary analyses for one quantitative results paper (paper A) presented in this thesis.

Appendix 11.1.1: Etoori D, Wringe A, Rice B, Renju J, Gomez-Olive FX, Kabudula C, Reniers G "Mobility and clinic switching among HIV patients considered lost to follow-up in north-eastern South Africa." Oral presentation at the African Population Conference (APC), Entebbe, Uganda; November 2019.

- Preliminary analyses for one quantitative results paper (paper B) presented in this thesis.

Appendix 11.1.2: Etoori D, Wringe A, Rice B, Renju J, Gomez-Olive FX, Kabudula C, Reniers G "Mobility and clinic switching among HIV patients considered lost to follow-up in north-eastern South Africa and consequences for estimating the second 90-90-90 target." Poster presented at the International Conference on AIDS and STIs in Africa (ICASA), Kigali, Rwanda; December 2019.

- Preliminary analyses for one quantitative results paper (paper B) presented in this thesis.

Plans for future publications in peer-reviewed journals include a paper on re-engagement in care following loss to follow-up. Papers based on the qualitative data are also planned, for example, a qualitative analysis of the differences in experiences of engagement with care for Option B+ women compared to the general treatment population will be undertaken as an extension of this body of work as one of the emerging themes from the qualitative data was how the treatment experiences of pregnant and postpartum women differ from those of the general ART cohort particularly because of their pregnancy and the extra services they must navigate for their infant's treatment.

A presentation on the quantitative component of my research is planned for a Measurement and Surveillance of HIV epidemics (MeSH) consortium meeting in late September 2020.

A pre-Viva seminar was undertaken to present the overall findings from my research to other researchers at LSHTM.

9.6.4. Feedback to funders

I collaborated with the deputy director of the MeSH consortium which funded my fieldwork. He has received regular updates and reports regarding my progress. He has also participated in the write-up and is a co-author on three of my publications. A presentation on the quantitative component of my research is planned for a MeSH consortium meeting in late September 2020.

9.6.5. Data sharing

The record review and tracing dataset will be anonymised and stored securely within the data infrastructure of the Agincourt HDSS. These data will be made available on request through the Agincourt HDSS data manager and following the signing of a data sharing agreement. The qualitative data may be available on request to me. Transcripts have been thoroughly checked to ensure data are confidential.

9.7. Conclusions

This thesis investigated loss to follow-up with specific considerations for women who initiated treatment for PMTCT under Option B+. The major finding of this research is that outcomes following lost to follow-up differ for pregnant women when compared to the general ART treatment cohort. As such findings from this research begin to explain the differences in retention rates for these two groups. Mortality and actual ART stoppages contributed very little to LTFU for women who initiated treatment for PMTCT under Option B+ and therefore interventions that target transfers to other facilities and re-engagement in care may be more effective for these patients. These interventions must strive to incorporate the constellation of practices that these women engage in, including practices connected to their infant, in order to account for any interactions and prevent unintended consequences.

Low retention rates for Option B+ programmes may negate their potential positive impacts and may explain the increasing occurrence of vertical

transmission in the postpartum period. Therefore, programmes should strive to reduce the occurrence of LTFU and actively trace patients who do become LTFU as this will have positive effects for the mother, her infant, future pregnancies, and serodiscordant partners.

Health systems may need to consider differentiated and patient-centred models of care to make treatment more convenient for patients. Similarly, addressing health system weaknesses in the ascertainment of patient outcomes following LTFU may have a great impact on retention estimates in this setting and in sub-Saharan Africa as a whole and therefore improve PMTCT programmatic outcomes.

Finally, while these findings are important and add to the compendium of research on LTFU from HIV programmes in sub-Saharan Africa, it takes one unexpected but widespread event like the COVID pandemic to demonstrate their fragility. The knock-on effect of COVID in terms of EID, testing, clinic visits, mobility, drug refills, and how all these might be influenced for women initiating treatment for PMTCT under Option B+ will be felt for a very long time and is therefore an important consideration for future research.

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11. Appendices

11.1. Conference presentations and posters

11.1.1. African Population Conference presentation slides

11.1.2. ICASA conference poster

11.1.3. IWHOD conference poster (Tracing outcomes)

11.1.4. IWHOD conference poster (Re-engagement)

11.1.5. AIDS 2018 conference poster

11.2. Ethical clearance certificates

11.2.1. Agincourt HDSS study activities

11.2.2. Fieldwork study

11.3. Fieldwork tools

11.3.1. Record review and tracing Visual Basic data entry forms

11.3.2. IDI consent form

11.3.3. IDI information sheet

11.3.4. IDI topic guide

11.1. Conference presentations and posters

11.1.1. African Population Conference presentation slides

Mobility and clinic switching among HIV patients considered lost to follow-up in north-eastern South Africa

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Outline

1. Background
   a. Loss to follow-up
   b. Mobility and clinic switching
2. Aim
3. Methods
   a. Setting
   b. Data sources
   c. Analyses
4. Results
5. Discussion and conclusions

Background: Loss to follow-up

- PMTCT studies report retention rates as low as 52% after 12-18 months on antiretroviral therapy (ART)
  - Increased transmission risk
  - Poorer health outcomes
  - Drug resistance
- Patients late for a scheduled ART refill are classified as lost to follow-up (LTFU)
  - Amalgamates undocumented transfers + ART interruptions + ART stoppages + deaths + misclassifications
- Accurately capturing outcomes of patients LTFU challenging across sub-Saharan Africa

Background: Patient mobility

- Particularly hard to capture in a setting where clinics are not linked together
  - Women more mobile before and after pregnancy
- The study setting (Agincourt Health and Demographic Surveillance System) is located in a former Bantustan
  - Historically agriculturally and economically inhospitable leading to high unemployment rates
  - Many inhabitants forced to migrate for work
  - Reliance on remittances as an important income source

Aim

General aim:

- To understand what happens to patients after they stop attending their scheduled clinic visits (when they become LTFU)

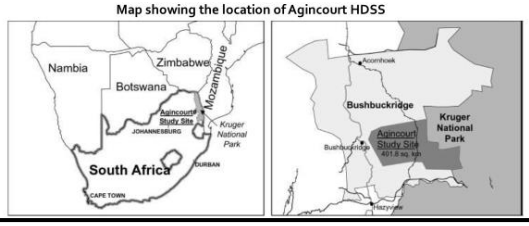
Specific objective:

- To describe the patterns of mobility and clinic switching among patients considered LTFU

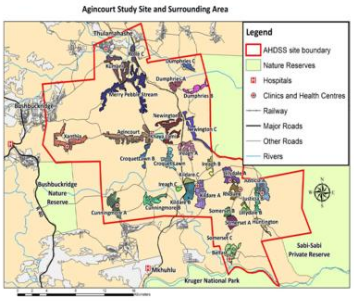
Methods: Setting

- Agincourt Health and Demographic Surveillance System (HDSS) is located in rural north-eastern South Africa.
- Established in 1992; ~475 km²
- ~115,000 residents (2014).
- Baseline survey in 1992, 3 update rounds until 1998, and annual surveys since 1999.

Map showing the location of Agincourt HDSS



Methods: Setting



Point-of-contact Interactive Record Linkage (PIRL):
Since 2014, chronic care patient visits in the clinics (NCD and HIV) have been recorded and linked to the patient's HDSS record, provided that they ever lived in the HDSS.

Methods: Tracing study

Extracted a list of patients who were LTFU from PIRL database on August 15, 2017.

- **Record review**
  - Compared list to all available clinic records
  - Checked HDSS records (migration or death)
- **Supplementary tracing**
  - Patients for whom an outcome was not ascertained
  - Patients who did not receive routine tracing
- **Final TIER.Net check**
  - At clinics in close proximity to the patient's residence
  - Capture any further silent transfers

TIER.Net (National electronic HIV treatment database)
Physical patient files
Right-to-care logbooks
Home based carers logbooks
PIRL database for duplicates (different clinic records linked to the same individual)
Agincourt HDSS database for residency and vital status

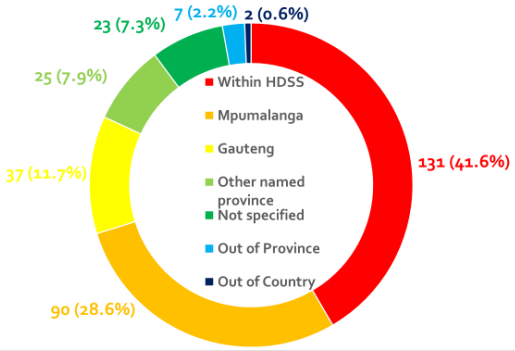
Methods: Analysis

- Calculated counts and proportions for baseline characteristics and final outcomes
- Graphically represented flows of patients from the different clinics within the HDSS
- A spatial analysis was conducted to assess patterns of movement between clinics.
  - Google maps was used to ascertain decimal degree coordinates
  - Using ArcMap 10.3.1, the coordinates were imported to shape files with a WGS 1984 coordinate system.

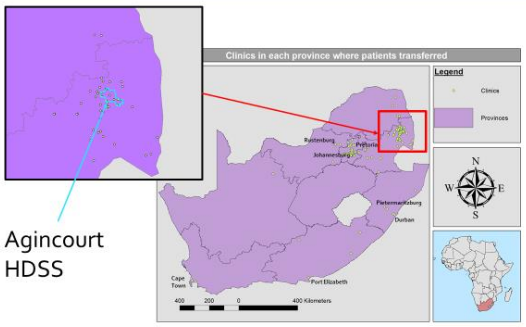
Results

Outcome	All patients (LTFU)	Pregnant women	Non-pregnant women	Men
Transferred	**315 (31.0%)**	82 (29.3%)	176 (36.1%)	57 (22.8%)
Deceased	**120 (11.8%)**	10 (3.6%)	60 (12.3%)	50 (20.0%)
Alive and not on treatment	**75 (7.4%)**	28 (10.0%)	20 (4.1%)	27 (10.8%)
Migrated	**49 (4.8%)**	21 (7.5%)	22 (4.5%)	6 (2.4%)
Re-engaged in care	**225 (22.1%)**	54 (19.3%)	110 (22.6%)	61 (24.4%)
Alive: treatment status unknown	**111 (10.9%)**	45 (16.1%)	45 (9.2%)	21 (8.4%)
Unresolved (still LTFU)	**112 (12.0%)**	40 (14.3%)	54 (11.1%)	28 (11.2%)
Total	**1017**	**280**	**487**	**250**

Results: Destination clinic

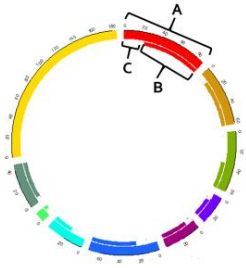


Results



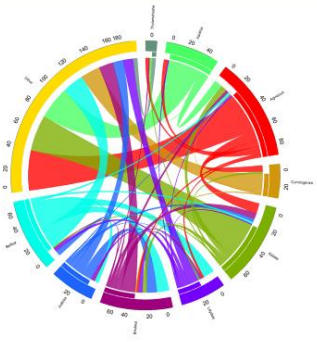
Agincourt HDSS

Results: Transfer flows with circular plots



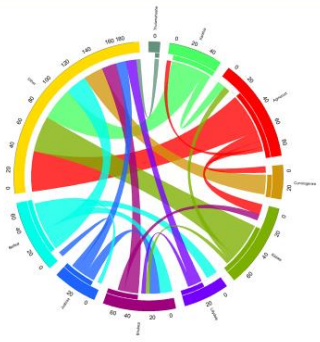
A –Total transfers
B – Transfers out
C – Transfers in

Results: All Transfers



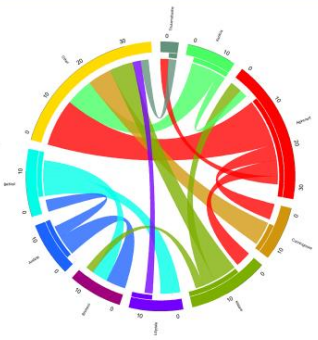
Results: All Transfers (largest 50%)

- 42% of transfers other facilities outside the HDSS
- More transfers out than transfers in
- Movements based on proximity



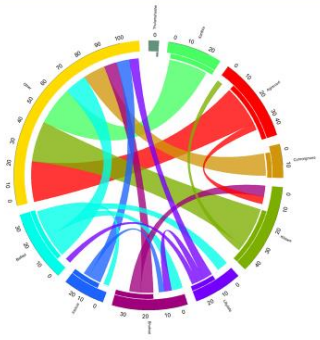
Results: Only pregnant women (largest 50%)

- 44% transferred to clinics outside the HDSS
- Proximity still a major factor



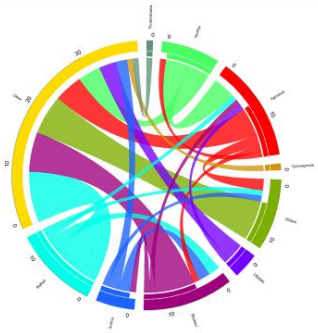
Results: Only non-pregnant women (largest 50%)

- 62% transferred to clinics outside the HDSS
- Proximity still a major factor



Results: Only men (largest 50%)

- 68% transferred to clinics outside the HDSS
- Proximity less important

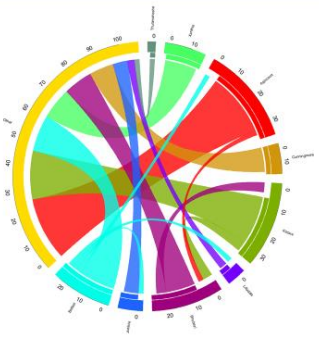


Results: Transfer types

Transfer type	All patients (LTFU)	Pregnant women	Non-pregnant women	Men
Documented	133 (42.2%)	25 (30.5%)	81 (46.0%)	27 (47.4%)
Undocumented	182 (57.8%)	57 (69.5%)	95 (54.0%)	30 (52.6%)
Total	**1017**	**82**	**176**	**57**

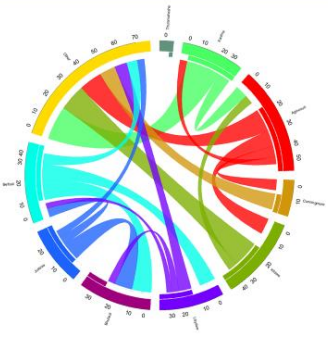
Results: Only documented transfers (largest 50%)

- 80% transferred outside the HDSS

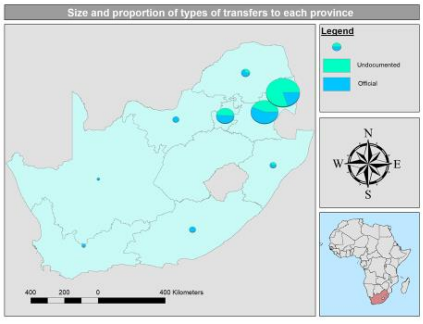


Results: Only undocumented transfers (largest 50%)

- 42% transferred outside the HDSS



Results



Discussion

- We found evidence of continued care after LTFU and identified local and nationwide clinic mobility among HIV patients.
- A linked database will be needed to improve ascertainment of patient outcomes among more mobile patients.

- Future analyses
  - Factors associated with transfers e.g. change in marital status
  - When transfers are happening especially for pregnant women
  - What regimen (first or second) especially for silent transfers

Thank you!

11.1.2. International Conference on AIDS and STIs in Africa (ICASA) conference poster

Mobility and clinic switching among HIV patients considered lost to follow-up in north-eastern South Africa and consequences for estimating the second 90-90-90 target

WEPEB091

David Etoori[1], Alison Wringe[1], Brian Rice[1], Jenny Renju[1,2], F. Gomez Olive-Casas[3], Chodziwadziwa Kabudula[3], Georges Reniers[1,3]

BACKGROUND

LOSS TO FOLLOW-UP

- PMTCT studies report retention rates as low as 52% after 12-18 months on antiretroviral therapy (ART)
  - Increased transmission risk
  - Poorer health outcomes
  - Drug resistance
- Patients late for a scheduled ART refill are classified as lost to follow-up (LTFU)
  - Amalgamates undocumented transfers + ART interruptions + ART stoppages + deaths + misclassifications
- Accurately capturing outcomes of patients LTFU challenging across sub-Saharan Africa

PATIENT MOBILITY

- Particularly hard to capture in a setting where clinics are not linked together
  - Women more mobile before and after pregnancy
- The study setting (Agincourt Health and Demographic Surveillance System) is located in a former Bantustan
  - Historically agriculturally and economically inhospitable leading to high unemployment rates
  - Many inhabitants forced to migrate for work
  - Reliance on remittances as an important income source

AIM

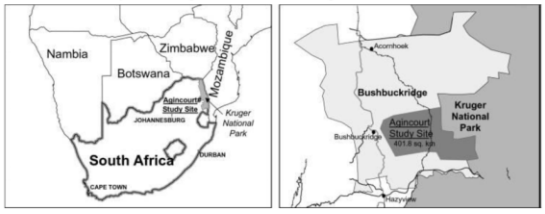
- To describe the patterns of mobility and clinic switching among patients considered LTFU

METHODS

SETTING

- Agincourt Health and Demographic Surveillance System (HDSS) is located in rural north-eastern South Africa.
- Established in 1992; ~475 km^2.
- ~115,000 residents (2014).
- Baseline survey in 1992, 3 update rounds until 1998, and annual surveys since 1999.

Map showing the location of Agincourt HDSS



POINT-OF-CONTACT INTERACTIVE RECORD LINKAGE

Since 2014, chronic care patient visits in the clinics (NCD and HIV) have been recorded and linked to the patient's HDSS record, provided that they ever lived in the HDSS.

TRACING STUDY

- Extracted a list of patients who were LTFU from PIRL database on August 15, 2017.

Record review
- Compared list to all available clinic records
- Checked HDSS records (migration or death)

Supplementary tracing
- Patients for whom an outcome was not ascertained
- Patients who did not receive routine tracing

Final TIER.Net check
- At clinics in close proximity to the patient's residence
- Capture any further silent transfers

- TIER.Net (National electronic HIV treatment database)
- Physical patient files
- Right-to-care logbooks
- Home based carers logbooks
- PIRL database for duplicates (different clinic records linked to the same individual)
- Agincourt HDSS database for residency and vital status

ANALYSIS

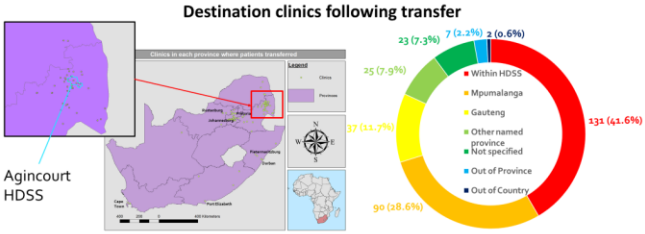
- Calculated counts and proportions for baseline characteristics and final outcomes
- Graphically represented flows of patients from the different clinics within the HDSS
- A spatial analysis was conducted to assess patterns of movement between clinics.
  - Google maps was used to ascertain decimal degree coordinates
  - Using ArcMap 10.3.1, the coordinates were imported to shape files with a WGS 1984 coordinate system.

RESULTS

Table showing outcomes for all LTFU patients following tracing

Outcome	All patients (LTFU)	Pregnant women	Non-pregnant women	Men
Transferred	315 (31.0%)	82 (29.3%)	176 (36.1%)	57 (22.8%)
Deceased	120 (11.8%)	10 (3.6%)	60 (12.3%)	50 (20.0%)
Alive and not on treatment	75 (7.4%)	28 (10.0%)	20 (4.1%)	27 (10.8%)
Migrated	49 (4.8%)	21 (7.5%)	22 (4.5%)	6 (2.4%)
Re-engaged in care	225 (22.1%)	54 (19.3%)	110 (22.6%)	61 (24.4%)
Alive: treatment status unknown	111 (10.9%)	45 (16.1%)	45 (9.2%)	21 (8.4%)
Unresolved (still LTFU)	112 (12.0%)	40 (14.3%)	54 (11.1%)	28 (11.2%)
Total	1017	280	487	250

Destination clinics following transfer



Circular plots showing origin and destination clinics for patients who transferred

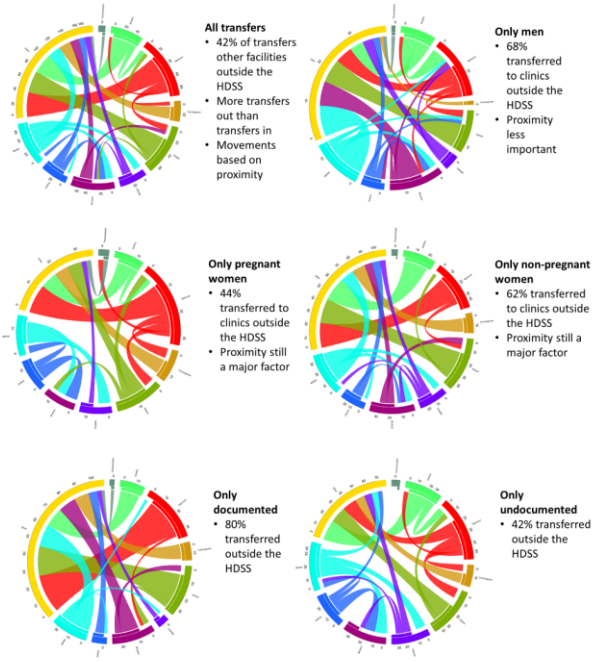


Table showing the types of transfers by sex and pregnancy status at ART initiation

Transfer type	All patients (LTFU)	Pregnant women	Non-pregnant women	Men
Documented	133 (42.2%)	25 (30.5%)	81 (46.0%)	27 (47.4%)
Undocumented	182 (57.8%)	57 (69.5%)	95 (54.0%)	30 (52.6%)
Total	315	82	176	57

DISCUSSION

- We found evidence of continued care after LTFU and identified local and nationwide clinic mobility among HIV patients.
- A linked database will be needed to improve ascertainment of patient outcomes among more mobile patients.

1 London School of Hygiene and Tropical Medicine, United Kingdom
2 Kilimanjaro Christian Medical University College, Tanzania
3 MRC/WITS Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, University of the Witwatersrand, South Africa

E·S·R·C Economic & Social Research Council
MeSH Consortium Measurement & Surveillance of HIV Epidemics

11.1.3. International Workshop on HIV and Hepatitis Observational Databases (IWHOD) conference poster (Tracing outcomes)

Use of linked clinic and demographic surveillance data to improve estimates of outcomes following HIV patient tracing in Agincourt Health and Demographic Surveillance System

David Etoori[1], Alison Wringe[1], Chodziwadziwa Kabudula[2], F. Xavier Gomez-Olive[2], Georges Reniers[1,2]

1 London School of Hygiene and Tropical Medicine, 2 MRC-WITS Agincourt Rural Public Health and Health Transitions Research Unit

BACKGROUND

- Antiretroviral therapy (ART) programmes in sub-Saharan Africa have reported varying levels of loss to follow-up (LTFU) among patients following ART initiation.
- Universal test-and-treat (UTT) may exacerbate LTFU if;
  i. Quality of care declines as a result of pressure on health systems to meet additional treatment needs
  ii. Asymptomatic patients are less motivated to remain on ART
- Patient tracing is often undertaken to identify and re-engage LTFU patients.
- Ascertainment of outcomes for LTFU patients is also important to estimate ART coverage, and provide inputs for modelling the impact of ART on mortality.

Aim:

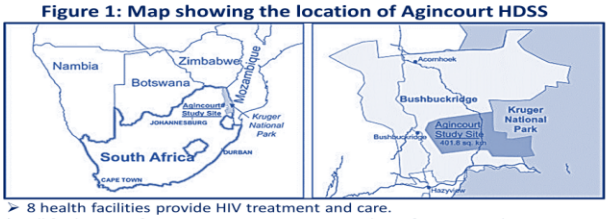
- To assess routine tracing in Agincourt Health and Demographic Surveillance System (Agincourt HDSS) and ascertain treatment outcomes for adult HIV patients LTFU in this setting.

METHODS

Study setting:

Agincourt HDSS is located in rural north-eastern South Africa. It was established in 1992 and is ~475 km². In 2014 it was estimated to have ~115,000 residents. Following the baseline demographic surveillance survey in 1992 and three update rounds until 1998, the site has conducted annual surveys since 1999.

Figure 1: Map showing the location of Agincourt HDSS



- 8 health facilities provide HIV treatment and care.
- All facilities perform routine tracing starting 5 days after a missed appointment
  - telephonic tracing assisted by Right-to-Care (RtC) an NGO
  - physical tracing conducted by Home Based Carers (HBC), a group of non-profit lay community health worker organisations

Point-of-contact Interactive Record Linkage (PIRL):

Since 2014, in addition to annual demographic surveillance rounds, chronic care patient visits in the clinics have been recorded and linked to the patient's Agincourt HDSS record, provided that they ever lived in the HDSS.

Study eligibility criteria:

- All people living with HIV
- 18 years or older
- Declared residency in the Agincourt HDSS
- Enrolled in HIV treatment after PIRL was established

Record review and tracing:

From the PIRL database we extracted a list of patients who were LTFU (more than 90 days late for a scheduled clinic visit) on August 15, 2017. We compared this list to;

- **TIER.Net (National electronic HIV treatment database)**
- **Physical patient files**
- **Logbooks kept by Right-to-Care**
- **Logbooks kept by Home Based Carers**
- **PIRL database for duplicates (different clinic records linked to the same individual)**
- **Agincourt HDSS database for residency and vital status**

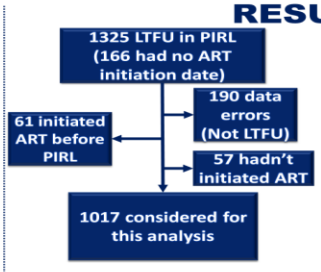
Supplementary tracing:

All patients for whom an outcome could not be established, or for whom routine patient tracing was not done were referred to the existing tracing channels for additional tracing.

Analysis:

- We calculated proportions and counts
- Competing risk survival analysis starting on the date of the last scheduled appointment

RESULTS



Data errors:

- 45 (23.7%) were early for their next scheduled visit
- 54 (28.4%) were on time for their appointment
- 91 (47.9%) were late for their appointment
  - Median days late 27 (IQR: 6,56)
  - 72 returned after 5 days

Demographic and clinical characteristics:

- Of 1017 patients considered eligible for this analysis
  - 767 (75.4%) females
  - 280 (27.5%) initiated ART for Prevention of mother-to-child transmission (B+), 737 (72.5%) for other reasons (CD4, TB coinfection, WHO stage)
  - 849 (83.5%) linked to an HDSS record

Age	N (%)
18-29	333 (32.7)
30-44	484 (47.6)
45-59	141 (13.9)
60+	58 (5.7)
Missing	1 (0.1)
Time on ART	
<=6 months	515 (50.6)
6-12 months	228 (22.4)
12-24 months	219 (21.5)
>24 months	55 (5.4)
Baseline CD4	
<100	206 (20.3)
100-349	446 (43.8)
350-499	193 (19.0)
500+	145 (14.2)
Missing	27 (2.7)
Time since last appointment	
<=1 year	526 (51.7)
1-2 years	369 (36.3)
>2 years	122 (12.0)

Table 1: Selected demographic and clinical characteristics

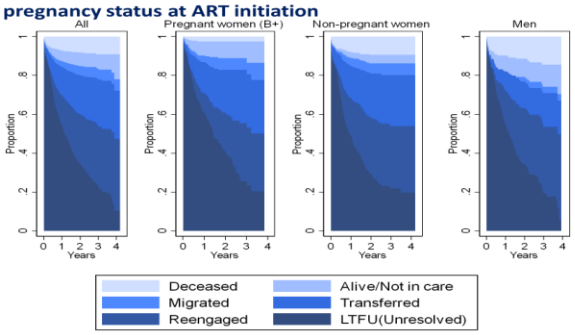
Sources of resolution:

- 588 (75.0%) through record review
- 22 (2.8%) through AHDSS residency and vital status data
- 27 (3.4%) through duplicates in the PIRL database
- 53 (6.8%) through supplementary tracing
- 72 (9.2%) through new visit data in the PIRL database
- 22 (2.8%) by searching other clinics near the patients' residence

Outcomes after record review and tracing:

- 120 (11.8%) deceased , 314 (30.9%) transferred to another facility, 75 (7.4%) stopped ART, 50 (4.9%) migrated, 225 (22.1%) reengaged in care, 233 (22.9%) remained unresolved.

Figure 2: Treatment and vital status of LTFU patients by sex and pregnancy status at ART initiation



- B+ women less likely to have died, the distribution of their outcomes is different from the general treatment cohort.
- Higher mortality among men.
- High rates of undocumented transfer with only 181 (57.6%) of 314 transfers recorded in TIER.Net.

CONCLUSIONS

- Late patients who returned after 5 days suggests there is still utility to routine tracing
- The different distribution of outcomes among B+ women means that different programme coverage correction factors will be needed as UTT becomes more established.
- Higher mortality among men emphasises the importance of programmatic efforts to reach men earlier.
- High rates of undocumented transfer may require a system more conducive to movement between clinics.

11.1.4. IWHOD conference poster (Re-engagement in care)

Re-engagement in care following loss to follow-up from HIV treatment and care: findings from a cohort study in rural South Africa

David Etoori[1], Alison Wringe[1], Chodziwadziwa Kabudula[2], F. Xavier Gomez-Olive[2], Georges Reniers[1,2]

1 London School of Hygiene and Tropical Medicine, 2 MRC-WITS Agincourt Rural Public Health and Health Transitions Research Unit

BACKGROUND

- An estimated 66% of people living with HIV in East and Southern Africa had access to antiretroviral therapy (ART) in 2017[1].
- As eligibility criteria have changed and more asymptomatic patients have initiated ART, retention in care has decreased, particularly among the least immunologically compromised group, women who initiate treatment for prevention of mother-to-child transmission Option B+ (PMTCT)[2,3].
- Recent studies show that 10-57% patients who are lost to follow-up (LTFU) re-engage in care[4,5]. However few studies have reported on re-engagement among PMTCT women.

Aim:

- To estimate re-engagement rates and understand the factors associated with re-engagement in care for patients who become LTFU.

METHODS

Setting:

Agincourt Health and Demographic Surveillance System (Agincourt HDSS) is located in rural north-eastern South Africa. It was established in 1992 and is ~475 km^2. In 2014 it was estimated to have ~115,000 residents. Since 1999, the site has conducted annual demographic surveillance surveys. HIV prevalence in the population 15 years or older was estimated at 19.4% in 2010[6].

- 8 health facilities provide HIV treatment and care.
- All facilities perform routine tracing
  - telephonic tracing assisted by Right-to-Care (RtC) an NGO
  - physical tracing assisted by Home Based Carers (HBC), a group of non-profit lay community health worker organisations

Point-of-contact Interactive Record Linkage (PIRL):

Since 2014, in addition to annual demographic surveillance rounds, chronic care patient visits in the clinics have been recorded and linked to the patient's HDSS record, provided that they ever lived in the Agincourt HDSS.

Eligibility criteria:

- All people living with HIV
- 18 years or older
- Declared residency in the Agincourt HDSS
- Enrolled in HIV treatment after PIRL was established

Record review and tracing:

From the PIRL database we extracted a list of patients who were LTFU (more than 90 days late for a scheduled clinic visit) on August 15, 2017. In order to understand re-engagement (currently back in care following the LTFU episode) we compared this list to;

TIER.Net (National electronic HIV treatment database)

Physical patient files

Logbooks kept by Right-to-Care

Logbooks kept by Home Based Carers

PIRL database for duplicates (different clinic records linked to the same individual)

Agincourt HDSS database for residency and vital status

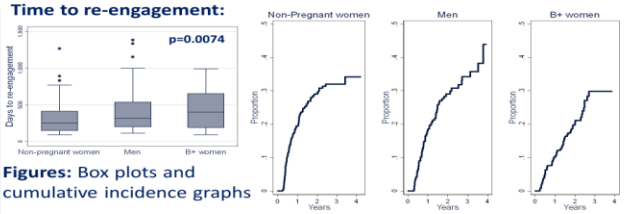
Analysis:

- The Kruskal-Wallis test was used to test for differences in continuous variables
- We present graphically time to re-engagement by ART start reason
- Competing risk survival analysis was conducted starting on the date of the last scheduled appointment
- A Fine and Gray proportional sub-distribution hazards model was used to determine the factors associated with re-engagement in care for patients who had ever initiated ART in the presence of competing risks (death, transfer, migration) stratified by ART initiation reason.
- All factors that were significantly associated with re-engagement in a univariable analysis and for which there was a plausible relationship, were added to the multivariable model.
- We used Wald tests to achieve a parsimonious model and report on factors that remained significant in the multivariable models.

RESULTS

- Of 1325 patients categorised as LTFU in the PIRL database, we excluded 61 who had initiated ART before PIRL was established, 57 who had not initiated ART when they became LTFU and 190 who were erroneously categorised as LTFU.
- Of the remaining 1017, 225 (22.1%) had re-engaged in care, 120 (11.8%) had died , 314 (30.9%) transferred to another facility, 75 (7.4%) stopped ART, 50 (4.9%) migrated, and 233 (22.9%) remained unresolved.

Time to re-engagement:



Figures: Box plots and cumulative incidence graphs

Factors associated with re-engagement in care:

	Non-pregnant women	Men	B+ women
	n=374	n=225	n=279
Clinic visit schedule	**SHR**	**SHR**	**SHR**
1 month	Reference		
2 months	1.09		
3 months	1.71		
>3 months	2.18*		
Previous re-engagement			
0	Reference		
1	0.37*		
2	2.04		
Times previously late for an appointment			
0			Reference
1			0.95
2			0.97
3			1.06
4			5.00E-9***
ART initiation year			
2014			Reference
2015			2.63
2016			5.57*
2017			17.98**
Ever migrated			
No	Reference		
Yes	0.57*		
Health Facility			
Agincourt	Reference	Reference	Reference
Belfast	0.29**	0.86	0.46
Cunningmore	1.36	0.33	1.19E-7***
Justicia	0.21	0.45	0.28*
Kildare	0.26**	0.10**	0.45
Lillydale	0.80	0.33*	2.80**
Thulamahashe	0.44	1.48E-9***	0.95
Xanthia	0.10*	0.19*	0.15
PIRL linkage			
Not linked	Reference		
Linked	1.09E8***		
Time since missed appointment			
<1 year	Reference	Reference	
1-2 years	0.29***	0.36**	
>2 years	0.07**	0.38*	
Time on ART			
<3 months	Reference	Reference	Reference
3-6 months	0.96	1.74	1.25
6-12 months	1.09	1.57	2.53
12-24 months	2.07*	2.44*	12.60***
>24 months	2.06	5.49***	76.91***

*p<0.05 **p<0.01 ***p<0.001

- For non-pregnant women, a longer clinic visit schedule, a proxy for previous good adherence, was associated with a higher probability of re-engagement. A longer time on ART was also associated with increased probability of re-engagement in care. The longer a patient was LTFU the less likely they were to re-engage.
- For pregnant women, later year of ART initiation was associated with higher probability of re-engagement in care probably highlighting issues with early implementation of Option B+
- For men, a longer time on ART was associated with higher probability of re-engagement and a longer time LTFU reduced the probability of re-engagement.

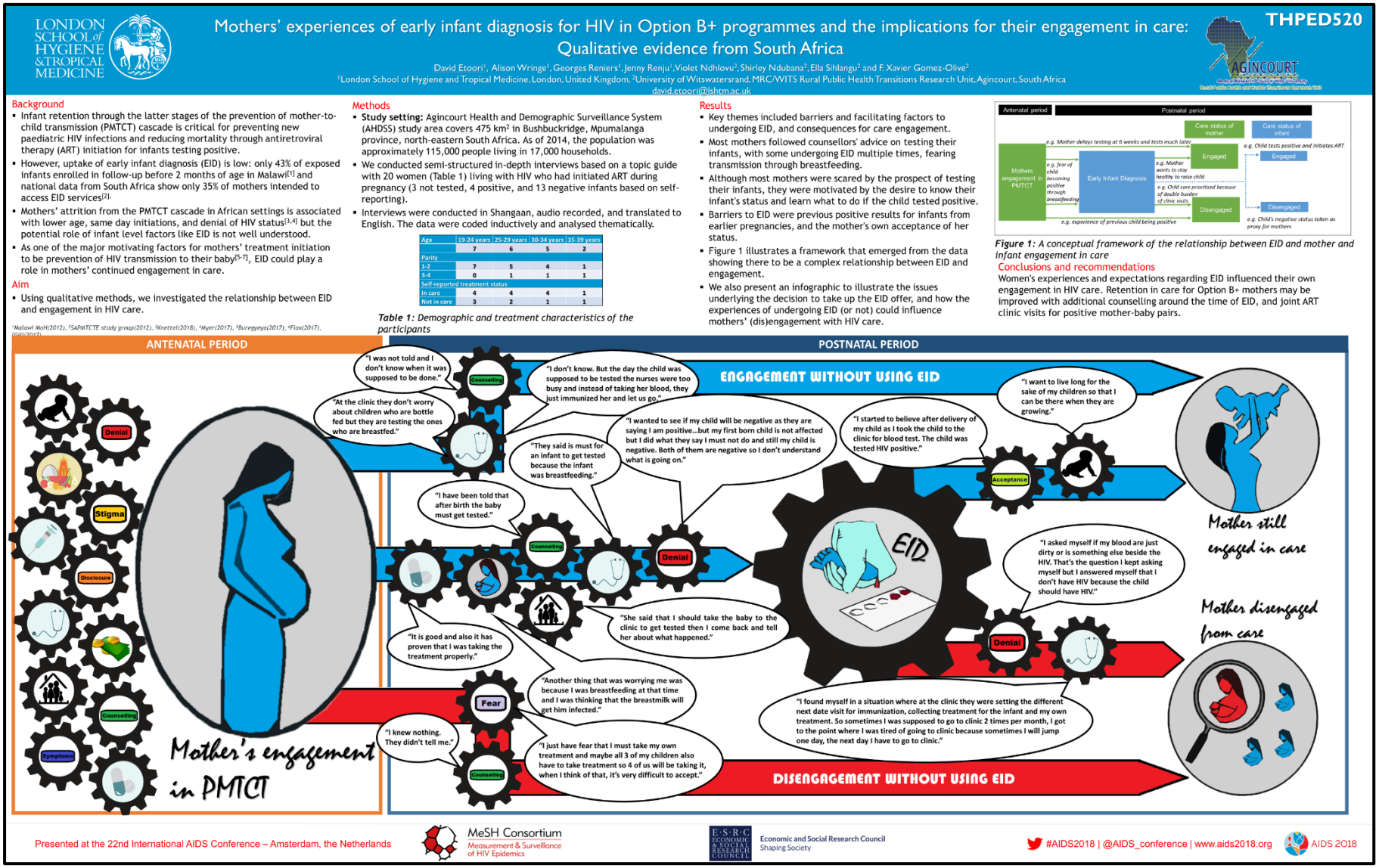
CONCLUSIONS

- Patients on longer refill schedules, a proxy for previous good adherence, are more likely to re-engage in care boding well for differentiated care models.
- Better re-engagement rates in later years for PMTCT probably points to better ART initiation practices (e.g. more focus on patient readiness before ART initiation) but may also show better understanding of the new guidelines by patients in later years leading to quicker readiness to start ART which has a positive effect on re-engagement later on
- Interventions to reduce the amount of time patients remain disengaged from care could be an efficient use of limited resources in similar settings.
- A limitation of the analysis is that we can only detect one re-engagement per patient but re-engagement rates fell in the range of previous studies.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE · E·S·R·C ECONOMIC & SOCIAL RESEARCH COUNCIL · AGINCOURT · MeSH Consortium Measurement & Surveillance of HIV Epidemics · SHAPE UTT

1 UNAIDS, 2 Nachega (2012), 3 Vitalis (2013), 4 Fernandez-Luis (2018), 5 Bershetyn (2017), 6 Gomez-Olive (2013)

11.1.5. AIDS 2018 conference poster



11.2. Ethical clearance certificates

11.2.1 Agincourt HDSS activities and use of surveillance data

LSHTM ethics approval to use secondary data from Agincourt HDSS activities

London School of Hygiene & Tropical Medicine
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United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Dr Georges Reniers
Associate Professor
Department of Population Health (DPH)
LSHTM

19 May 2017

Dear Dr Georges Reniers ,

Study Title: Outcomes of patients starting ART in rural South Africa - continuation

LSHTM ethics ref: 13424

Thank you for your application for the above research, which has now been considered by the Observational Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Local Approval	DH_2016_Julie_Ambia_Local_Ethics_Approval_v01_4Apr	27/11/2015	1
Investigator CV	reniers- cv - 1612	31/12/2016	1
Investigator CV	CV-David Etoori	16/02/2017	1
Investigator CV	Julie Ambia_CurriculumVitae_16Feb2017	16/02/2017	1
Protocol / Proposal	Patient LTFU - protocol for ethics submission - 170223docx	23/02/2017	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Approval for annual demographic surveillance

University of Witwatersrand ethics approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL)
Ref: R14/49 Tollman

CLEARANCE CERTIFICATE PROTOCOL NUMBER M 960720

PROJECT	Investigating and responding to changes in the health and population dynamics of rural South Africans
INVESTIGATORS	Dr S Tollman
DEPARTMENT	HSDU/Community Health, Acornhoek
DATE CONSIDERED	970726
DECISION OF THE COMMITTEE *	Approved unconditionally Generic Protocol - "Blanket approval"
DATE	970731

CHAIRMAN. [redacted] .....(Professor P E Cleaton-Jones)

c c Supervisor: Dr S Tollman
Dept of Community Health, Medical School

==========

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10001, 10th Floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee.

DATE..7/8/96.....SIGNATURE ..[redacted].

The University's United States Federal Wide Assurance Number is: SF,IORG0000862,IRB00001223.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Approval for linkage of clinic and demographic surveillance records

University of Witwatersrand ethics approval

R14/49 Prof Stephen Tollman et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M151162

NAME: (Principal Investigator)	Prof Stephen Tollman et al
DEPARTMENT:	MRC/Wits Rural Health and Health Transitions Research Unit (Agincourt) 15 Study Sites,Bushbuckridge Sub-District, Ehlanzeni District, Mpumalanga
PROJECT TITLE:	Record-Linkage of Health Facility Registries with the Agincourt Health Demographic Surveillance System (HDSS) Database
DATE CONSIDERED:	27/11/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	
APPROVED BY:	[redacted] Professor A Woodiwiss, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	11/12/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Mpumalanga Department of Health ethics approval

MPUMALANGA PROVINCIAL GOVERNMENT

Building No.3
No. 7 Government Boulevard
Riverside Park Extension 2
Nelspruit
1200
Republic of South Africa

Private Bag X 11285
Nelspruit, 1200
Tel: 013 766 3429
int: +27 13 766 3429
Fax: 013 766 3458
int: +27 13 766 3458

Department of Health

Litiko Letemphilo | Umnyango WezaMaphilo | Departement van Gesondheid

Enquiries: Themba Mulungo (013) 766 3511

06 May 2013

Dr. F. Xavier Gómez-Olivé
P.O. Box 2
ACORNHOEK
1360
South Africa

Dear Dr. F. Xavier Gómez-Olivé

APPLICATION FOR RESEARCH & ETHICS APPROVAL: RECORD-LINKAGE OF HEALTH FACILITY REGISTRIES WITH THE AGINCOURT HEALTH AND DEMOGRAPHIC SURVEILLANCE SYSTEM (AHDSS) DATABASE.

The Provincial Research and Ethics Committee has approved your research proposal in the latest format that you sent.

Kindly ensure that you provide us with the soft and hard copies of the report once your research project has been completed.

Kind regards

[redacted]

Mr. Molefe Machaba
Research and Epidemiology

10/05/2013
Date

We care. Do you? Siyanakekela

MPUMALANGA
A Pioneering Spirit

11.2.2. Fieldwork study ethics

LSHTM ethics approval

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Mr David Etoori
LSHTM

14 September 2017

Dear Mr David Etoori

Study Title: HIV patient outcomes after initiating HIV care and treatment

LSHTM Ethics Ref: 14296

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Information Sheet	Information sheet	01/06/2017	Version 1
Information Sheet	Consent form	01/06/2017	Version 1
Investigator CV	CV Ally Wringe	02/06/2017	1
Investigator CV	F Xavier Gomez Olive_CV	02/06/2017	1
Investigator CV	CV-David Etoori	02/06/2017	1
Protocol / Proposal	Qualitative Interview topic guide	13/06/2017	Version 1
Investigator CV	reniers- cv - 1702	14/06/2017	1
Protocol / Proposal	Study Protocol	14/06/2017	Version 1
Covering Letter	LSHTM clarification	18/08/2017	1
Information Sheet	Information sheet_2	18/08/2017	2
Information Sheet	Consent form_2	18/08/2017	2

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

University of Witwatersrand Ethical approval

R14/49 Georges Reniers et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170850

NAME: (Principal Investigator)	Georges Reniers et al
DEPARTMENT:	School of Public Health MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt)
PROJECT TITLE:	HIV Patient Outcomes after Initiating HIV Care and Treatment in Agincourt
DATE CONSIDERED:	25/08/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	
APPROVED BY:	[redacted] Professor C. Penny, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	22/09/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in August and will therefore be due in the month of August each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Mpumalanga Department of Health ethics approval

health
MPUMALANGA PROVINCE
REPUBLIC OF SOUTH AFRICA

No.3, Government Boulevard, Riverside Park, Ext. 2, Mbombela, 1200, Mpumalanga Province
Private Bag X11285, Mbombela, 1200, Mpumalanga Province
Tel I: +27 (13) 766 3429, Fax: +27 (13) 766 3458

Litiko Letemphilo | Departement van Gesondheid | UmNyango WezeMaphilo

Enquiries: Themba Mulungo (013) 766 3511

Dr. Xavier Gomez-Olive
P.O Box 02
Acornhoek
1360

Dear Dr. Xavier Gomez-Olive

APPLICATION FOR RESEARCH & ETHICS APPROVAL: HIV PATIENT OUTCOMES AFTER INITIATING HIV CARE AND TREATMENT IN AGINCOURT

The provincial health research committee has approved your research proposal in the latest format you sent.

- Approval Ref Number: MP_MP_201709_12
- Approval period: 01/10/2017 – 31/07/2018
- Facilities: Agincourt CHC, Belfast Clinic and Lillydale CHC, Kildare A Clinic, Xanthia Clinic Justicia Clinic, Cunningmoore A Clinic and Rolle Clinic.

Kindly ensure that the study is conducted with minimal disruption and impact on our staff, and also ensure that you provide us with the soft or hard copy of the report once your research project has been completed.

Kind regards

[redacted]

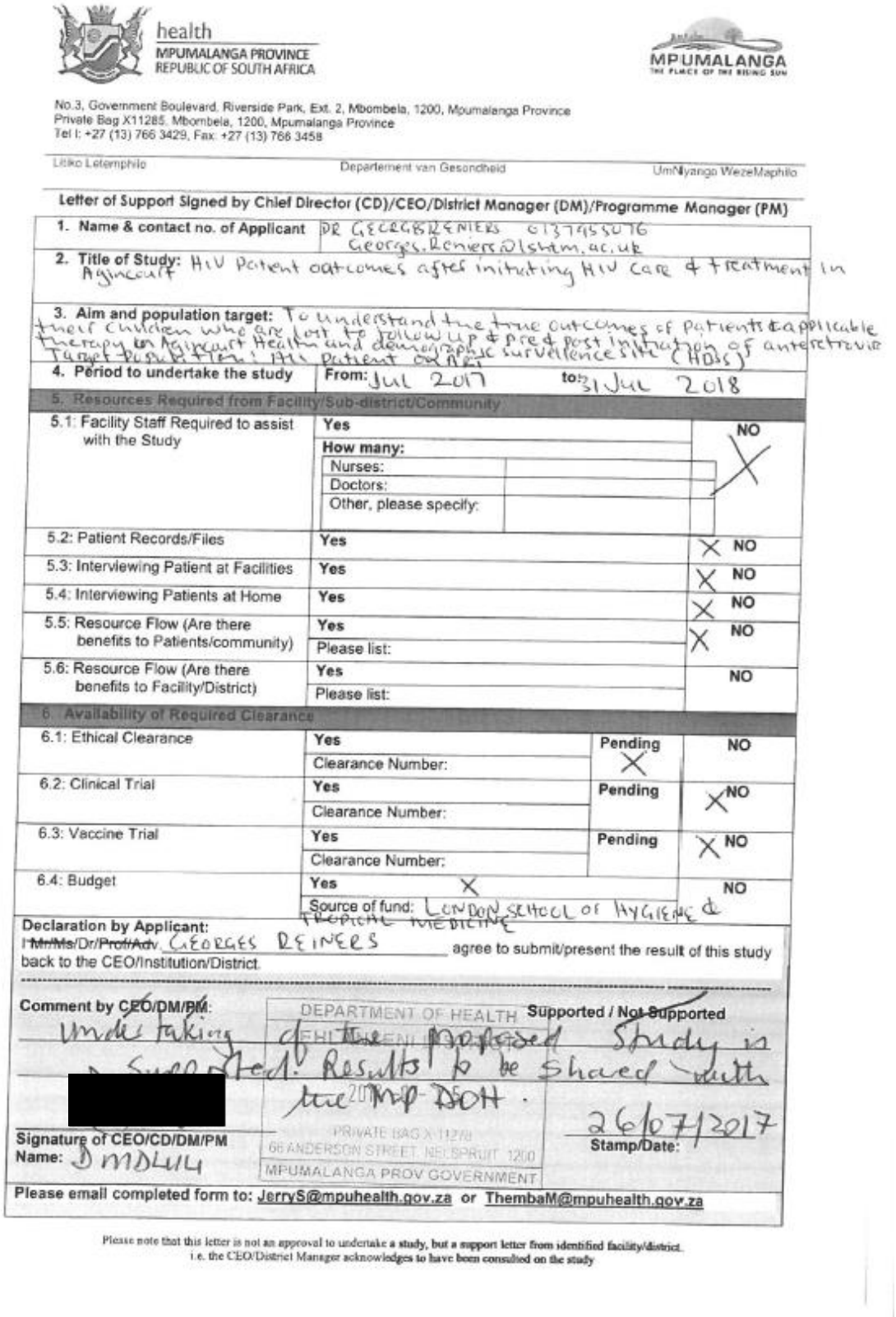
MR. J. SIGUDLA
MPUMALANGA: PHRC

MPUMALANGA PROVINCE
DEPARTMENT OF HEALTH
PLANNING & INFORMATION
2017 -10- 11
PRIVATE BAG X 11285
NELSPRUIT 1200

11/10/2017
DATE

MPUMALANGA
THE PLACE OF THE RISING SUN

Mpumalanga Department of Health permission to work in health facilities



health
MPUMALANGA PROVINCE
REPUBLIC OF SOUTH AFRICA

MPUMALANGA
THE PLACE OF THE RISING SUN

No.3, Government Boulevard, Riverside Park, Ext. 2, Mbombela, 1200, Mpumalanga Province
Private Bag X11285, Mbombela, 1200, Mpumalanga Province
Tel I: +27 (13) 766 3429, Fax: +27 (13) 766 3458

Lesiko Letemphelo | Departement van Gesondheid | UmNyango WezeMaphilo

Letter of Support Signed by Chief Director (CD)/CEO/District Manager (DM)/Programme Manager (PM)

1. Name & contact no. of Applicant	DR GEORGES REINERS 0137455076 Georges.Reiners@lshtm.ac.uk		
2. Title of Study: HIV Patient outcomes after initiating HIV care & treatment in Agincourt			
3. Aim and population target: To understand the true outcomes of patients & applicable their children who are lost to follow up & pre & post initiation of antiretrovir therapy in Agincourt Health and demographic surveillance site (HDSS) Target Population: HIV Patient cohort			
4. Period to undertake the study	From: Jul 2017	to: 31 Jul 2018	
5. Resources Required from Facility/Sub-district/Community			
5.1: Facility Staff Required to assist with the Study	Yes How many: Nurses: Doctors: Other, please specify:		NO X
5.2: Patient Records/Files	Yes		X NO
5.3: Interviewing Patient at Facilities	Yes		X NO
5.4: Interviewing Patients at Home	Yes		X NO
5.5: Resource Flow (Are there benefits to Patients/community)	Yes Please list:		X NO
5.6: Resource Flow (Are there benefits to Facility/District)	Yes Please list:		NO
6. Availability of Required Clearance			
6.1: Ethical Clearance	Yes Clearance Number:	Pending X	NO
6.2: Clinical Trial	Yes Clearance Number:	Pending	X NO
6.3: Vaccine Trial	Yes Clearance Number:	Pending	X NO
6.4: Budget	Yes X Source of fund: LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE		NO

Declaration by Applicant:
I ~~Mr/Ms~~/Dr/~~Prof/Adv~~ GEORGES REINERS agree to submit/present the result of this study back to the CEO/Institution/District.

Comment by CEO/DM/PM: Supported / ~~Not Supported~~
Undertaking of the proposed Study is supported. Results to be shared with the MP-DOH.

DEPARTMENT OF HEALTH
2017
PRIVATE BAG X 11285
66 ANDERSON STREET, NELSPRUIT, 1200
MPUMALANGA PROV GOVERNMENT

[redacted]
Signature of CEO/CD/DM/PM
Name: D MDLULI

Stamp/Date: 26/07/2017

Please email completed form to: JerryS@mpuhealth.gov.za or ThembaM@mpuhealth.gov.za

Please note that this letter is not an approval to undertake a study, but a support letter from identified facility/district i.e. the CEO/District Manager acknowledges to have been consulted on the study

Mpumalanga Department of Health extension

health
MPUMALANGA PROVINCE
REPUBLIC OF SOUTH AFRICA

No.3, Government Boulevard, Riverside Park, Ext. 2, Mbombela, 1200, Mpumalanga Province
Private Bag X11285, Mbombela, 1200, Mpumalanga Province
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Litiko Letemphilo | Departement van Gesondheid | UmNyango WezeMaphilo

Enquiries: Themba Mulungo (013) 766 3511

Dr. Xavier Gomez-Olive
P.O Box 02
Acornhoek
1360

Dear Dr. Xavier Gomez-Olive

APPLICATION FOR RESEARCH & ETHICS APPROVAL: HIV PATIENT OUTCOMES AFTER INITIATING HIV CARE AND TREATMENT IN AGINCOURT

The provincial health research committee has approved your research proposal in the latest format you sent.

- Approval Ref Number: MP_MP_201709_12
- Approval period: 01/10/2017 – 31/07/2018, Extension: 20/11/2018 To 31/07/2019
- Facilities: Agincourt CHC, Belfast Clinic and Lillydale CHC, Kildare A Clinic, Xanthia Clinic Justicia Clinic, Cunningmoore A Clinic and Rolle Clinic.

Kindly ensure that the study is conducted with minimal disruption and impact on our staff, and also ensure that you provide us with the soft or hard copy of the report once your research project has been completed.

Kind regards

[redacted]

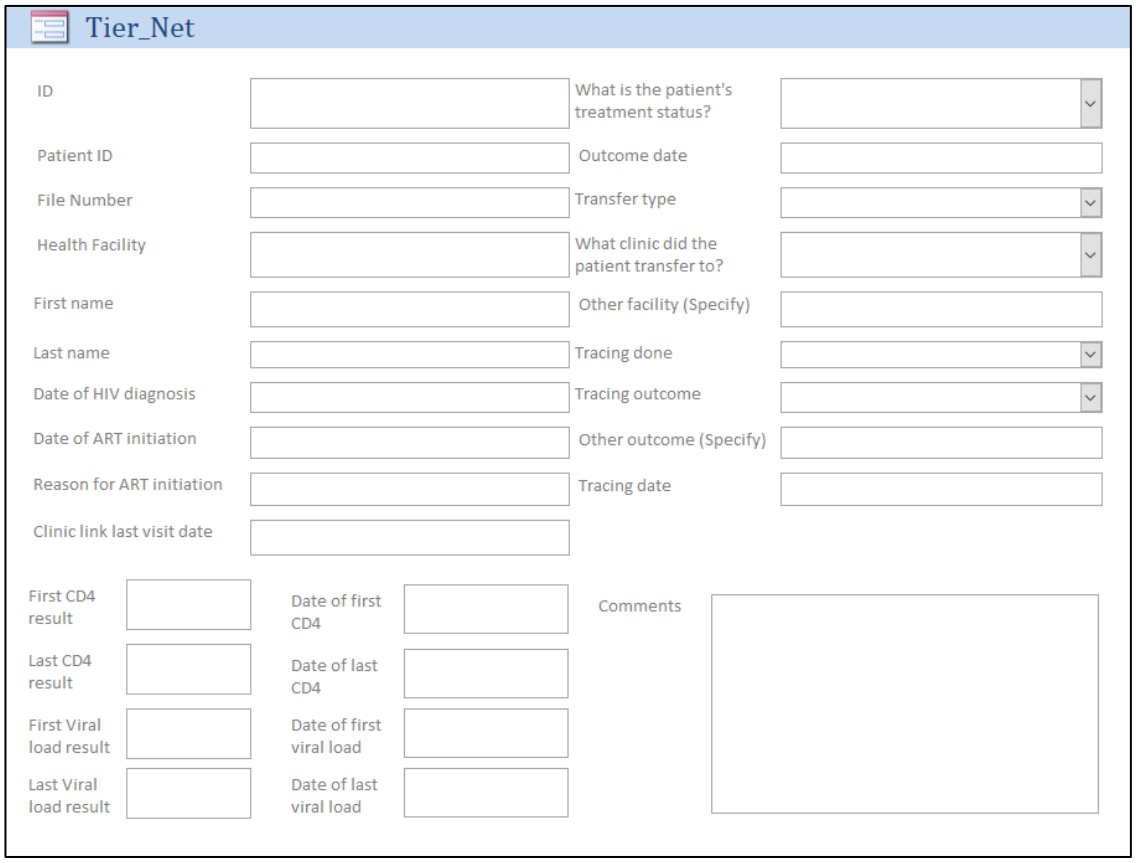
MS. T.Z MADONSELA
MPUMALANGA PHRC

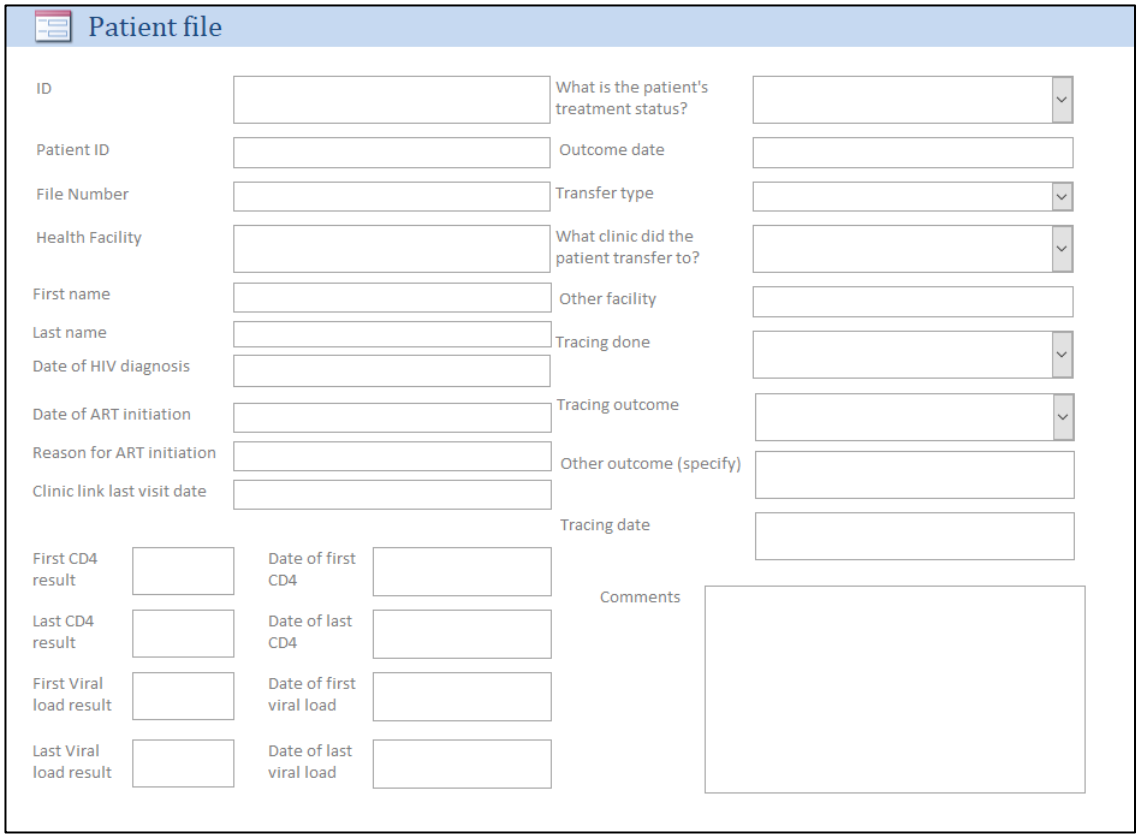
2018/11/20
DATE

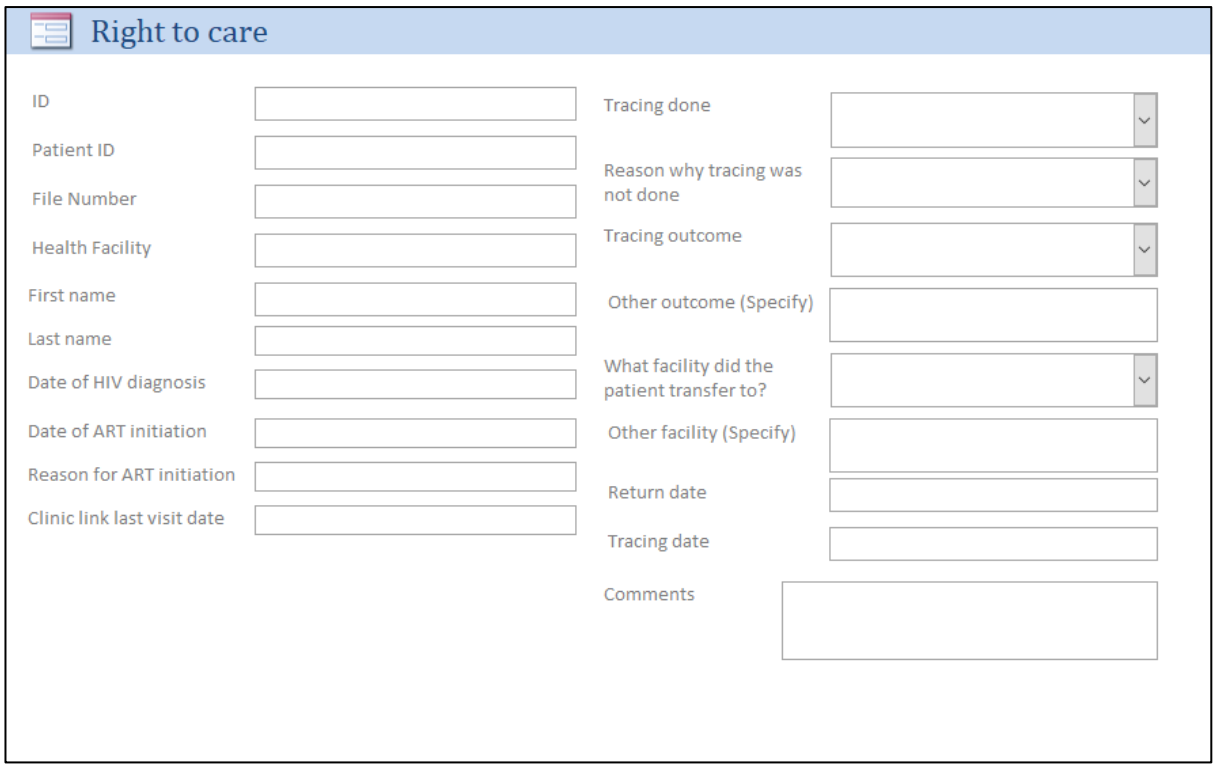
MPUMALANGA
THE PLACE OF THE RISING SUN

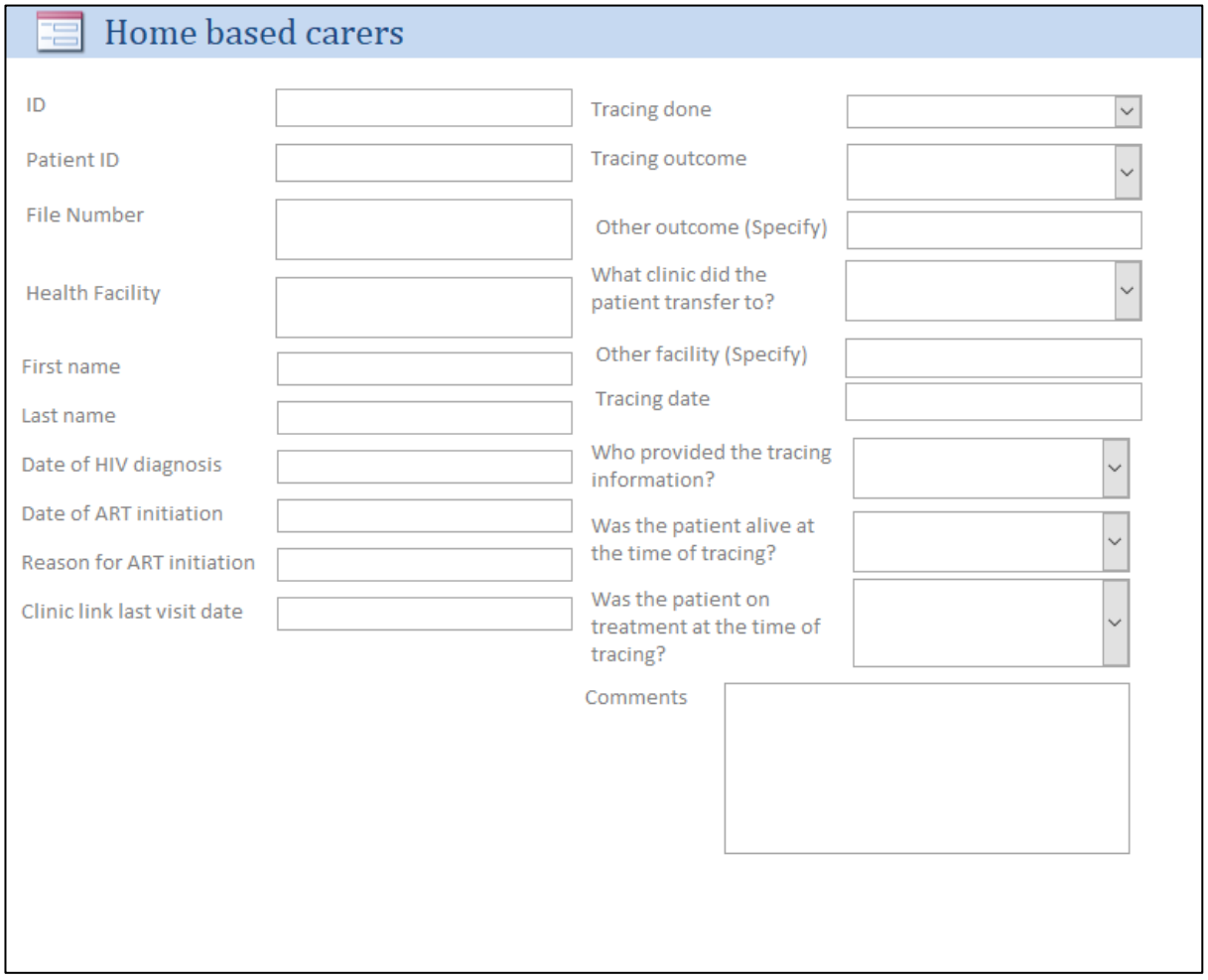
11.3. Fieldwork tools

11.3.1. Record review and tracing Visual Basic data entry forms






Right to care
ID
Patient ID
File Number
Health Facility
First name
Last name
Date of HIV diagnosis
Date of ART initiation
Reason for ART initiation
Clinic link last visit date
Tracing done
Reason why tracing was not done
Tracing outcome
Other outcome (Specify)
What facility did the patient transfer to?
Other facility (Specify)
Return date
Tracing date
Comments


Home based carers
ID
Patient ID
File Number
Health Facility
First name
Last name
Date of HIV diagnosis
Date of ART initiation
Reason for ART initiation
Clinic link last visit date
Tracing done
Tracing outcome
Other outcome (Specify)
What clinic did the patient transfer to?
Other facility (Specify)
Tracing date
Who provided the tracing information?
Was the patient alive at the time of tracing?
Was the patient on treatment at the time of tracing?
Comments

11.3.2. IDI consent form

English version

Part 2: Consent form for participants.

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the information sheet above or the explanation given to you please ask the researcher before you decide to take part. You will be given a copy of the information sheet to keep.

Informed consent:

- I have been informed by the researcher of the purpose and procedures of the study, and of the possible benefits and drawbacks of my participation.
- Any questions I had about my participation in this study have been answered to my satisfaction. I will receive a copy of the document I have signed.
- I was given enough time to make my decision.
- I am participating in this study on a voluntary basis. I may withdraw at any time without giving a reason and my decision not to take part will not affect my care as a patient, my position or reputation as a community member, or the services that I receive in any way.
- I agree to allow the researchers, and the Ethics Commissions to see my **anonymised** data, with the understanding that this data will remain confidential.
- I agree for my **anonymised** data to be stored for a period of up to 7 years and shared with other researchers on request, with the understanding that any personal information or data will remain confidential and all data shared will be untraceable back to me as an individual.

I,_____ consent voluntarily to being a participant of this study

I consent to this interview being recorded ☐

Signed _____ Date _____

Signature of the researcher: _____ Date _____

Shangaan version

MRC/Wits Rural Public Health and Health Transitions Research Unit
School of Public Health, Education Campus, 27 St Andrew's Road, Parktown 2193, South Africa
Telephone: +27 11 717 2085 (Johannesburg) +27 13 795 5076 (Acornhoek) www.agincourt.co.za

PAPILA RA MPFUMELELANO RA VANGHENELERI

Hi khensa ku va mi tekile xiboho xo nghenelela eka ndzavisiso lowu. Munhu loyi a lulamisaka ndzavisiso lowu u fanele ku hlamusela ndzavisiso lowu eka n'wina mi nga si pfumela ku nghenela. Loko mi ri na swivutiso swo karhi leswi humaka eka papila ra vuxokoxoko leri nga laha henhla kumbe nhlamuselo leyi mi nyikiweke yona hi kombela mi vutisa mulavisisi mi nga si teka xiboho xo nghenela. Mi ta nyikia khopi ya papila ra vuxokoxoko leswaku mi ri hlayisa.

Papila ra mpfumelelano

- Ndzi byeriwile hi mulavisisi xikongomelo na maendlelo ya ndzavisiso, xikan'we na ku vuyeriwa loku nga vaka kona xikan'we na ku tihumesa ka mina eka ndzavisiso.
- Swivutiso hinkwaswo leswi a ndzi ri na swona mayelana na ku nghenela ka mina eka ndzavisiso lowu swi hlamuriwile hi ku enela. Ndzi ta kuma khopi ya papila leri ndzi nga ri sayina.
- Ndzi nyikiwile nkarhi wo ringanela ku va ndzi teka xiboho
- Ndzi nghenela eka ndzavisiso lowu hi ku tinyikela. Ndzi nga tihumesa eka nkarhi wun'wana na wun'wana handle ko nyika xivangelo naswona xiboho xa mina xo nghenela a xi nga khumbi mpfuno wa mina tanihi mungheneleri, xiyimo xa mina tanihi muaka-tiko, kumbe vukorhokeri lebyi ndzi byi kumaka hi ndlela yihi kumbe yihi.
- Ndza pfumela ku pfumelela valavisisi, na Khomixini ya Swamilawu ku vona vuxokoxoko bya mina lebyi nga ndzi humelerisiki, hi ku twisisa leswaku vuxokoxoko lebyi byi ta va xihundla.

Mina, _____ ndzi pfumela hi ku tinyikela ku va mungheneleri eka ndzavisiso lowu.

Ndza pfumela leswaku mbhurisano lowu wu kandziyisiwa ☐

Ku sayiniwile _____ Siku _____

Nsayino wa mulavisisi: _____ Siku _____

11.3.3. IDI information sheet

English version

HIV PATIENT OUTCOMES AFTER INITIATING HIV CARE AND TREATMENT IN AGINCOURT.

INFORMATION SHEET FOR PARTICIPANTS

The University of Witswatersrand along with the London School of Hygiene and Tropical Medicine and International Epidemiology Databases to Evaluate AIDS (IeDEA) are carrying out a study investigating people's experience with health services in Agincourt, aiming to understand how particular health conditions may be managed. These health services and health conditions may include HIV, pregnancy, and family planning among others.

Purpose of the research

The purpose of this study is to learn about people's views and experiences with medical services and with managing health conditions. From this, we hope to be able to make recommendations about how services might be improved in the future. As someone who lives in Agincourt and who uses health facilities here, you have been invited to take part in this study to share your views on the study topic so that we can learn from your experiences using these services. We are inviting you to participate in this study by undergoing one interview, which will last about one hour. If any of the information given here is not clear or incomplete. If anything is not clear, you need more information or if you have any questions please feel free to ask.

Benefit and potential risk for the individual and the community

There will be no direct benefit to you from taking part in the study. However, the information you share will help us understand how patient support and health services might be improved in South Africa. Participating in interviews has no direct risk for you as a participant.

Voluntary participation

Your participation is voluntary. You may stop the interview at any time without giving reason and you can choose not to answer certain questions or discuss certain topics if you do not wish to. If you decide not to participate, it will not affect the services you receive either now or in the future, and it will not result in any loss of benefits regarding medical treatment.

There are no right or wrong answers to any of the questions. For example, we would like to hear about your views about the health services, regardless of whether they are positive or negative.

To ensure we capture everything, we would like to record the interviews if you consent to this.

Confidentiality

The information given in the interviews will be accessible only to those in the study team. They are all qualified researchers who understand the importance of confidentiality and follow a professional code of conduct. This means they will not discuss what you say with anyone outside the study. The audio recording will not include your name, and it will only be heard by the research team. The recorded

conversation will be typed onto paper, without your name on it, and the original recording and written documents will be kept securely and destroyed after the conclusion of the study

At the end of this study, an anonymized transcript of this conversation will be made available to other scientists through a public data repository. This means that we will first delete your name and other information that could be used to identify you before sharing it with others. Anonymized quotes from this interview may be used in publications and reports.

As a participant in the study, you have the right to access your recorded interviews if you wish. The researchers will make every effort to ensure everything you share remains confidential. Your identity will not be revealed in any publications, presentations or reports resulting from this study.

Should you have questions regarding your rights as a participant in the study please contact the Scientific and Ethics Committee of the Department of Health (Office 14, Jaspis St, Aeorand, Middelburg, 1050, South Africa. Tel: +27-13-766-3429). In case you have any further queries about the study, you may contact: Dr. F. Xavier Gómez-Olivé, P.O. Box 2 Acornhoek, 1360, South Africa Tel: +27-13-795-5076.

Shangaan version

MRC/Wits Rural Public Health and Health Transitions Research Unit
School of Public Health, Education Campus, 27 St Andrew's Road, Parktown 2193, South Africa
Telephone: +27 11 717 2085 (Johannesburg) +27 13 795 5076 (Acornhoek) www.agincourt.co.za

LESWI ENDLEKEKE EKA VAVABYI LAVA NGA NA HIV ENDZHAKU KA LOKO VA NGHENISIWILE EKA MPFUNO NA VUTSHUNGURI E AGINCOURT

Yunivhesiti ya Witwatersrand xikan'we na London School of Hygiene and Tropical Medicine n ava International Epidemiology Databases to Evaluate AIDS (IeDEA) va endla ndzavisiso ku kuma ntokoto wa vanhu mayelana na vukorhokeri bya swarihanyu e Agincourt, laha va kongomeke ku twisisa ndlela leyi swiyimo swo karhi swarihanyo swi nga lawuriwaka ha kona. Vukorhokeri lebyi bya rihanyo xikan'we na swiyimo swa rihanyo swi nga katsa HIV, vuyimani na nkunguhato eka van'wana.

Xikongomelo xa ndzavisiso

Xikongomelo xa ndzavisiso lowu l ku dyondza mayelana na mavonelo ya vanhu xikan'we na ntokoto wa vona eka vukorhokeri bya swarihanyo xikan'we na malawulelo ya swiyimo swarihanyo. Ku suka eka leswi, hi tshemba leswaku hi ta endla swibumabumelo mayelana na ndlela leyi vukorhokeri byi nga antswisiwaka ha kona eka nkarhi lowu taka. Tanihi munhu loyi a hanyaka e Agincourt no tirhisa tindzhawu ta swarihanyo laha, mi rhambiwile ku va mi nghenela eka ndzavisiso lowu k uvula mavonelo ya n'wina eka nhloko-mhaka ya ndzavisiso ku va hi ta dyondza ku suka eka ntokoto wa n'wina wo tirhisa vukorhokeri lebyi. Hi mi rhamba ku nghenela eka ndzavisiso lowu hi ku endla mbhurisano wun'we, lowu nga ta teka awara yin'we. Loko swi nga endleka leswaku vuxokoxoko lebyi nyikiweke laha byi nga ri erivaleni kumbe byi nga helelanga. Loko swin'wana swi nga ri erivaleni, mi lava vuxokoxoko hi xitalo kumbe loko mi ri na swivutiso swo karhi hi kombela mi tshunxeka ku va mi vutisa.

Mbuyelo na makhombo lawa ya nga vaka kona eka munhu na muganga

A ku nga vi na ku vuyeriwa loku kongomeke eka n'wina hi ku va mi nghenerile eka ndzavisiso lowu. Kambe, vuxokoxoko lebyi mi nga ta byi vula byi ta hi pfuna ku va hi twisisa ndlela leyi nseketelo wa vavabyi xikan'we na vukorhokeri bya swarihanyo swi nga antswisiwaka ha kona e Afrika Dzonga. Ku nghenela eka mimbhurisano a ku na makhombo lawa ya mi kongomeke tanihi mungheneleri.

Ku nghenela hi ku tinyikela

Ku nghenela ka n'wina l ku tinyikela. Mi nga tshika mbhurisano eka nkarhi wun'wana na wun'wana handle ko nyika xivangelo naswona mi nga hlawula ku va mi nga hlamuli swin'wana swa swivutiso kumbe vulavula hi tinhloko-mhaka to karhi loko mi nga swi tsakeli. Loko mi nga teka xiboho xo ka mi nga ngheneli, a swi nga khumbi vukorhokeri lebyi mi byi kumaka sweswi kumbe eka nkarhi lowu taka, naswona a swi nga yisi eka ku lahlekeriwa hi ku vuyeriwa mayelana na vutshunguri bya swarihanyo.

MRC/Wits Rural Public Health and Health Transitions Research Unit
School of Public Health, Education Campus, 27 St Andrew's Road, Parktown 2193, South Africa
Telephone: +27 11 717 2085 (Johannesburg) +27 13 795 5076 (Acornhoek) www.agincourt.co.za

A ku na nhlamulo ya ntiyiso kumbe yo ka yi nga ri ntiyiso eka swivutiso swihi kumbe swihi. Xikombiso, hi tsakela ku twa mayelana na mavonelo ya n'wina hi vukorhokeri bya swarihanyo, hambi byi ngava byi ri kahle kumbe byi nga ri kahle.

Ku tiyisisa leswaku hi kuma swilo hinkwaswi, hi ta tsakela ku kandziyisa mimbhurisano loko mi pfumela.

Xihundla

Vuxokoxoko lebyi nyikiweke eka mimbhurisano leyi byi ta fikeleriwa ntsena hi lava va nga le ka ntlawa wa ndzavisiso. Hinkwavo l valavisisi lava tokoteke lava twisisaka nkoka wa xihundla no landzela matirhelo ya ntokoto. Leswi swi vula leswaku a va nga buli hi leswi mi swi vuleke na munhu un'wana loyi a nga riki wa ndzavisiso. Nkandziyiso a wu nga katsi vito ra n'wina, naswona wu ta twiwa ntsena hi ntlawa wa valavisisi. Vuxokoxoko lebyi kandziyisiweke byi ta tsariwa ephepheni , byi nga ri na vito ra n'wina, naswona minkandziyiso hinkwayo xikan'we na mapapila lawa ya tsariweke swi ta hlayisiwa kahle na ku herisiwa endzhaku ka loko ndzavisiso wu fikile emakumu.

Emakumu ka ndzavisiso lowu, mahungu lawa ya tsariweke ya ri hava vito ra munhu wo karhi ya ta va kona eka vativi va sayense van'wana hi ku tirhisa vuhlayiselo bya vuxokoxoko lebyi nga bya mani na mani. Leswi swi vula leswaku hi ta rhanga hi susa vito ra n'wina na vuxokoxoko byin'wana lebyi byi nga tirhisiwaka ku mi humelerisa hi nga si nyika van'wana vuxokoxoko lebyi. Swihungwana leswi mi swi vuleke leswi nga ta va kona eka mbhurisano lowu swi ta tirhisiwa eka swihangalasa-mahungu na swiviko.

Tanihi mungheneleri eka ndzavisiso, mi na mfanelo your fikelela nkandziyiso wa mbhurisano wa n'wina loko mi swi tsakela. Valavisisi va ta tirha hi matimba swinene ku tiyisisa leswaku hinkwaswo leswi mi swi vulaka swi tshama swi ri xihundla. A mi nga humelerisiwi eka swihangalasa-mahungu, mahungu kumbe swiviko swihi kumbe swihi leswi nga ta huma eka ndzavisiso lowu.

Loko mi nga tshuka mi va na swivutiso mayelana na timfanelo ta n'wina tanihi mungheneleri eka ndzavisiso hi kombela mi tihlanganisa na Komiti ya Swamilawu na Sayense ya le ka Ndzawulo ya Rihanyo (Office 14, Jaspis St, Aeorand, Middelburg, 1050, South Africa, nomboro ya riqingho: +27 13 766 3429). Loko mi nga tshuka mi va na swivutiso swo karhi ku yisa emahlweni mayelana na ndzavisiso, mi nga tihlanganisa na Dr F. Xavier Gomez-Olive, P.O. Box 2, Acornhoek, 1360, South Africa, nomboro ya riqingho: +27 13 795 5076.

11.3.4. IDI topic guide

English version

HIV PATIENT OUTCOMES AFTER INITIATING HIV CARE AND TREATMENT IN AGINCOURT.

QUALITATIVE INTERVIEW TOPIC GUIDE

This is an outline of areas to include in the interviews; they are examples of potential questions and should not be followed rigidly. As much as possible the interview should be led by the respondent's account, the interviewer should endeavour to probe (even silently) and encourage elaboration.

Make sure that they are aware that we have not come to try to force them back in to care, we want to have a conversation with them just to understand their experiences.

Life history:

Could you tell me about a typical day for you? What do you usually do?

- **Area or community you live in**
  - What is the area you live in like?
  - Where do you live now?
  - What is the community like?
  - How do your family fit into this community?
- **Family structure**
  - What is your family structure like? Who do you live with (at homestead)?
  - Do you have any children (both men and women)? Are you currently pregnant (women)? Have you lost any children?
  - Do you want any (more) children? (Both men and women)
- **Relationship views and experiences**
  - Could you tell me about your relationships growing up until now?
  - What were these relationships like?
  - If in current relationship, could you describe what your relationship is like/tell me about it?
    - What does your partner do for you?
    - What do you do for [him/her]?
    - What is important for you in the relationship?
  - If not in current relationship, what do you want for the future?
    - Probe relationship expectations versus reality
    - Probe what is important versus unacceptable in a relationship

Testing experience:

- **Health seeking and general health management**
  Views and experiences with health services, access…management of health
- **HIV testing experience**
  Could you tell me in your own words your experiences when you tested for HIV from the beginning?

- For women who started ART because they were pregnant, probe motivation to test: were they given sufficient information, were they coerced in any way e.g. with refusal of other services if they did not test?

- **HIV health seeking and management**
  What did you know about HIV before you were diagnosed?
- **ART initiation decision making**
  Experience being offered ART, what health care worker said, what happened, what they thought about it (coercion? especially for PMTCT)
- **Any lifestyle changes since diagnosis**
  Anything they used to do that they do not do now, anything that they changed after they initiated ART?

ART treatment follow-up:

- **Treatment taking experience**
  Challenges, motivation, times when it was difficult to go for refills or take treatment? How did you cope with these?
- **Living with HIV and on ART**
  Health maintenance, any changes e.g. physical or other, relationships and sexual practices

Loss to follow-up:

Have you ever experienced a time when you stopped taking treatment?

- Can you tell me about one of those times?
- What happened?
- What was going through your mind at that time?
- What were the reasons why? Can you tell me about another time you stopped… were the reasons you stopped similar? (Any different reasons?)

- **Major reasons for stopping treatment**
  - Tell me in your own words about when you stopped taking treatment?
  - How did you feel about your decision?
  - How do you feel about that decision now?
- **Living with HIV after ART stoppage**
  Any perceived or real changes e.g. deteriorating health…, how is health now

Re-engagement in care:

Have you ever experienced a time when you stopped taking treatment and started taking treatment again?

- Can you tell me about one of those times?
- What happened?
- What prompted you to start again?
- Were there any other times you stopped taking treatment and started again?
  - ➢ Did you restart for similar reasons or were there different reasons?

- **Major reasons for restarting treatment**
  Challenges, motivation
- **Treatment interruption**

How long did it last, had they interrupted HIV care before?

- **Health system obstacles**
  Were health care workers helpful in the process, were there hindrances

Infant testing: (**Only ask women who were on ART while pregnant or who started ART for PMTCT**)

- **Health system experience**
  Could you tell me everything the health care worker told you about testing your infant for HIV?
  When did this happen? (Near the end of pregnancy, right after HIV diagnosis) Who spoke to you about it? What did you think of this?
- **Knowledge**
  What did you know about infant testing before this?
- **Practice**
  Was infant tested? What were motivations for testing or not testing the infant? Is the child alive? Did the child receive any treatment (prophylaxis or ART)?

Shangaan version

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Papila ra tinhloko-mhaka ta mbhurisano

Lowu I nkomiso wa tindzhawu leti ti faneleke ku katsiwa eka mimbhurisano; I swikombiso swa swivutiso leswi nga vutisiwaka naswona a swi fanelanga ku landzeleriwa hi ku landzelelana ka swona. Mbhurisano wu fanele ku rhangeriwa hi ku ya hi muhlamuri, muburisani u fanele a ringeta ku vutisisa ku ya emahlweni (hambi a nga swi humelerisi) naswona a hlohletela ku nghenelela.

Tiyisisa leswaku va swi twisisa leswaku a hi telanga ku ringeta ku va sindzisa ku va eka mpfuno, hi lava ku burisana na vona ku va hi twisisa ntsena ntokoto wa vona.

Endzhaku ka xiyenge-nkulu xin'wana na xin'wana, nyika nkomiso wa swilo swa nkoka eka mungheneleri (nyika mungheneleri nkarhi loko swi nga endleka leswaku a tsundzuka swin'wana kumbe a lava ku basisa swin'wana) kutani u hlamusela nhloko-mhaka leyi landzelaka na swivangelo swo lava ku vulavula hi swona.

Ha khensa ku va mi pfumerile ku nghenela eka mbhurisano lowu. Ndzi khensa ku va mi tekile nkarhi ku hlamula swivutiso swa mina. Loko eka nkarhi wun'wana mi nga twa ongeti hi fanele ku yima hikwalaho ka swivangelo swo karhi xikombiso loko mi lava ku vutisa xivutiso, mi nga kanakani k uvula tano. Loko mi twa ongeti kun a xivutiso lexi mi nga khomekiki kahle ku va mi vutisiwa, ndzi kombela leswaku mi ndzi byela naswona ndzi ta hundzela eka xin'wana.

Swivutiso swo endla ku va munhu a tshunxeka

Xo sungula ndzi ta tsakela ku vulavula na n'wina mayelana na n'wina ku endlela leswaku ndzi ta twisisa ku antswa leswaku hi n'wina mani. Xana leswi swa amukeleka eka n'wina? Hi nga sungula?

[Xiyenge lexi a xa n'wina xo va mi pima xiyimo xa mbhurisano, loko mi twa ongeti muhlamuri u tshunxekile naswona u lulamerile ku hlamula swivutiso leswi nga le ka xiyenge lexi landzelaka mi nga teki nkarhi wo leha laha kambe loko swi nga ri tano n'wi vutiseni swivutiso leswi ku endlela leswaku a titwa a tshunxekile tanihileswi leswi swi nga ta tlakusa ku tsakela ka yena ku hlamula hi ntiyiso]

- Mi nga ndzi byela hi n'wina?
- Xana siku ra ntolovelo ri va njhani eka n'wina? Xana mi endla yini hi xitalo?
- Xana mi na vana? **Loko ku ri INA** – ma ha lava van'wana?
- Xana mi ngava mi ri eka vuxaka? **Loko ku ri INA** – mi nga ndzi hlamusela leswaku vuxaka bya n'wina byi njhani/ndzi byeleni ha byona?

Ndza khensa ku va mi ndzi byerile vutomi bya n'wina bya siku rin'wana na rin'wana….

Ndzi ta tsakela ku burisana na n'wina mayelana na ntokoto wa n'wina na maendlelo eka mpfuno wa swarihanyo ku sukela loko mi ta va mi kumile leswaku mi na HIV. Ndzi tsakela ku kuma ku twisisa ko antswa ndlela leyi mi swi koteke ha yona eka siku rin'wana na rin'wana ku sukela loko mi ta va mi byeriwile.

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Hi ntolovelo, loko munhu a kumiwile a ri na HIV, u sungula ku teka vutshunguri. Sweswi ndzi ta tsakela ku mi vutisa swivutiso swi nga ri swingani mayelana na ntokoto lowu eka n'wina ku endlela leswaku ndzi ta twisisa ku antswa leswi swi nga xiswona eka n'wina ku va mi teka vutshunguri.

Ku vuyela nakambe eka mpfuno:

Ha swi tiva leswaku eka vanhu vo tala lava va tekaka ART, ku na ku tikeriva ku tshamela ku teka vutshunguri naswona hi ta tsakela ku twisisa swivangelo swo tshika. Ndzi byeleni hi marito ya n'wina mayelana na nkarhi lowu mi tshikeke ku teka vutshunguri?

[Xana mi ngava mi tshame mi tokota nkarhi lowu mi tshikeke ku teka vutshunguri?]

- **Swivangelo-nkulu swo tshika vutshunguri**
  - Mi nga ndzi byela hi wun'we wa minkarhi yoleyo?
  - Loko mi hleketa endzhaku hi wun'we wa minkarhi leyi, swi ta pfuna swinene ku twisisa leswi a mi swi hleketa hi nkarhi wolowo?
    - Xana a ku ri swihi swivangelo swo va mi tshika?

      <u>Ku vutisisa ku ya emahlweni loku nga vaka kona:</u>
      - Ndzi kombela mi ndzi byela ndlela leyi mi nga kumeka mi ya eku kambeleni?
      - Xana mi ngava mi titwe ongeti a mi fanele mi arile ku kuma nkambelo?
      - Xana a ku ta va ku humelele yini loko a mi arile ku kuma nkambelo?
      - Xana mi titwile mi lulamerile ku sungula vutshunguri loko mi ta sungula?
      - Mi nga ndzi byela leswaku mi sungurile vutshunguri hi ndlela yihi?
      - Xana leswi hinkwaswo swi ngava swi humelerile rini/ mi ngava mi sungule (hi siku rero, endzhaku ka vhiki, ka n'hweti)?
      - Xana mi ngava mi hlanganile na ku tikeriwa ku va mi teka vutshunguri?
      - Xana a mi byi kumisa ku yini vutshunguri bya n'wina?
      - Xana vatirhi va swarihanyo va mi pfunile hi nkarhi lowu?
    - Xana a mi kuma nseketelo ku suka eka un'wana (munghana kumbe minkarhi yin'wana ndyangu)?
    - Xana xiboho xa n'wina xi ngava xi hlohletele hi un'wana kumbe swin'wana leswi nga humelela?
    - Xana mi vulavurile na un'wana mi nga si teka xiboho?
  - Xana ku vile na minkarhi yin'wana laha mi nga tshika ku teka vutshunguri?
    - Xana swivangelo swo va mi tshika swi ngava swi fana? (Swivangelo swin'wana na swin'wana leswi hambaneke?)

[Twisisa swivangelo-nkulu swo sungula vutshunguri nakambe: Vuyimani byintshwa? Ku tlhelela ekaya na ku vuyela nakambe eka maendlelo? Ku vuya eka mpfuno wa ricece? -> hlanganisa na EID]

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Ndza khensa ku va mi hlamuserile leswi nga humelela loko mi ta tshika mu teka ART, endzhaku ka sweswo [yana eka leswi va swi vuleke endzhaku] xana mi ngava mi sungurile ku teka ARTnakambe? Loko ku ri INA – hi kombela mi hi hlamusela leswaku ku humelele yini leswi swi nga endla leswaku mi tlhela mi sungula ku teka ART nakambe?

- Xana mi ngava mi lo teka nkarhi wo karhi mi nga tirhisi vutshunguri kumbe a mi teka vutshunguri kun'wana? Xana ku humelele yini hi nkarhi lowu a mi yimile ku teka vutshunguri?
- Xana mi vulavurile na un'wana mi nga si teka xiboho xo sungula nakambe?
- Xana vatirhi va le ka swarihanyo va mi pfunile hi nkarhi lowu wo teka vutshunguri nakambe?

Naswona swi nga endleka endzhaku ka [nghenisa vuxokoxoko bya nkarhi wun'wana lowu va nga tshika] mi ngava mi sungurile ku teka ART nakambe? Loko ku ri INA – hi kombela leswaku mi hlamusela leswi swi humeleleke leswi endleke leswaku mi sungula ART nakambe? Xana mi tshame mi tokota nkarhi lowu mi tshikeke ku teka vutshunguri naswona mi tlhela mi sungula vutshunguri nakambe?

- Xana mi ngava mi tlhele mi sungula hikwalaho ka swivangelo leswi fanaka kumbe a ku ri na swivangelo swin'wana?

- **Ku kavanyetiwa ka vutshunguri**
  - Ndzi ta tsakela ku tiva swo tala mayelana na nkarhi lowu mi tshikeke ku teka vutshunguri, swi teke nkarhi wo fika kwihi, xana mi tshame mi kavanyeta mpfuno wa HIV?
  - Xana mi endlise ku yini hi mpfuno wa n'wina hi nkarhi lowu wa nkavanyeto?

- **Swiphiqo swa maendlelo ya swarihanyo**
  - [Xana ku va mi rhumeriwile/ndlela yo mi rhumela ku ya kuma mpfuno yi ngava yi pfunile?]
    - Xana swi olova ku fika kwihi ku cinca ku ya eka ndzhawu yin'wana ya swarihanyo?

Ku kamberiwa ka ticence: (Vutisa ntsena vavasati lava va tekeke ART hi nkarhi wa vuyimani kumbe lava va sunguleke ART ya PMTCT)

Hi vulavurile ngopfu sweswi mayelana na n'wina na ntokoto wa n'wina hi HIV, ART na vukorhokeri bya swarihanyo. Sweswi ndzi ta tsakela ku tiva swotala mayelana na mpfuno wa n'wana wa n'wina.

Ndzi kombela mi ndzi byela leswi vuyimani bya n'wina byi fambiseke xiswona? Xana n'wana u njhani?

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[Tsundzuka ku komba ku twela vusiwana loko n'wana a lovile; nyika muhlamuri nkarhi loko a fanele ku tihlengeleta kumbe loko a lava ku wisanyana]

- **Ntokoto wa maendlelo ya swarihanyo**
  - Ndzi kombela mi ndzi byela hinkwaswo leswi mutirhi wa swarihanyo a mi byeleke swona mayelana na ku kambela ricece ra n'wina HIV?
  - Xana swi sungurile rini? (Ekusuhi na nkarhi wo hetelela wa vuyimani, endzhaku ka ku kumiwa ka HIV) I mani loyi a vulavuleke na n'wina hi swilo leswi? Xana mi hleketile yini hi swilo leswi?

- **Vutivi**
  - Xana a mi tiva yini mayelana na ku kamberiwa ka ticence mi nga si endla leswi?
- **Maendlelo**
  - Xana ricece ri kamberiwile? Xana nkambelo lowu wu humelerile rini? Xana a ku ri yihi minhlohletelo yo kamberisa kumbe ku ka mi nga kamberisi ricece? Xana n'wana wa hanya? Xana n'wana u kumile vutshunguri byo karhi? (prophylaxis kumbe ART)
  - **Loko n'wana a ha hanya** – Xana n'wana wa ha mama vele?
    - **Loko ku ri EE** – Xana n'wana a ngava a kamberiwile nakambe endzhaku ko n'wi tshikisa ku mama? Xana a ku ri yihi minhlohletelo yo n'wi kamberisa endzhaku ko tshika ku mama?
    - **Loko ku ri INA** –Xana hi wahi makungu ya n'wina mayelana no kamberisa n'wana endzhaku ka loko a tshikile ku mama?