Understanding women's engagement in HIV care after initiating antiretroviral therapy during pregnancy in South Africa

by

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Abstract

Background: Sustained engagement in HIV care, including adherence to antiretroviral therapy (ART) and retention in HIV services, is essential to optimize maternal health and prevent perinatal, postnatal and sexual HIV transmission. However, engagement in care remains a substantial challenge for pregnant and postpartum women. Women's experience of and response to barriers to engagement in care, including ART side effects, transfer of care and mobility, may be altered by the transitions experienced in pregnancy and motherhood, and there have been few quantitative analyses of these risk factors in maternal ART cohorts. The way engagement in HIV care is measured also varies widely and no gold standard measures of ART adherence or retention exist. Composite assessments of adherence and retention, including drug concentrations, longitudinal self-reported adherence, and interlinked routine electronic health data, have not been thoroughly evaluated among African women living with HIV. To address these gaps in knowledge, this thesis investigates novel measures of ART adherence, and evaluates interlinked routine electronic health data to measure retention in a South African maternal ART cohort. It describes maternal engagement in HIV care, and examines barriers to engagement that require consideration specific to maternal ART.

Methods: This research included women who initiated ART during pregnancy in a large integrated antenatal care and ART clinic in Gugulethu, South Africa (2013-2014). Until July 2013, only women who met certain clinical criteria (CD4 cell count <350 cells/μL or disease stage III or IV) were eligible for lifelong ART, thereafter guidelines changed to recommend lifelong ART for all pregnant women living with HIV. In this setting, all women receive ART and antenatal care in an integrated clinic during pregnancy and are required to transfer to a general ART clinic postpartum. Data were obtained from questionnaires (including demographics, self-reported ART adherence and self-reported side effects) and blood specimens (for HIV viral load) collected at study visits approximately every three months from pregnancy through 18 months postpartum. One additional visit took place 3-4 years postpartum where blood specimens for drug concentrations were also collected. In parallel, routine electronic data, linked across clinics and data sources including HIV clinical visits, laboratory testing and pharmacy dispensing data, were obtained through 30 months on ART.

Findings: Substantial disengagement from care, both non-adherence and non-retention, was observed in all analyses. At least one ART side effect was reported by 97% of women during

pregnancy and high overall side effect burden was associated with reported missed ART doses. Retention worsened over the first two years on ART and 21% of women were lost immediately after transfer from the integrated clinic. Women who linked to care spread to multiple different ART clinics after transfer; 21% moved clinics two or more times. Using combined routine medical records, only 59% of women had evidence of accessing routine HIV care in consecutive 12-month windows through 24 months on ART. Among women with viral loads available, attending ≥2 clinics was associated with viraemia.

In analyses of ART adherence, TFV-DP in DBS provided a more nuanced adherence measure but plasma efavirenz and tenofovir assays had similar ability to predict viral suppression. Areas under the Receiver Operating Curve were higher for all drug concentrations (all >0.850) compared to self-reported adherence using a cross-sectional three-item scale (0.756). Longitudinal measurement of the same self-reported adherence scale showed that reporting worse adherence on any of three items over consecutive visits could predict viremia (>50 and >1000 copies/mL), particularly among women who were suppressed at the initial visit.

Measuring retention using routine interlinked electronic data facilitated tracing of women beyond transfer from the integrated clinic to any clinic where they accessed HIV care postpartum. Estimates of retention varied widely using different retention definitions and data sources. Overall, electronic primary health care data, linked across clinics, performed better than laboratory data alone and was a robust measure for monitoring retention in HIV care.

Conclusions: Taken together, these findings underscore a concerning level of disengagement from HIV care during and after pregnancy. Potential ART side effects, required transfer of care, the potential challenges of mobility and the importance of sustained engagement in care beyond pregnancy and breastfeeding, should be emphasised in ART counselling. Drug concentrations in DBS and plasma strongly predict viral suppression, but these data on longitudinal self-reported adherence provide a proof of concept for a low resource interim adherence measure that warrants further investigation in routine care settings with limited resources for viral load or drug concentration testing. Transfer of care and postpartum mobility mean that interlinked data sources are essential to obtain accurate estimates of retention postpartum. Further evaluation of the optimal approaches to transferring maternal ART care and the development of interventions to support engagement both in and beyond the clinic of ART initiation will be critical to sustain maternal engagement in HIV care in the long term.

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In isiXhosa there is a saying “umntu ngumntu ngabantu” that means a person is because of other people. This thesis would never have been possible and I would not be where I am without the contributions, support, and encouragement of so many others.

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Preface

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

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

1. Phillips TK, Cois A, Remien RH, Mellins CA, McIntyre JA, Petro G, Abrams EJ, Myer L. Self-reported side effects and adherence to antiretroviral therapy in HIV-infected pregnant women under option B+: A prospective study. *PLoS One* 2016; **11**: e0163079. doi:10.1371/journal.pone.0163079.

2. Phillips TK, Sinxadi P, Abrams EJ, Zerbe A, Orrell C, Hu N-C, Brittain K, Gomba Y, Norman J, Wiesner L, Myer L. A comparison of plasma efavirenz and tenofovir, dried blood spot tenofovir-diphosphate, and self-reported adherence to predict virologic suppression among South African women. *J Acquir Immune Defic Syndr* 2019;81(3):311-318. doi: 10.1097/QAI.0000000000002032.

3. Phillips TK, Wilson IB, Brittain K, Zerbe A, Mellins CA, Remien RH, Orrell C, Abrams EJ, Myer L. Decreases in self-reported ART adherence predict HIV viremia in a longitudinal cohort of pregnant and postpartum women in Cape Town, South Africa. *J Acquir Immune Defic Syndr* 2018; 80(3):247-254. doi:10.1097/QAI.0000000000001909.

4. Phillips TK, Orrell C, Brittain K, Zerbe A, Abrams EJ, Myer L. Estimating retention in HIV care: data sources and definitions in a South African cohort of pregnant and postpartum women. *Being prepared for submission.*

5. Phillips TK, Clouse K, Zerbe A, Orrell C, Abrams EJ, Myer L. Linkage to care, mobility and retention of HIV-positive postpartum women in antiretroviral therapy services in South Africa. *J Int AIDS Soc* 2018; **21**:e25114. doi:10.1002/jia2.25114.

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

6. Phillips TK, Brittain K, Mellins CA, Zerbe A, Remien RH, Abrams EJ, Myer L, Wilson IB. A self-reported adherence measure to screen for elevated HIV viral load in pregnant and postpartum women on antiretroviral therapy. *AIDS Behav* 2017; **21**:450–461. doi:10.1007/s10461-016-1448-0.

The contribution of the candidate to each manuscript is outlined at the start of each chapter. The candidate was the lead and corresponding author on all manuscripts, prepared the datasets for analysis, conducted all analyses except for the latent class analysis in Chapter 3 which was conducted by Dr Annibale Cois, and drafted all versions of the manuscripts. All co-authors reviewed and approved the submitted manuscripts and the candidate reviewed co-author comments and integrated them into the manuscripts prior to submission.

All analyses are based on data collect as part of the MCH-ART study. The candidate was employed as the study coordinator on this project from 2013 to 2016 and played a central role in data collection and study implementation. During this time, she developed, in consultation with her supervisors, the independent concepts for the analyses presented in this PhD theses. The candidate's primary supervisor has confirmed to the University of Cape Town Doctoral Degrees Board that the included papers all overwhelmingly reflect the candidates own scientific work.

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Signed: Signed by candidate Date: 18 June 2019

List of abbreviations

AIC	Akaike Information Criterion
AIDS	Acquired immune deficiency syndrome
ANC	Antenatal care
ART	Antiretroviral therapy
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
CNS	Central nervous system
DBS	Dried blood spot
DOT	Directly observed therapy
EDM	Electronic drug monitoring
EFV	Efavirenz
GEE	Generalized estimating equations
GIT	Gastrointestinal tract
HIV	Human immunodeficiency virus
HRSA-HAB	Health Resources and Services Administration, HIV/AIDS Bureau
IQR	Interquartile range
JITAI	Just-in-time adaptive intervention
LACE	Long-term Adherence and Care Engagement
LCA	Latent class analysis
LLOQ	Lower limit of quantification
LTFU	Loss to follow-up
MCH	Maternal and child health
MOU	Midwife obstetric unit
MTCT	Mother-to-child transmission
NHLS	National Health Laboratory Services
NICHD	National Institute of Child Health and Human Development
NNRTI	Non-nucleoside reverse transcriptase inhibitor

NPV	Negative predictive value
OR	Odds ratio
PEPFAR	President's Emergency Plan for AIDS Relief
PHDC	Provincial Health Data Centre
PMTCT	Prevention of mother-to-child transmission
PPV	Positive predictive value
PrEP	Pre-exposure prophylaxis
ROC	Receiver operating characteristics
RR	Risk ratio
SD	Standard deviation
SE	Standard error
SMS	Short-Text Messaging Service
SSA	Sub-Saharan Africa
TFV	Tenofovir
TFV-DP	Tenofovir-diphosphate
VL	Viral load
VS	Virologic suppression
WHO	World Health Organization

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Chapter 1: Introduction

1.1 Introduction

1.1.1 The global HIV epidemic

Almost 37 million people are living with human immunodeficiency virus (HIV) worldwide [1]. Despite substantial progress in HIV treatment and prevention, in 2017 there were still an estimated 1.8 million new infections globally and 940 000 deaths dues to acquired immune deficiency syndrome (AIDS) [2]. Since 2016, the World Health Organization (WHO) has recommended universal initiation of lifelong antiretroviral therapy (ART) for all people living with HIV [3]. The goal of ART is to suppress the level of virus in the body which in turn reduces HIV/AIDS related morbidity and mortality and minimizes the risk of HIV transmission [4–10].

Alongside the scale up of universal ART are the Joint United Nations Program on HIV and AIDS (UNAIDS) 90-90-90 targets: 90% of people living with HIV must know their status, 90% of those who know their status must be on ART, and 90% of those on ART must be virologically suppressed [11]. Modelling estimates have shown that reaching these targets by 2020, and continuing to 95-95-95 by 2030, will enable the control of HIV transmission and the end of the AIDS epidemic. Sustained retention in care and adherence to ART are required to achieve and sustain viral suppression (Figure 1-1) [8,12,13] and to achieve the benefits of lifelong ART. However, sustained engagement in care – including both retention in HIV care and adherence to ART - remains a persistent challenge globally [1,14].

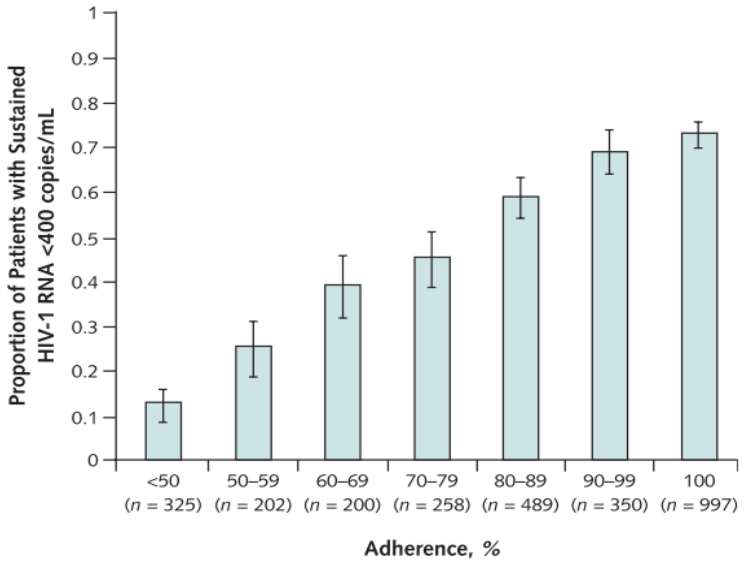

Figure 1-1 The association between adherence to antiretroviral therapy and sustained viral suppression, from Nachega *et al* [13].

1.1.2 HIV in pregnant and postpartum women

In Sub-Saharan Africa (SSA), women bear a disproportionate burden of the HIV epidemic. SSA home to approximately 70% of all people living with HIV and 56% of them are women [1]. In 2017, women accounted for 59% of new HIV infections in SSA and around 90% of all pregnancies among women living with HIV occur in this region [2,15]. “Test and treat” or universal treatment for all people living with HIV is included in the WHO recommendations for prevention of mother-to-child transmission of HIV (PMTCT) [3]. Encouragingly, over 90% of pregnant women known to be living with HIV globally received antiretrovirals (ARVs) for prevention of mother-to-child transmission (PMTCT) of HIV in 2017 resulting in less than 10% transmission [2]. Even with this progress, there were still 92 000 new HIV infections in children and 160 000 AIDS-related deaths among women in SSA in 2017 [2].

Among pregnant and postpartum women living with HIV, sustained engagement in HIV care has the potential to impact on individual-, family- and population-level health outcomes [3]. Firstly, just as in all people living with HIV, ART reduces morbidity and mortality for the individual [4,8]. This has obvious benefit for a woman’s quality of life but also means that she is more likely to live a long healthy life and to be able to care for herself and her family. Preventing perinatal and postnatal transmission in the incident pregnancy is often the immediate priority and with sustained ART, this benefit extends to all future pregnancies [10]. Lastly, remaining engaged in care and virologically suppressed will prevent transmission of HIV to HIV-uninfected sexual partners, a critical component for ending the HIV epidemic [5].

Despite the important benefits of sustained engagement in ART care, many women do not remain retained in care and adherent to ART. A 2018 systematic review of ART retention among pregnant and breastfeeding women living with HIV in Africa found retention ranged from 47% to 88% only six months after starting ART [16]. Data from Malawi showed that 70% of women were retained after three years on ART [17], and only 70% of women had >90% drug coverage using pharmacy refill data through two years on ART [18].

1.1.3 HIV prophylaxis and treatment guidelines for pregnant and postpartum women

Over the past 20 years there has been a paradigm shift in our approach to PMTCT services with increasing recognition of the value of HIV treatment for maternal health and population health outcomes [10]. Global guidelines have evolved from the first recommendation of

single-dose and short-course ARV prophylaxis for PMTCT in 2001 [19], through lifelong ART for those meeting strict disease stage criteria and short-term prophylaxis for those not eligible for ART [20–22], to lifelong ART for all pregnant and breastfeeding women regardless of disease stage [23] (Figure 1-2). This shift represents an evolution in our understanding of HIV transmission, the role of ARV drugs in HIV treatment and prevention, and the potential for PMTCT services as an entry into lifelong HIV care [24].

YEAR	Prevention of mother-to-child transmission prophylaxis	Triple drug antiretroviral therapy (ART)
2001	Four weeks of zidovudine, zidovudine and lamivudine, or single dose nevirapine	No recommendation for lifelong antiretroviral therapy
2004	Zidovudine from 28wks + single dose nevirapine in pregnancy	If CD4 ≤ 200
2006	Zidovudine from 28wks + single dose nevirapine + zidovudine and lamivudine for 7 days	If CD4 ≤ 200
2010	**Option A** Zidovudine from 14 weeks gestation or **Option B** ART during pregnancy and breastfeeding	If CD4 ≤ 350
2013	**Option B** ART during pregnancy and breastfeeding or **Option B+** ART for all pregnant and breastfeeding women living with HIV	If CD4 ≤ 500
2015	**Option B+** ART for all pregnant and breastfeeding women living with HIV	
2016 **2018**	**Universal ART** ART for all people living with HIV	

Figure 1-2 Evolution of World Health Organization guidelines for antiretrovirals in pregnant and postpartum women

Universal lifelong ART for pregnant and breastfeeding women was first implemented in 2011 in Malawi [25]. Since then there has been an unprecedented scale-up with almost all countries adopting this approach by November 2017 [26]. This policy change has resulted in antenatal services, particularly in high HIV prevalence areas, becoming an important entry point into lifelong ART programmes for women [27]. HIV testing during pregnancy is the norm in high burden countries and, although barriers to ART uptake still exist, great advances have been made in ensuring women initiate ART following an HIV diagnosis in pregnancy. The removal of the need for CD4 cell count testing to establish ART eligibility and simplified

treatment guidelines have minimised delays in ART initiation during pregnancy and treatment initiation on the day of diagnosis is now common [10,28,29]. Despite the achievements with treatment uptake, the success of lifelong ART is threatened as major challenges persist with keeping women engaged in ART services in the long term.

1.1.4 ART regimens for pregnant and postpartum women

From the time this thesis was conceived, the first-line regimen recommended by the WHO and in the South African national treatment guidelines has been a fixed-dose, once-daily combination of efavirenz (EFV), emtricitabine/lamivudine and tenofovir (TFV) [30]. EFV and TFV have been found to be safe in pregnancy with no evidence of increased risk of birth defects [31,32], and this regimen is widely used across SSA. TFV can cause side effects such as nausea, headaches and dizziness, but is usually well tolerated [32–34]. The most worrying potential toxicity from TFV is renal disfunction and kidney function is routinely monitored through creatinine levels and glomerular filtration rates among patients on TFV containing regimens [3,35,36]. There are concerns about adverse effects of EFV, specifically central nervous system (CNS) effects such as dizziness, abnormal dreams and insomnia, as well as depression and suicidality [34,37,38]. In 2017, the WHO included recommendations for dolutegravir as an alternative to EFV in first-line regimens with many countries adopting this new regimen [26,39]. Dolutegravir has superior efficacy and tolerability compared to EFV, however concerns remain about dolutegravir safety in the first trimester of pregnancy. It is therefore not currently recommended for women planning to conceive or for women in the first eight weeks of pregnancy [40–42].

1.1.5 Providing ART for pregnant and postpartum women

When triple drug ART was first recommended for the treatment of HIV it required specialist treatment services. ARV prophylaxis for PMTCT has almost always been provided by nurses within antenatal care (ANC) clinics, but lifelong ART has historically been provided in HIV clinics with treatment initiated and managed by doctors. Under this model of care many pregnant women who were eligible for ART did not successfully link to HIV treatment services from ANC and did not initiate treatment before delivery [43,44]. The need for specialist clinicians also hampered the potential to scale up ART programmes in many low- and middle-income countries [45]. Task-shifting, the process of delegating tasks to cadres of staff with lower-level qualifications, is one approach that has been widely used to expand

access to HIV services in SSA. A formal guideline on task-shifting and training nurses to provide primary HIV care services was released by the WHO in 2008 [46] and many ART services are now predominantly nurse led [47]. With task-shifting came the potential to integrate ART services into ANC settings run by nurses. Integration of antenatal and HIV services has substantially increased ART uptake during pregnancy and is now the standard of care in most high burden countries [48,49].

Models of care for providing ART to pregnant and postpartum women still vary. Van Lettow *et al* conducted a survey on implementing universal ART for pregnant and breastfeeding women in Malawi and identified three models of care: Model 1 provided integrated ANC and ART through 6 weeks postpartum with subsequent transfer to general ART clinics; Model 2 provided immediate referral from ANC to a general ART clinic for ART initiation; and Model 3 provided the first dose of ART in the ANC clinic followed by immediate transfer to a general ART clinic [50]. Women who entered care in Model 1 or 3 were much more likely to initiate ART, however retention in care among women who successfully initiated ART was best in Model 2. These findings point to a potential delay in disengagement from care, fixing a vulnerable point in the cascade and shifting the loss to the next vulnerable point. Another study in Malawi reported similar results however they also presented a cumulative cascade [28]. This showed that, despite greater early losses among women successfully started on ART in the integrated care model (Model 1) compared to those who started ART in the referral model (Model 2), the impact of improved uptake of ART services resulted in lower overall loss from the care cascade by six months on ART (Figure 1-3).

Even with the improved coverage of ART in pregnancy that resulted from integrating ART services into ANC, many settings still require women to transfer their ART care from integrated ANC and ART services to routine adult ART clinics after delivery. The timing of transfer varies across settings, ranging from six weeks to two years postpartum, but may also be a vulnerable point for disengagement from care [50–54]. Further extending integrated antenatal services to include maternal ART and routine child health services postpartum has been found to improve maternal retention and viral suppression, and to improve adherence to the early infant diagnosis cascade [55–57]. This has clear benefits for the periods of greatest risk for perinatal and postpartum HIV transmission, but it is not yet clear if the benefit for engagement in care is sustained following transfer to general adult care [55,56]. Taken together, this evidence suggests that integrated services improve ART uptake and outcomes as long as women are retained in the integrated services. They may not prevent

disengagement from care in the long-term, an idea that has also been posited in the context of universal ART [58].

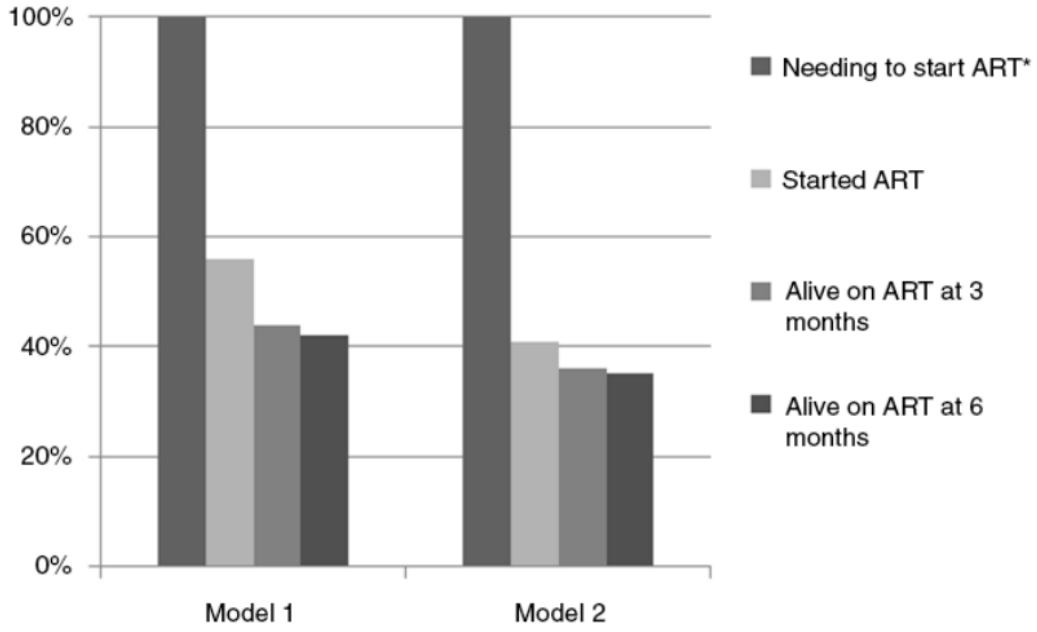

Figure 1-3 The proportion of women starting and remaining in ART care when ART in integrated in antenatal care (Model 1) and when women are required to transfer from antenatal care to ART services (Model 2), from Chan *et al* [28].

1.1.6 The construct of engagement in HIV care: adherence and retention

Throughout this thesis the term "engagement in HIV care" will be considered as an umbrella term for both retention in HIV care and adherence to ART [59]. The WHO define loss to follow-up (LTFU, or not retained on ART) as "patients receiving ART and not seen at the clinic, or pharmacy, >90 days after the date of their last missed appointment or last missed drug pick-up and who are not known to have transferred out or died" and ART adherence as "the extent to which a person's behaviour corresponds with the agreed recommendations from a health care provider" [60,61]. Gardner *et al* described a spectrum of engagement based on the Health Resources and Services Administration (HRSA) continuum of engagement in ART care (Figure 1-4) [14]. Based on this spectrum, people living with HIV may lie anywhere between not knowing their HIV status, to being in care but not adherent to ART or to being fully engaged in HIV care.

The spectrum of engagement in HIV care						
Not engaged in care ⟷ Fully engaged in care						
Does not know HIV status	Known HIV status but never linked to HIV/ART care	Linked to HIV/ART care but never initiated ART	Initiated ART but dropped out of care	Moves in and out of HIV/ART care	Retained in HIV/ART care with but not adherent to treatment	Retained in HIV/ART care and adherent to treatment

Figure 1-4 The spectrum of engagement in ART care **(**adapted from Gardner et al [14] and the Health Resources and Services Administration (HRSA) continuum of engagement in ART care [62])

Vrijens *et al* also proposed a definition of adherence which encompasses both adherence and retention as well as a time dimension [63]. The definition consists of initiation, implementation, persistence and discontinuation. Initiation includes the initial prescription and first ART dose, implementation speaks to adherence and non-adherence as defined above, and persistence is how long patients maintain being in care as prescribed without discontinuing care or being LTFU. This framework is useful in thinking about sustained engagement in HIV care in the long-term. Myer *et al* presented what this might look like for women starting ART in pregnancy, with many women engaged in care in the first few months on ART and gradually increasing proportions either in care but not adherent, or not retained in care, both of which are considered disengagement (Figure 1-5) [59].

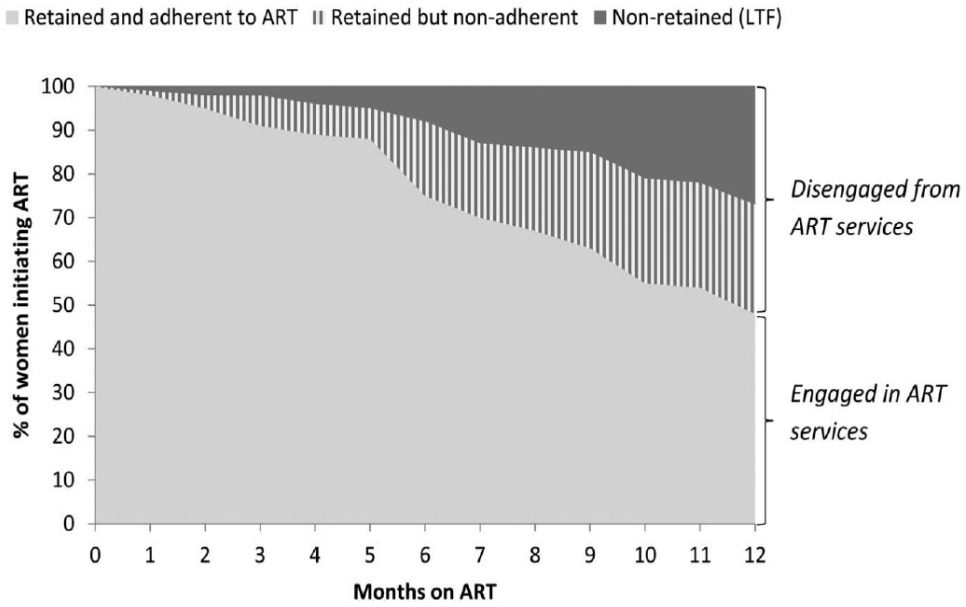

Figure 1-5 Hypothetical depiction of engagement in HIV care (adherence and retention), from Myer *et al* [59].

Another component of engagement in care is viral suppression. Viral suppression, driven by retention and adherence to ART, is the key factor in the success of ART for treatment and prevention of HIV and viral load monitoring is a core component of ART programs [23,64]. Currently the WHO recommends viral load testing at six and 12 months after ART initiation and annually thereafter, with additional testing following a high viral load (>1000 copies/mL) [65]. Some countries, including South Africa and Kenya, recommend more frequent viral load testing during pregnancy and breastfeeding due to the risk of transmission, although to date there are no global recommendations on optimal viral load monitoring for pregnant and breastfeeding women [36,66–68]. By the end of 2017, 58% of low- and middle-income countries were fully implementing WHO recommended viral load monitoring [26] but numerous barriers exist to the implementation of frequent viral load testing in low-resource settings [64,69]. Viral load measures near the time of delivery are important to help classify HIV-exposed children as low or high risk for transmission and to provide additional infant prophylaxis if needed. In SSA, many barriers persist to the implementation of viral load monitoring feedback of viral load results during pregnancy [67]. Viral load testing is also periodic and is not informative about patterns of adherence or gaps in care [70]. Although primarily driven by engagement in care, viral load is also affected by other factors such as ARV resistance, comorbidities and acute infection [71]. As such, even with full implementation of viral load monitoring, measures of retention and adherence are needed in order to assess and intervene on patient care real-time, to monitor ART programmes and to evaluate outcomes in research [72].

In low-resource settings where frequent viral load testing is not possible, interim measures of adherence and retention are required to measure patterns of engagement in care and to flag patients requiring intervention. Methods used to measure retention and adherence are highly variable and no gold standard measures exist [73–75]. The common approaches to measuring these constructs and the challenges with each are discussed in detail in the literature review.

1.2 Problem statement and rationale

Despite the success in scaling up access to ART for pregnant and postpartum women, engagement in HIV care remains a persistent challenge. Without continued engagement in care, women are at risk of HIV-related morbidity and mortality, there is increased risk of perinatal and postnatal transmission of HIV in the incident pregnancy and subsequent pregnancies, and there is risk of transmission to sexual partners. There is a need to investigate

barriers to engagement in care that may have particular considerations in pregnant and postpartum women. There are also no gold standard measures of adherence and retention and approaches to measuring these constructs remain highly variable. Novel adherence measurement approaches need to be investigated for use in conjunction with viral load monitoring and for use in research. Given the frequent requirement for transfer of ART care from integrated ANC and ART services postpartum, there is also a need to understand the measurement of retention beyond the facility of ART initiation and potential for using routine interlinked data sources for this purpose. To monitor ART programmes, evaluate interventions and successfully intervene in patient care, further investigation into both the barriers to engagement and measurement approaches are required.

1.3 Aim and objectives

The overall aim of this research was to investigate barriers to engagement in HIV care with specific considerations among pregnant and postpartum women as well as to explore novel adherence measurement approaches and the use of routine interlinked data sources to measure retention in HIV care after ART initiation in pregnancy in South Africa.

The specific objectives were:

1. To review the literature on engagement in HIV care during and after pregnancy in SSA, including barriers, facilitators and methodological considerations for measuring adherence and retention in care.
2. To describe engagement in care during and after pregnancy and to explore two known barriers to engagement in care that have specific considerations in the context of maternal ART:
    a. To examine the occurrence and patterns of self-reported ART side effects among women starting first-line EFV-based regimens in pregnancy, and to explore the relationship between self-reported ART side effects and missed ART doses.
    b. To explore the impact of postpartum transfer out of integrated antenatal and ART services on linkage, mobility to access HIV care and retention in care.
3. To investigate and compare novel measures of ART adherence in a cohort of African women:

a. To compare the ability of self-reported adherence using a simple three-item scale and drug concentrations of plasma EFV, plasma TFV and tenofovir-diphosphate (TFV-DP) in dried blood spots (DBS), to predict viral suppression.

b. To explore the use of longitudinal change in self-reported ART adherence to predict viremia.

4. To evaluate the use of routine interlinked electronic health data to measure retention in HIV care, specifically:

    a. To examine the impact of using different routine care data sources and different retention definitions on i) the estimate of retention in care, ii) the consistency of associations between selected covariates and estimated retention, and iii) the association between retention and viral load.

    b. To investigate the use of routine interlinked health data to measure linkage to care and mobility to access HIV care after transferring out of integrated antenatal and ART services.

1.4 Data sources

Data for this thesis were drawn from three sources: a prospective cohort study (the maternal and child health [MCH]-ART study, ClinicalTrials.gov NCT01933477); an additional cross-sectional study including women who participated in the MCH-ART study (the long-term adherence and care engagement [LACE] study); and routine electronic medical records from the Provincial Health Data Centre (PHDC) of the Western Cape Department of Health, obtained retrospectively for all women who enrolled in the MCH-ART cohort.

These data sources provided parallel study and routine health data for the same cohort of women as presented in Figure 1-6. Objectives 2, 3 and 4 used data collected during the MCH-ART study, Objective 3a used data from the LACE study, and Objective 4 used data collected during the MCH-ART study combined with parallel routine programme data from the PHDC. These data sources and their contributions are described in detail below.

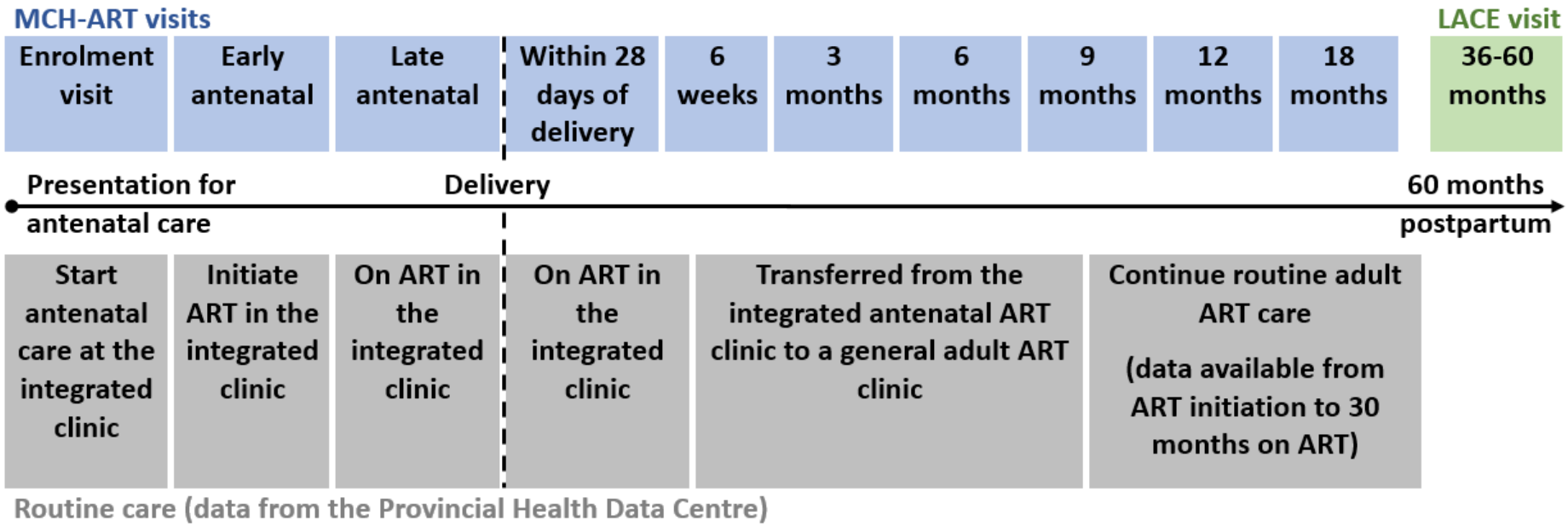

Figure 1-6. Time line of data sources include in this thesis: MCH-ART study visits (blue), the LACE study visit (green) and parallel routine medical record data (grey); ART – antiretroviral therapy.

1.4.1 The MCH-ART study

Strategies to optimize antiretroviral therapy services for maternal & child health: the MCH-ART study (HREC REF: 451/2012, appendix 9.1.1) was a multi-phase implementation science trial that began in March 2013, at the Gugulethu Midwife Obstetric Unit (MOU) in Cape Town, South Africa. The overall aim of the MCH-ART study was to evaluate two different strategies for delivering HIV care and treatment services during the postpartum period to women living with HIV who initiated ART during pregnancy and their HIV-exposed infants.

The study design had three interrelated phases:

Phase 1: a cross-sectional evaluation of consecutive HIV-infected pregnant women seeking ANC at the study clinic (n=1554).

Phase 2: an observational cohort of all women from Phase 1 who were eligible for initiation of ART (n=628), followed in three study measurement visits, from their second antenatal clinic visit until their first postpartum clinic visit. ART initiation and management were integrated into antenatal follow-up that took place at the Gugulethu MOU according to standard provincial protocols.

Phase 3: a randomised trial of strategies for delivering ART to women during the postpartum period (n= up to 471). Women enrolled in Phase 2 who were breastfeeding their infants were approached to participate in the trial at the end of the first routine postpartum clinic visit. Women were randomised to one of two approaches to providing ART during the postpartum period to HIV-infected mothers who are breastfeeding:

> *Arm A*: referral of women to their nearest general ART services at approximately 4-8 weeks postpartum (the current standard of care in this setting).
>
> *Arm B*: continued receipt of ART in the antenatal clinic, as part of an MCH-focused ART service at the Gugulethu MOU that only referred women to general ART services after cessation of breastfeeding and once the child's final HIV status was determined.
>
> The two arms both employed standard provincial protocols for ART services and routine child health (with identical medications and routine monitoring); they differed

by the length of time women remained in the MCH-focused ART service at the Gugulethu MOU before they were referred to general ART clinics.

All women participating in Phase 3 were followed through 18 months postpartum. The total length of participation in the study varied based on gestational age at enrolment into Phase 2, ranging from a minimum of approximately 52 weeks to a maximum of approximately 80 weeks. Study measurement visits were conducted in a separate building on the Gugulethu clinic premises, away from routine antenatal, postnatal or ART services. All research activities were conducted by separate research staff and routine clinical care was managed as usual by the clinic. Measurements included questionnaires and HIV viral loads at each visit, as well as abstraction of clinical data on routine antenatal, postnatal and ART services received, for both mothers and infants. The study viral loads were batch tested at the end of each study phase by the National Health Laboratory Services (NHLS) using the same assays as routine care viral loads. Active participant follow-up ended in June 2016 and 87% of women enrolled into phase 3 were retained in the study through 12 months postpartum.

Contribution of these data to the thesis

Women who enrolled into phase 2 or phase 3 of the MCH-ART study were included in the analyses presented in this thesis. A detailed structured questionnaire on patient-perceived ART side effects during pregnancy, based on the Division of AIDS adverse event grading table [76], was used to examine patterns of side effects reported during pregnancy (Objective 2a). Self-reported adherence, using a novel three-item scale developed in United States [77], was assessed at every study visit and provided the data for the longitudinal analyses of reported adherence in Objective 3b. Plasma HIV viral load was also measured at each study visit, independent of routine care. These study viral loads allowed ascertainment of viral suppression even if women were not retained in routine care and were used to examine the association between adherence and viral load for Objective 3, and retention and viral load to address Objectives 2b and 4. A limitation of the analyses for Objective 2a is that viral load data could not be included as the batched study viral load results were not available at the time.

Important to note is that the impact of the postpartum trial arm was not the focus of this thesis and these results have been reported elsewhere [55]. The intervention arm resulted in significant improvement in maternal retention and viral suppression at 12 months postpartum. Therefore, where appropriate, an indicator of whether a woman was in only phase 2, in phase

3 in the standard of care arm, or in phase 3 in the intervention arm, was included in analyses to account for design effects.

1.4.2 The LACE study

Following completion of the MCH-ART study, further funding was obtained to conduct one additional study visit at a later postpartum time point. The primary aim of the study was to explore long-term adherence and care engagement and to examine whether there was any sustained impact of the MCH-ART intervention at this later time (HREC-REF 866/2016, appendix 9.1.2). Women who had enrolled in phase 3 of MCH-ART were recruited into the LACE study between 36 and 60 months postpartum; 75% of the original cohort was recruited between May 2017 and May 2018. Women who enrolled completed a face-to-face study visit equivalent to those in MCH-ART. Venous blood and DBS specimens were collected at the study visit to measure plasma HIV viral load, plasma EFV, plasma TFV and DBS TFV-DP concentrations.

Contribution of these data to the thesis

The drug concentration measures, viral load and self-reported adherence (using the same measure used in the MCH-ART study) collected during the LACE study were used to address Objective 3a of this thesis.

1.4.3 Routine health data

The PHDC is a patient-level interlinked health information exchange within the Western Cape Government Department of Health [78,79]. The information exchange combines a variety of routine electronic health data platforms from hospitals and primary care clinics across the province (Figure 1-7). These platforms include a combination of clinical, clerical and administrative data bases such as facility-captured HIV registers [80], birth registers, hospital and primary care patient information systems including visits and admissions, laboratory test data and electronic pharmacy dispensing data [78]. Deaths recorded in health facilities are also included. The Western Cape Province implemented a unique patient identifier in the early 2000s which now extends through all hospitals and primary care clinics in the province [79]. The PHDC uses the unique identifier, together with other captured identifiers, to link patients across facilities, with deduplicating algorithms to identify patients with more than one provincial identifier [78,79].

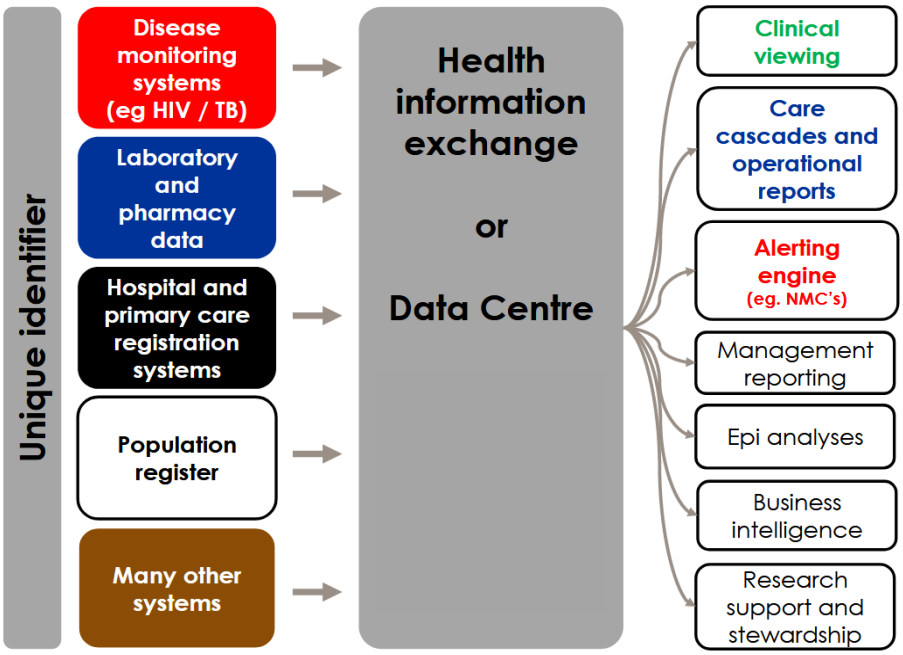

Figure 1-7. A schematic of the Western Cape Provincial Health Data Centre (Courtesy of Andrew Boulle)

In addition to data obtained from the PHDC, the NHLS database, including laboratory testing from all public health facilities in South Africa, was searched. Each woman enrolled in phase 2 of the MCH-ART study was searched for in the databased using the identifiers she had provided at study enrolment and HIV-related laboratory test results were abstracted.

Contribution of these data to the thesis

Routine HIV care data were requested from the PHDC for all women who had enrolled into phase 2 of the MCH-ART study. This provided the routine care data from the time of presentation for ANC and ART initiation, through to 30 months on ART. Available data for HIV care contacts included ART clinic visits (routinely captured by clerks at each facility into the local clerical information systems and electronic registers) [80] and ART pharmacy dispensing data from the local pharmacy administrative databases. This provincial data was merged with the laboratory test data (CD4 cell counts and HIV viral loads) from the NHLS database to ascertain retention in HIV care. In both routine data sources, the source, data and place of care access was recorded. Attempt was made to remove acute health care contacts and contacts with non-routine services where possible. These data were used to investigate the use of interlinked routine data sources to measure retention in HIV care and addressed Objective 2b and Objective 4.

1.5 Ethics approvals

The MCH-ART and LACE studies were approved by the University of Cape Town Human Research Ethics Committee and the Columbia University Institutional Review Board. Both studies only enrolled women aged 18 years and older due to the need for parental consent for younger women. All women enrolled in the MCH-ART study provided written informed consent which included consent to abstract routine medical records, including linkage to electronic databases. Identifying information including the unique provincial patient identification number as well as name, surname, date of birth and South African identification number if available, were collected during the study for purpose of abstracting medical records. Linked data for all available data sources were obtained from the PHDC for all women who enrolled in phase 2 of the MCH-ART study. Ethics approval for the analyses presented in this thesis was obtained from the University of Cape Town Human Research Ethics Committee (HREC-REF 117/2017, appendix 9.1.3).

1.6 Overview and structure of the thesis

This thesis consists of an introductory chapter, a literature review, five results chapters, a discussion chapter synthesising the findings of the overall thesis and supporting appendices. This introduction chapter places the issues of engagement in HIV care, specifically for pregnant and postpartum women in SSA, into context and describes the objectives of the thesis, which were conceptualised in 2016.

Chapter 2, the literature review, presents a critical review of the barriers and facilitators related to women's engagement in HIV care during pregnancy, breastfeeding and post-breastfeeding motherhood, as well as a review of common approaches to measuring adherence and retention in care in this population. It is not intended to be an exhaustive review but rather to present key aspects of the engagement in HIV care literature pertinent to pregnant and postpartum women in SSA and to summarise the main methods of measuring ART adherence and retention in HIV care. To note, Part A of this review chapter is adapted from a narrative review, first-authored by the candidate, that is currently undergoing peer-review at Expert Review of Anti-Infective Therapy (submitted 1 September 2018).

Five results chapters are included. They present results from a cohort of women living with HIV who initiated ART during pregnancy in a large integrated ANC and ART clinic in Gugulethu, South Africa in 2013-2014. Eighty percent of the cohort started ART under the

policy of Option B+, universal ART for all pregnant and breastfeeding women. All results chapters are manuscripts that are either published, submitted or being prepared for submission (Table 1-1):

- Objectives 2a and b are explored in Chapter 3 and Chapter 7, respectively. Chapter 3 used data on self-reported ART side effects and missed ART doses during pregnancy. The chapter explores patterns of reported side effects, both system-specific and overall, and investigates the association between reported side effects and missed ART doses. Chapter 7 used interlinked routine electronic health data for the same cohort from ART initiation through 30 months on ART to describe linkage to care, mobility for HIV care access, and retention in care after women were transferred out of the integrated ANC and ART clinic postpartum.

- Objective 3a is addressed in Chapter 4 where self-reported adherence, plasma EFV and plasma TFV concentrations are compared to TFV-DP in DBS in their ability to predict viral suppression in a sub-set of women 3-4 years postpartum. The findings of Chapter 4 provide novel data on the use of TFV-DP in DBS to measure adherence among African women living with HIV. Chapter 5, which addressed Objective 3b, goes on to present a proof of concept for using change in self-reported adherence across consecutive visits to improve the value of self-reported adherence to predict viral load.

- Chapters 6 and 7 fulfil Objective 4 and focus on the measurement of maternal retention in HIV care using interlinked routine electronic data. The results of Chapter 6 show how using different data sources and definitions of retention can result in a range of different retention estimates and explores the associations of covariates with retention estimates as well as associations between retention estimates and viral suppression. This is followed by a detailed analysis of the issues around clinic transfer of care from integrated ANC and ART services and where women continue their HIV care postpartum in Chapter 7.

The findings of this combined body of work are discussed and synthesised in Chapter 8. A summary of the key contributions of this thesis are presented along with recommendations for policy and future research. Supplementary material, including a formative publication that presents a validation of the self-reported adherence scale used in Chapter 4 and 5, as well as supplementary inserts from each results chapter, follows in Chapter 9.

Table 1-1. Summary of thesis results chapters (Ch), objectives, manuscripts and data sources

Chapter and objective		Manuscript title and status	Data source
Ch 3	**2a:** To examine the occurrence and patterns of self-reported ART side effects among women starting first-line EFV-based regimens in pregnancy, and to explore the relationship between self-reported ART side effects and missed ART doses.	Phillips TK, Cois A, Remien RH, *et al*. Self-reported side effects and adherence to antiretroviral therapy in HIV-infected pregnant women under option B+: A prospective study. *PLoS One* 2016; 11:e0163079	MCH-ART
Ch 4	**3a:** To compare the ability of self-reported adherence using a simple three-item scale and drug concentrations of plasma EFV, plasma TFV and TFV-DP in DBS, to predict viral suppression.	Phillips TK, Sinxadi P, Abrams EJ, *et al*. A comparison of plasma efavirenz and tenofovir, dried blood spot tenofovir-diphosphate, and self-reported adherence to predict virologic suppression among South African women. *J Acquir Immune Defic Syndr* 2019;81(3):311-318.	MCH-ART and LACE
Ch 5	**3b:** To explore the use of longitudinal change in self-reported ART adherence to predict viremia.	Phillips TK, Wilson IB, Brittain K, *et al*. Decreases in self-reported ART adherence predict HIV viremia in a longitudinal cohort of pregnant and postpartum women in Cape Town, South Africa. *J Acquir Immune Defic Syndr* 2018; 80(3):247-254.	MCH-ART
Ch 6	**4a:** To examine the impact of using different routine care data sources and different retention definitions on i) the estimate of retention in care, ii) the consistency of associations between selected covariates and estimated retention, and iii) the association between retention and viral load.	Phillips TK, Orrell C, Brittain K, *et al*. Estimating retention in antiretroviral therapy services: the impact of definitions and data sources in a South African maternal cohort. *Being prepared for submission*	MCH-ART and PHDC
Ch 7	**2b:** To explore the impact of postpartum transfer out of integrated antenatal and ART services on linkage and retention in care. **4b:** To investigate the used of routine interlinked health data to measure linkage to care and mobility to access HIV care after transferring out of integrated antenatal and ART services	Phillips TK, Clouse K, Zerbe A, *et al*. Linkage to care, mobility and retention of HIV-positive postpartum women in antiretroviral therapy services in South Africa. *J Int AIDS Soc* 2018; **21**:e25114	MCH-ART and PHDC
Ch 9	**Appendix supporting objective 3:** This validation of the three-item self-reported adherence scale for use in Xhosa speaking populations in South Africa provided the foundation for analyses included in this thesis using this measure (Chapters 3 and 4).	Phillips TK, Brittain K, Mellins CA, *et al*. A self-reported adherence measure to screen for elevated HIV viral load in pregnant and postpartum women on antiretroviral therapy. *AIDS Behav* 2017; 21:450–461.	MCH-ART

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Chapter 2: Literature review

2.1 Overview

This literature review consists of the following parts: Part A provides an overview of the engagement in HIV care literature specific to pregnant and postpartum women on antiretroviral therapy (ART), and Part B is a review of the methods used to measure adherence and retention in care in the Option B+ (universal ART for pregnant and breastfeeding women) literature. It is not intended to be an exhaustive review, but rather to present key aspects of the literature that are pertinent to understanding maternal engagement in HIV care.

PubMed was searched for literature on adherence or retention under Option B+ in sub-Saharan Africa (SSA). The search was restricted to articles published from January 2011, the earliest roll-out of Option B+ in Malawi, and the search was closed on 15 May 2018. The search terms used were: (HIV AND (pregnan* OR postpartum OR antenatal OR postnatal OR maternal) AND (antiretroviral therapy OR ART OR HAART OR "Option B+") AND (adherence OR non-adherence OR compliance OR non-compliance OR "medication taking" OR persistence OR retention OR non-retention OR LTFU OR engagement OR disengagement OR "loss to follow-up" OR default*)). Overall, the search yielded 595 articles of which 70 focused on retention and/or adherence under universal ART for pregnant and postpartum women in SSA and were reviewed in detail. Reference lists of identified studies were also screened and articles highlighting key aspects of maternal engagement in care were selected. Part A presents a framework to consider the engagement in care issues specific to pregnant and postpartum women and reviews the evidence on maternal engagement in care as well as the associated barriers and facilitators. The methodology used in articles with an outcome of adherence or retention in care is reviewed in Part B. Pertinent literature on approaches to measuring adherence or retention in adult ART cohorts is also included.

Note: Part A of this review was adapted into a narrative review article published in the journal Expert Review of Anti-infective Therapy (Shifting to the long view: engagement of pregnant and postpartum women living with HIV in lifelong antiretroviral therapy services, Expert Review of Anti-infective Therapy, 2019; 17(5):349-361). The article was conceived of and written by the Candidate, with support from Professor Landon Myer.

2.2 Part A: Engagement in ART care during and after pregnancy

2.2.1 What is unique about pregnant and postpartum women?

Although engagement in lifelong ART is a concern in all populations living with HIV [1], particular concerns have been raised about pregnant and postpartum women. A number of studies have shown that pregnant and postpartum women have worse adherence to ART and poorer retention in care than men and non-pregnant women [2–5]. For all women, regardless of HIV-status, the periods of pregnancy and postpartum are times of change: there is the life transition into pregnancy and motherhood, which comes with its unique stressors, and there are changes in the structure and location of health services. The primary focus of health services is often the immediate health needs of the mother and the health of the baby with perhaps less recognition of the multitude of physiological, psychological, social and economic changes taking place for a woman during and after pregnancy [6,7].

One of the central challenges in focusing on engagement in ART services for pregnant and postpartum women specifically is the absence of a conceptual framework that positions HIV and ART within the context of women's lives. The Partnership for Maternal, Newborn and Child Health presented a framework for connecting care across the continuum of maternal, newborn and child health over time and place, moving from pre-pregnancy through childbirth and into ongoing maternal and child health [8,9]. Placing this framework in the context of maternal HIV and ART, the maternal treatment cycle could be conceptualized as parallel periods of life transitions and changes in HIV care as outlined below and depicted in Figure 2-1. By considering some of the factors impacting women during the unique life stages of pregnancy, breastfeeding and post-breastfeeding motherhood, we can identify gaps and opportunities to optimize engagement in ART care in the long term.

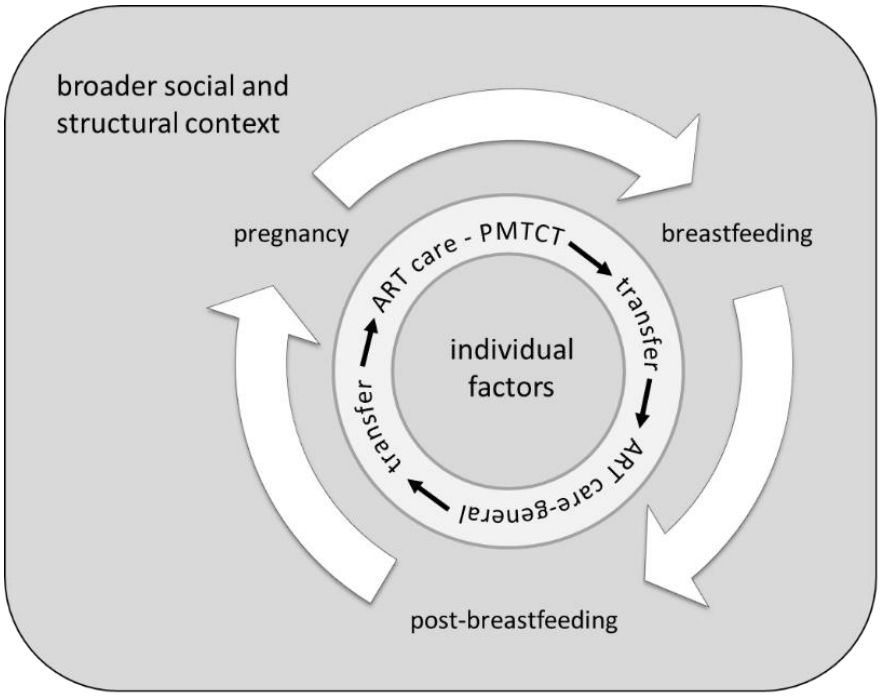

Figure 2-1. The maternal ART cycle, connecting HIV care through pregnancy, breastfeeding and post-breastfeeding motherhood. Adapted from The Partnership for Maternal, Newborn and Child Health framework [8] and Kerber *et al* [9].

Pregnancy

Coupled with the many benefits of early presentation for antenatal care (ANC) [10] is the need, among women living with HIV, for prompt ART initiation or rapid intervention on adherence or ART regimen to ensure virologic suppression by delivery. Many women face multiple concomitant barriers during this time. For women diagnosed with HIV during pregnancy, Stinson *et al* described a triple burden of transitioning into pregnancy, accepting an HIV diagnosis, and the urgent requirement to start lifelong ART as soon as possible [11].

Issues of reproductive healthcare, including contraceptive choices and safer conception practices, are beyond the scope of this review but are also critical for prevention of mother-to-child transmission (PMTCT) and sustained maternal health [12–15]. Unplanned pregnancy is an important contributor to mother-to-child transmission (MTCT) and maternal engagement in ART care [16,17]. A "double disclosure bind" has been described for women dealing with disclosing a new HIV diagnosis and an unintended pregnancy with stigma associated with both events [18]. An estimated 44% of pregnancies between 2010 and 2014 were estimated to be unintended [19] and in African cohorts living with HIV, cross-sectional

studies that took place between 2012 and 2016 found that 45-70% of women report unplanned pregnancies [20–22].

During pregnancy, women commonly experience a number of pregnancy-related symptoms. Although the side effect profiles of ARV regimens have improved over time, many pregnancy-related symptoms, including nausea, fatigue and gastrointestinal disturbances, are very similar to the potential side effects of ART [23]. ART side effects are frequently reported as barriers to ART adherence and retention [24] and for women newly initiating ART in pregnancy it may be difficult to tell whether it is the pregnancy or the new treatment that is causing their symptoms.

Despite these barriers, higher levels of ART adherence and viral suppression have been reported during pregnancy compared to postpartum [25–27] and several reasons have been suggested for this. Women report being strongly motivated to take ART to secure the health of their child [28–33]. Although women are starting lifelong treatment both for the health of their child and to optimize their own health, both adherence messaging and a mother's interest during pregnancy may be focused on the health of the baby and preventing transmission [4,34]. During pregnancy women are also expected to attend health services regularly making it easier for women who have not disclosed their HIV status to explain why they are attending a health facility and why they need to take daily medication [31,32].

It is also important to consider that pregnancy can provide a unique opportunity to engage women in healthcare. The United Nations Children's Fund reports that 86% of women access at least one ANC visit but only half attend the recommended four visits in pregnancy [35]. Although barriers to accessing ANC services still exist and are beyond the scope of this review, for women who do engage in ANC services there is an important opportunity to deliver interventions. These interventions may be HIV specific, including ART initiation or re-engaging women in HIV care, or they may address other concerns such as preparedness for ART and lifelong care, depression, substance use, partner violence or chronic conditions that can hinder HIV care and general maternal health in the short and long term [36–38].

Breastfeeding

With the success of antenatal ART, an increasing proportion of HIV transmission from mother to child is now attributable to the postpartum period through breastfeeding [39]. With the use of lifelong ART, the risk of transmission through breastfeeding is very low and if a woman is virologically suppressed the risk of breastfeeding is far outweighed by the

overwhelming health benefits outside of the context of HIV [39]. Breastfeeding prevents infectious morbidity and improves short- and long-term child development and health outcomes which is particularly pertinent in low-resource settings where malnutrition, diarrhoea and pneumonia are common causes of childhood mortality [40]. The World Health Organisation (WHO) now recommends breastfeeding for up to 24 months postpartum regardless of HIV status in low-income settings [40]. Breastfeeding is also being considered as an option for women living with HIV in high-income countries where formula feeding is the norm [41].

During this early postpartum period a mother is adjusting to her new baby, perhaps still coming to terms with her HIV status, and starting to return to her usual life. Psaros *et al* described a combined burden on women to adhere to infant feeding recommendations, to administer antiretroviral prophylaxis to their infant as prescribed, and to remain adherent to their own treatment [42]. The duration of breastfeeding will vary depending on local feeding preferences and guidelines, cultural norms and other factors such as employment [43]. If the risk of HIV transmission through breastfeeding is understood by a mother, motivation to remain engaged in HIV care to protect the health of the child may be similar to that during pregnancy, but a sense of relief if the child is healthy and tests negative after delivery may be a barrier to continued ART [32,44].

The breastfeeding period is a time when women are still required to attend the clinic regularly for routine child care. Integrated maternal and child care provides an opportunity for a single visit for mother and child with continued counselling on MTCT and maternal ART, as well as reproductive health. Integrated postpartum services provide routine child health care alongside maternal services, perform early infant diagnosis and either provide care or appropriate referral for infants infected with HIV. Some countries provide integrated maternal and child care through 12 or 24 months postpartum, the WHO recommended breastfeeding duration, but not all do. Postpartum women may be required to transfer their ART care to an adult ART clinic, or a new provider in the same clinic, removed from the focused mother and child care received during pregnancy [45,46]. The impact that transferring care may have on engagement in maternal ART services, adherence to infant prophylaxis and to infant feeding practices is not yet well understood, yet it is likely that difficulty juggling multiple visits and fear of being recognised at the clinic with inadvertent HIV status disclosure may prevent some women from continuing their ART care after delivery [30,44].

Post-breastfeeding motherhood

To date, almost all research and health programmes for pregnant and postpartum women living with HIV have been focused heavily on the periods of pregnancy and breastfeeding, with relatively little attention given to the ongoing care of mothers after the risk for MTCT has ended. This short-term view has in some regards undermined the goals of HIV programmes with many women disengaging from care after delivery or cessation of breastfeeding [42,47]. Transitioning out of the unique periods of pregnancy and breastfeeding and back into regular life presents a new set of challenges that will differ for each woman. Without the risk of MTCT there is a shift of focus from the short-term priority of PMTCT to a woman's own long-term health. Even after the direct risk of transmission is removed, frequently women report that their motivation to stay on ART is to stay healthy for their children [29,48] and some women report feelings of hope for the future that ART can provide them [33].

The period following weaning involves a return to many usual life activities and their associated stressors. Studies have reported that women feel overwhelmed in this period and are often too busy with other things to continue their treatment [28,31,32]. Without the regular need to attend the clinic as they had to during pregnancy and early postpartum, women report finding it more difficult to continue ART and avoid disclosure of their HIV status to partners, family, friends and employers [32,33]. In some settings it is also not uncommon for a child to be left in the care of family or friends but the implications of this for maternal and child care engagement have not been described [49]. As mentioned above, transfer to adult ART services after delivery is usually inevitable, even if it is just to a new nurse or venue in the same facility [45,50–52], and this may present an additional barrier to engagement in care.

Postpartum women also need to access additional services, such as continued reproductive health care and child health services. Continued parallel engagement in reproductive health services, including contraceptives when women do not desire a pregnancy, and counselling on safer conception when they do, is an equally important consideration for both PMTCT, maternal health and sexual transmission risk [13,15]. Again, integrated services may reduce the need to attend multiple appointments at different clinics and offer an opportunity to continually promote engagement in care [14]. Even in the absence of integration, these additional routine health services could be leveraged to identify and re-engage women who have disengaged from care.

Women may cycle in and out of the pregnancy, breastfeeding and post-breastfeeding periods and parallel HIV services over their reproductive years, particularly in regions with high fertility. Others may enter general adult ART care post-breastfeeding and not have a repeat pregnancy. Even in the latter case, there are likely to be further life transitions and movement between ART facilities over time due to mobility or preference [53]. In order to optimize maternal health, reduce sexual transmission and prevent perinatal and postnatal transmission of HIV in both the incident and all subsequent pregnancies, it is critical to focus on the long view of sustained engagement of pregnant and postpartum women in lifelong ART services.

2.2.2 What do we know about maternal engagement in HIV care in sub-Saharan Africa?

How often do women disengage?

The scale-up of universal ART for all people living with HIV has raised concerns about long-term engagement in routine ART care among pregnant or breastfeeding women. Most studies to date have focused on the short view, reporting outcomes up to 12 months on ART, but reports of retention in routine ART programmes three to four years following ART initiation in pregnancy are starting to emerge [54,55]. Estimates of maternal retention in routine ART care after 12 months on ART range from 58% in Rwanda [56] to over 90% in Uganda [55,57] and a recent meta-analysis reported a pooled retention estimate of 76% at 12 months [47]. This is slightly lower that the average retention estimated among adults at 12 months after ART start in Africa (81%), prior to the role out of universal ART [58]. In Malawi, 70% of women were estimated to be engaged in care three years following ART initiation in pregnancy or breastfeeding [54]. The authors highlight that this is above the roughly 50% norm for engagement in care for other chronic conditions, but it is still well below the UNAIDS targets of 90% of people living with HIV being on treatment [48]. Important to note is that the measures and definitions of retention in all these studies vary widely making direct comparisons difficult.

ART adherence under Option B+ also varied across studies. Studies that reported on adherence during pregnancy found high levels of adherence using pill counts [59] and self-report [60–62]. A South Africa study that measured the presence of ARVs in dried blood spots (DBS) found 74% of women had at least two detectable ARVs at 32 weeks gestation [63]. Similarly, using pharmacy refill measures, 73% of women in a study in Malawi had ≥90% drug coverage during pregnancy [27]. This dropped to 66% in the first three months postpartum but increased again to 75% from 4-21 months postpartum; around 70% of women

had ≥90% drug coverage through two years on ART but only 30% were adherent at each visit in that time. Another study in Zimbabwe, also using pharmacy refill, found that only 39% of women had ≥95% drug coverage through to one year on ART and they observed a steady decline in adherence over time [64]. Looking at only postpartum women in Uganda, Decker *et al* found that only half of women were adequately adherent from six weeks to six months postpartum using a combination of pharmacy refill and self-report; no woman in the study was fully adherent through 18 months postpartum [65].

When do women disengage?

There is overwhelming consistency in the finding that women starting ART during pregnancy more frequently exit care soon after ART initiation with decreasing proportions of women lost from care at later time points [4,66–70]. This loss has been observed either immediately after ART initiation with no return for further follow-up, or within the first year on ART, often shortly after delivery or following cessation of breastfeeding [31,66,69,70]. There are various possible explanations for the timing of loss from care. Some studies have suggested that rapid ART initiation following HIV diagnosis in pregnancy could result in patients being overwhelmed and underprepared and more likely not to return for any follow-up after ART initiation [52,70–74]. Two studies looking specifically at ART initiation on the same day of HIV diagnosis in pregnancy have reported mixed results [67,75] and a systematic review, not limited to pregnant women, found no adverse impact of rapid ART initiation [76]. Some women have reported that having a full appreciation of the benefits of ART and feeling the improvement in their health has helped them to stay adherent and in care while others report lack of understanding of HIV as a reason for stopping ART [48,77]. A change in motivation to continue ART after delivery or weaning is also a possible contributor to postpartum disengagement [28,31,32]. These findings link to the life transitions described above yet it is increasingly recognized that the factors associated with disengagement from ART care are often complex and interrelated. One recent study from eSwatini described discontinuing ART as "an inextricably interwoven chain of events" including numerous individual, social and structural barriers [78].

The dynamic nature of long-term engagement in care

It is well documented that engagement in HIV care is not static and yet our care cascades are often presented as such. Engagement in care has been described as a spectrum along which patients may move throughout their time on treatment [79]. Nsanzimana *et al* used the term

"churning" to describe patients engaging, disengaging and re-engaging in HIV care [80], Powers *et al* presented a framework of "HIV states and transitions" to better capture the dynamic pathways in and out of HIV services [81], while a very recent publication called for thinking "beyond binary retention in HIV care" and described the dynamic processes of moving in and out of care in adult patients living with HIV in the United States [82]. This aligns with thinking on medication taking behaviours which are also dynamic, as changing adherence patterns have also been well documented among both people living with HIV and those with other chronic conditions [83–85].

Changes in engagement in care have the potential to impact on individual health outcomes as well population health, particularly for the treatment of a chronic infectious disease such as HIV [86,87]. Little is known about the long-term patterns of engagement in HIV care among women who initiate lifelong ART during their reproductive years or what the predictors of re-engagement in care are. In adult ART cohorts, poor treatment by health providers, poverty, stigma and treatment fatigue have been identified as barriers to re-engagement in HIV care [88,89]. Acute illness or a repeat pregnancy may bring women back into care but opportunities to re-engage women before these events may exist. Women who disengage from HIV care may be accessing other non-HIV services such as reproductive health or care for other chronic conditions; many women will also be accessing routine child health services with their children. Finding interventions that can maximize periods of engagement and leverage opportunities to identify and re-engage those who do disengage will be critical approaches [90].

2.2.3 What influences engagement in lifelong ART in pregnant and postpartum women?

The WHO considers five dimensions of adherence (Figure 2-2) that can help to conceptualise the numerous factors at play [91]. The factors influencing engagement in care are highly interconnected and do not fit neatly into these boxes, but this framework will be used here to structure the discussion on the various influences on engagement in HIV care for pregnant and postpartum women.

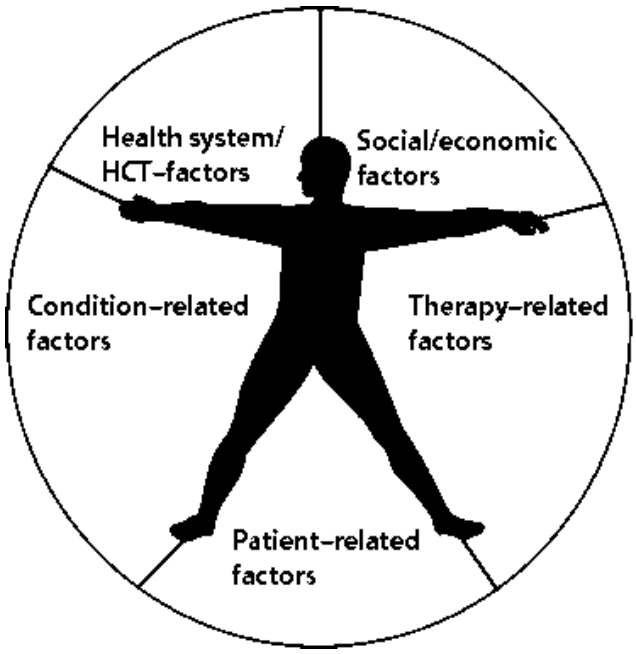

Figure 2-2 Five dimensions of adherence from the 2003 World Health Organization Adherence to long-term therapies: evidence for action [91].

Condition- and therapy-related factors

Some barriers to engagement in HIV care stem directly from the HIV diagnosis, the condition itself or the treatment. Individuals who present to care at a more advanced disease stage will be experiencing condition-related factors including physical symptoms and opportunistic infections that may make them vulnerable to disengagement from care [24,69,92]. Over the past decade there has been a major decline in the proportion of individuals initiating ART at an advanced disease stage with around 27% of people living with HIV in South Africa starting ART with CD4 cell counts <50 cells/μL [93]. This proportion is higher in men than women and is likely to be lower among women starting ART in pregnancy who are generally healthier and perhaps more likely to access care early through antenatal services [93,94]. Most women are now initiating ART before they experience any symptoms of HIV infection yet feeling well and not feeling a need for treatment has also been reported as a barrier to remaining engaged in ART services [29,32,34].

Therapy-related side effects are also frequently reported as barriers to treatment adherence and non-retention [34,47,95,96]. In qualitative studies among women starting ART in pregnancy, both fear of and the experience of side effects have been cited by women as reasons for disengaging from care [29,60,77]. Efavirenz, currently recommended for first-line regimens, has elicited particular concerns around neuropsychiatric or central nervous system (CNS) side effects including dizziness, insomnia, unusual dreams as well as depression and suicidality [97,98]. In 2018, dolutegravir was recommended as an alternative for first-line

regimens as it has superior efficacy and tolerance to most other regimens [99]. However, concerns still remain about the safety of dolutegravir in early pregnancy and efavirenz is still recommended for women planning to conceive and women in the first eight weeks of pregnancy [100,101]. To date, most of the literature on ART side effects and adherence has focused on clinician reported adverse events, mainly from clinical trials [102–104]. It is known that perceived side effects may differ from clinician-reported side effects and can influence adherence [95,105–107], yet this has not been quantitatively investigated among pregnant women.

The impact of both condition-related and therapy-related factors is likely to be dependent on the individual's perceptions about the disease and the treatment [91,108]. Pregnant women are unlikely to be able to separate out what symptoms are a result of their pregnancy, the HIV infection or the ARVs [108]. As such their response to remain in care or to disengage will be informed by their understanding of the disease, treatment and their health status. This is captured by the 2003 WHO report on Adherence to Long-Term Therapies that states "Unique characteristics of diseases and/or therapies do not outweigh the common factors affecting adherence, but rather modify their influence" [91]. Being pregnant or postpartum could modify the patient experience of condition- and therapy-related factors and may influence whether women remain in care despite these challenges.

Patient-related factors

Age is a basic consideration in thinking about health behaviours and their determinants, and young people encounter unique challenges when engaging in chronic healthcare [109]. Adolescents and young adults living with HIV have been found to have worse HIV treatment outcomes than adults [110–113]. Similarly, in the context of pregnancy and postpartum specifically, adolescents and young women have been found to be at higher risk of loss to follow-up (LTFU), poor ART adherence and MTCT [47,70,77,114,115]. Late presentation for ANC, which has been linked to younger age and could be a marker of general health seeking behaviours, is also associated with poor engagement in HIV care and increased risk of MTCT [64,68,116,117]. Overall trust in the health system and health providers can also influence engagement in HIV care and other health services [118,119]. This was highlighted in a recent study investigating maternal priorities for HIV care that found that trust in providers was the most highly prioritized factor both during and after pregnancy [120].

Psychosocial concerns, including depression and alcohol or substance use, are prevalent among women living with HIV and known to be associated with poor adherence and retention [83,121,122]. Adverse events experienced during childhood are also prevalent among people living with HIV and can have a long-lasting impact on mental health and a woman's ability to cope with a lifelong illness [123]. Current stressful life events - food and housing security, partner violence, crime, death of family or friends, loss of employment, migration and travel - can result in disruption of treatment [77,124–128].

Social and economic factors

There is also an intersection between patient-related and social factors. Lack of support from partners, family and the community is commonly cited as a barrier to engagement in HIV care in the literature [24,33,34,129]. Stigma, both perceived and experienced, can prevent women from disclosing their HIV status [34,130]. Disclosure can open the door to better support, but many women may fear violence, shunning or loss of social support if their HIV status is disclosed [66,74,131,132]. In many settings women are reliant on approval or financial support from their partner or family in order to attend health services [131,133]. Without the cover of frequent ANC or routine child health visits, women who have not disclosed or fear inadvertent disclosure may find it difficult to continue to remain engaged in ART care as their child gets older [28]. Stigma remains a significant barrier to long-term engagement in ART care despite the global focus on its eradication. Turan *et al* have presented a framework highlighting the mechanisms through which different dimensions of stigma may affect engagement in HIV care and health outcomes [134]. They stress the need for stigma interventions that are focused on specific mechanisms and that target the community level in order to influence stigmatization mechanisms [134]. For pregnant and postpartum women, strategies that build social support and safe disclosure, such as partner and family involvement in HIV testing and treatment as well as community-level engagement, will be needed to promote a supportive environment for lifelong maternal ART [130,134–137].

Women living in poverty and living with HIV may experience many of these factors more frequently and often simultaneously with negative impacts on engagement in HIV care [138–140]. There is growing recognition that these risk factors can act in a syndemic nature, increasing the disease burden through their interactions [141,142]. Combination interventions

addressing these intersecting risk factors will be needed to promote long-term engagement in ART services.

Health system factors

Along with transitioning through the life stages of pregnancy and breastfeeding, the health system often also requires pregnant and postpartum women to transfer their health care. We know from the paediatric HIV literature that transitioning from paediatric to adult ART care can be a vulnerable time [143]. Similarly, transferring from maternal and child focused antenatal or postpartum care into general adult ART services can be a point of disengagement [46,144]. The structure of the health system, in parallel to life transitions, is also likely to impact the most vulnerable times for disengagement, although this aspect is frequently not well described in the literature.

Integration of antenatal and ART care, compared to referring pregnant women to separate adult ART services, dramatically improves the uptake of ART during pregnancy and is the standard of care in many countries [144–148]. In some countries, integrated care for mothers and their children is continued postpartum and this approach has been shown to improve postpartum retention [149–151]. However, even with integrated antenatal, ART and child health services, many ANC clinics are not designed to keep adults in care indefinitely and there is often a need to transfer to general adult ART clinics at some time postpartum. The timing of this transfer is not consistent in different countries and regions: in South Africa women are often transferred to general adult ART care at 6-10 weeks postpartum [46]; in Malawi it ranges from 6 weeks to 12 months [45,77]; in Zimbabwe and Mozambique, women and children remain in integrated services for up to two years postpartum [51]. In other settings, all services (including antenatal and postnatal care, routine child health services and lifelong ART) are provided in one facility and there is no need to transfer location, but women may move to a different part of the same clinic [66,152]. Some studies of postpartum engagement in ART care mention the need to transfer postpartum but do not specify the timing while others do not describe where care is routinely received after delivery. The impact of transferring ART care postpartum is not yet well understood but, similar to referral to initiate ART during pregnancy or to the adolescent transition from paediatric to adult care, the transfer step may be a vulnerable point for disengagement [46,143].

Other structural barriers such as transport costs, payment for services, long waiting times and poor patient-provider relationships also remain barriers to continued engagement in care in

many settings [24,34]. With the routinising of ART services globally and rapidly increasing access to treatment for all, people living with HIV will have more choices about where and how they access ART. The choice of health facility will be influenced by a combination of individual, societal and health systems factors. In some settings people must travel long distances to access ART services while in many urban settings there are multiple clinics offering ART services in one area. A study in South Africa showed how postpartum women who were thought to be lost from care had actually moved between multiple different clinics, even over a relatively short follow-up time [53]. A study in adults on ART highlighted that HIV disclosure, individual agency over their ART care and flexibility of ART providers in times of transition were key to ensuring continuity of lifelong ART [153]. Overall, interventions, health systems and healthcare providers must be able to adapt to support continued engagement in care through required and preferred health care transfers and through the life transitions of pregnancy, breastfeeding and beyond.

2.3 Part B: Measurement of ART adherence and retention in Option B+ cohorts in sub-Saharan Africa

In both research and routine care, ART adherence and retention in care are measured for a variety of reasons including: i) to monitor and intervene in patient care, ii) for programme monitoring, and iii) to measure outcomes and compare interventions in research. To date there is no standard method for measuring any component of these definitions, either in research or in routine programmes. As noted in Part A above, there is substantial variation in the methods used to measure adherence and retention. Here, the commonly used methods and considerations for measuring ART adherence and retention in care, with particular focus on Option B+ cohorts in SSA, are described.

2.3.1 Adherence measures

There is no single measure which encompasses all the components of medication adherence and there is no gold standard measure of adherence [154,155]. Each measure has drawbacks, and all are only estimates rather than direct measures of an individual's medication taking practices [140,156–159]. Measures of treatment implementation, the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen and the adherence construct focused on in this thesis can be broadly divided into objective and subjective measures. The evidence for and use of each measure is discussed below.

Objective measures

Directly observed therapy (DOT) involves supervised medication taking. Predominantly used as an adherence support method, DOT provides a direct measure of the exact dose and timing of dose taken. DOT is frequently used for tuberculosis treatment and has also been used for HIV [160]. One study under Option B+ that investigated a community-based DOT intervention, combined with short-text messaging service (SMS) support, to improve adherence found that women were willing to nominate a friend or family member to be their DOT supporter, but concerns were raised about time constraints and logistics [161] . Although this is an objective measure of adherence, it is impractical given the volumes of patients on ART and the resources required to implement DOT. Randomised trials in both high- and low- resource settings have found little evidence that DOT improves adherence or biological markers and DOT is not currently recommended to measure ART adherence [85,140].

Drug concentrations in biological samples provide the closest measure of actual drug exposure in the body. They are frequently used to measure adherence in clinical trials, but they are expensive and require complex laboratory assays [162]. Drug concentrations usually only provide information on adherence in the short term, limited to the half-life of the ARV being measured. Measures of tenofovir-diphosphate (TFV-DP) in DBS have been successfully used to measure adherence to pre-exposure prophylaxis (PrEP) [162] but only two published studies have assessed TFV-DP in DBS as an adherence measure among people living with HIV [163,164]. Antiretroviral pharmacokinetics are known to vary by gender and ethnicity. In particular, data from the US has shown differences in therapeutic thresholds of TFV-DP in DBS among males and females [165] and among Black compared to White or Hispanic individuals [163]. However, there are no published studies on TFV-DP in DBS to measure adherence in African women living with HIV. TFV-DP in DBS provides information on ARV intake over the past 17 days [165], a major advantage in comparison to plasma efavirenz (EFV) and tenofovir (TFV) assays that are informative about drug intake in the past 4-5 days [166,167], but these methods have not been compared head-to-head. DBS specimens have the advantage of being easy to collect but TFV-DP assays in DBS are complex and expensive to run [162]. The use of hair to measure drug concentrations has also been successfully used and shows a strong correlation with HIV viral load. Hair may be easier to collect than other samples and is relatively easy to store and transport [168]. Although adherence thresholds are currently only established for TFV, hair can be used for

many antiretrovirals [162]. Hair samples still have the limitation of requiring laboratory testing and there may be individual and cultural concerns about hair sampling [169]. Using drug concentrations with short half-lives to measure adherence has raised concern about "white coat adherence" which occurs when people take their ARVs as prescribed only just before a clinic appointment [162,170]. Due to the cost and complexity, drug concentrations are not routinely recommended for adherence monitoring but are frequently used in research [85,140,164,171,172].

Pill counts by clinic staff are widely used to assess adherence in routine care settings, however there is conflicting evidence on the association between pill counts and treatment outcomes [140,173,174]. Three Option B+ studies used pill counts to measure adherence, but none correlated pill count to another adherence measure or clinical outcome [59,175,176]. Pill counts are time intensive and may be subject to manipulation by patients due to social desirability [140,159,177,178].

Pharmacy refill data are recommended for adherence monitoring in settings where patients must collect treatment from a pharmacy. Pharmacy refill does not measure medication taking behaviour but is a useful proxy under the assumption that if a patient has not been dispensed ARVs they cannot be taking their treatment as prescribed or at all. This is not true if patients are able to access treatment through another facility or avenue, making this most useful in interlinked systems where any dispensing of drug within the system would be known. Pharmacy refill data has been found to be a valid adherence measure [140,172,178–180] and is a frequently used measure in the Option B+ literature, usually using medication possession ratios or the proportion of time with drug in hand [27,64,181].

Electronic drug monitoring (EDM) devices have consistently been associated with treatment outcomes and provide a good measure of adherence. If the device is not used correctly it may underestimate adherence and it is also possible for the patient to manipulate the results by opening and closing the device but not necessarily taking the treatment. EDM devices are expensive and may be a burden to patients so use has mostly been limited to research settings [140,172,173,178]. No published articles using EDM in the context of Option B+ were located but EDM devices, such as the Wisepill, are being used in ongoing research in South Africa and Uganda both to measure adherence and to prompt real-time intervention among pregnant and postpartum women [182].

Subjective measures

Self-reported adherence measures are widely used in research and routine care and reported adherence has been recommended for use in routine ART services [140,159,183,184]. Self-reported adherence has generally been found to have reasonable predictive value in relation to EDM devices and viral load [157,158]. There are numerous different tools to measure self-reported adherence and although a lot of work has been done towards optimizing the response options and recall period, there is still substantial variability in self-reported adherence measures in use [184]. Self-report of ART doses taken or missed over a recall period ranging from 3-30 days is commonly used. Multi-item scales and visual analogue tools are also widely used to assess adherence. In the Option B+ literature, studies using self-reported adherence mostly reported on missed ART doses with recall periods ranging from three to 30 days [62,65,185]. Others used combinations of self-reported adherence questions [60,185]. No single measure stood out as most frequently used. Despite frequent use, self-reported adherence measures can be subject to recall and social desirability bias and may result in overestimation of medication taking [178,183]. Results are often positively skewed towards good adherence (known as the "ceiling effect") which increases the risk of patient misclassification and makes it difficult to measure meaningful differences in adherence [178,186].

2.3.2 Retention measures

Various measures and definitions of retention in ART care have been described in the literature and it has been demonstrated in adult ART cohorts that changes in definitions and measurement strategies can substantially alter estimates of retention in HIV care [187–191]. Two studies have evaluated the ability of different retention measures to predict viral load and have found that all measures correlate with having a suppressed viral load, with similar moderate predictive ability across measures [190,192]. Some authors have stressed that there is no gold standard measure or standard definition of retention and LTFU and that the measurement of retention should be tailored to the local context [189,190]. Yet, given the wide variation in measures and difficulties comparing outcomes within and between cohorts, other authors have advocated for a universal approach to measuring retention, particularly for monitoring and comparing ART programme outcomes [187,188].

There is little literature specifically interrogating retention measures and definitions in pregnant and postpartum women. Rollins *et al* noted that women initiating ART under Option

B+ guidelines should be monitored in the same way as other adult ART patients following final ascertainment of vertical transmission as well as adherence and retention in care at the time of breastfeeding cessation [193]. However, during pregnancy and breastfeeding slightly different measurement intervals and strategies may be required. In the same paper they offered some guidance in approaching retention measurement and analysis, highlighting the need for measures of retention over time to assess continuity of care. In another paper discussing the INSPIRE network studies [194], all of which evaluated interventions to improve maternal retention in care, Rollins and colleagues discuss the difficulty in making comparisons across the six studies due to the heterogeneity in retention definitions adopted. They suggested a move towards standard definitions and approaches to measuring retention.

Through the review of literature on retention under Option B+ in SSA, a wide variety of definitions and approaches to measuring retention were observed and the key methodological aspects of each study are displayed in Table 2-1. Retention measures differed in three main domains: i) the source of data, ii) the reference or follow-up period, iii) the retention definition.

Data source

The vast majority of studies estimating retention in the adult ART literature use facility-based data sources, either paper records and registers or electronic patient records [195]. In this review of the Option B+ literature, two thirds of studies used facility-specific data sources to estimate retention. An additional seven studies used facility-specific data but with active attempts to trace patients who were considered lost from care. Patients who were transferred out were usually excluded or censored at the time of transfer although one study assumed that transferred patients were retained in care [51]. This approach can result in either over or underestimating retention as patients who are formally transferred do not always link to care and patients who are considered lost are often in care elsewhere [46,53,196]. As discussed in part A above, mobility and transfer of ART care are key considerations in measures of engagement in all ART cohorts, but quite uniquely among pregnant and postpartum women. Transfer from ANC to ART services is often required, either at the time of presentation for ANC if services are separated, or at some time postpartum if ART services are integrated into ANC [45,46]. This makes it important to consider retention beyond just the facility of ART initiation.

The WHO recommends interlinked patient monitoring systems to "link a single patient across his or her records (patient cards or registers) through identifying data elements such as name, date of birth, sex or unique ID to ensure de-duplication of record-keeping and continuity of care across service delivery points (both programme and facility) and time" [197]. Currently these data systems are rarely available. Only two studies appeared to use interlinked data sources to estimate retention across clinics in a region, both were conducted in South Africa [53,150].

Follow-up period

The follow-up period considered in the articles reviewed ranged from six months to over three years on ART. Some studies measured time from ART start while others measured time from delivery. Counting studies through one year postpartum as more than one year on ART, ten studies reported on outcomes beyond one year on ART; only three studies reported outcomes beyond two years on ART. This is in part due to the recency of the Option B+ roll out with longer term outcomes available from countries such as Malawi, where Option B+ was first implemented [27,54].

Retention definitions

The retention definitions used in the Option B+ literature, and in the adult ART literature, can be broadly grouped into cross sectional, longitudinal and gap in care definitions (Table 2-1) [191]. *Cross-sectional* definitions estimate retention at a single instant or window of time. These definitions do not consider care access prior to the timepoint of interest. *Longitudinal* definitions use estimates in multiple windows of time to measure consistent retention over a longer time period. This is often an accumulation of cross-sectional estimates of retention or visit constancy. Lastly, gaps in care are often used to estimate retention. These could be gaps in time with no visits or a gap in time after the last scheduled visit (time with no ARVs in hand). Gap in care definitions are usually analysed as time to first gap in care using time-to-event methods.

Even within definitions there is variation in the length of windows of time, thresholds for loss and how definitions are used in analyses. For gap in care definitions, Grimsrud *et al* found different ways of implementing the definition in analyses, for example which date was assigned to being lost, could result in substantial variation of estimates [187]. Some studies

use combinations of definitions to try to capture both retention at a particular instant as well as sustained retention or adherence to scheduled visits over time [117,198,199].

2.3.3 Viral load

Viral load, the most common biomarker of HIV treatment success, is frequently used as a proxy marker of treatment adherence and retention. Although viral load can be influenced by other factors including resistance, comorbidities and adverse effects, adherence to ART is a major driver of viral load [200]. Viral load monitoring for detection of treatment failure and as an adherence monitoring tool is strongly advocated for by the WHO and is being scaled up globally [201–204]. Despite the advocacy for increased viral load monitoring, particularly during pregnancy and breastfeeding, viral load measures remain infrequent in many low- and middle-income countries [202,203]. Some studies do report on viral load in conjunction with adherence and retention measures [61,150], but viral load measures are often not available.

2.4 Summary

These multiple potential domains of variation make it very difficult to compare results, either in a single programme over time, across ART programmes or when comparing interventions or research studies [187,190,194]. Which measures of engagement are optimal likely depend on the purpose and the availability of different data sources. Review of paper or electronic medical records is frequently used but these are often not linked across facilities. Laboratory databases may be more likely to be centralised but without unique patient identifiers may not be interlinked across facilities. Laboratory results can also provide some indication of a patient's health status, but they only provide high-level evidence that a patient has touched the health care system. Although studies have compared retention outcomes using different definitions, few have focused on the impact of different data sources and most studies do not used interlinked data to account for outcomes beyond the facility of interest.

2.4.1 Summary and gaps in the literature

Poor engagement in care after ART initiation in pregnancy is a major concern and considerable methodological challenges exist in the measurement of both ART adherence and retention in care. Numerous gaps exist in our understanding of the predictors and appropriate measures of maternal engagement in care, all of which hamper efforts to monitor ART

programmes as well as to design, evaluate and implement acceptable and effective interventions to improve patient care. Four specific gaps will be addressed in this thesis.

What is the impact of patient-reported ART side effects on ART adherence during pregnancy?

Although ART side effects are frequently reported in both the quantitative and qualitative literature as a reason for poor ART adherence, no quantitative analyses exist on system-specific or overall patterns of patient-perceived ART side effects following ART initiation in pregnancy and their associations with ART adherence.

How do plasma and dried blood spot antiretroviral concentrations compare to self-reported adherence to predict viral suppression among African women?

Although there is a push towards more frequent viral load monitoring to ensure prompt intervention when needed, some countries only implement viral load testing every 1-2 years. No gold standard measure of adherence exists but interim adherence measures, in conjunction with viral load monitoring, are needed. Measuring ARV concentrations is the most direct way of measuring ARV exposure and thus adherence to ART, but no data exist on the use of DBS TFV-DP assays to measure adherence to ART in African women. Nor do data exist comparing the relatively less expensive plasma EFV and TFV assays to TFV-DP in DBS and even more simple and less expensive self-reported adherence.

What is the potential of longitudinal self-reported adherence measures?

Self-report adherence is known to be subject to bias and other more objective measures are recommended, but self-reported adherence is still widely used in research and routine care settings. Most studies have assessed cross-sectional self-reported adherence. Longitudinal methods have the potential to overcome some of the weaknesses of self-reported adherence data, yet they remain relatively unexplored.

How can interlinked data sources be used to improve the measurement of retention in care?

Measuring retention in HIV care is a key component of monitoring HIV programmes, informing clinical care and measuring outcomes in research. As with adherence, no gold standard measure of retention in care exists. Despite the recommendation by the WHO and known issues of transfer and mobility, few studies use interlinked data sources to assess retention beyond the facility of ART initiation. Postpartum transfer of ART care is often

required for women who start ART in pregnancy yet there are no data characterising linkage to care and mobility for HIV care from ART initiation in pregnancy through the transfer into general ART care.

Summary

A lot of work is being done to develop and evaluate interventions to support maternal engagement in HIV care, yet the evidence is largely weak, and methods are highly variable making comparisons difficult. By contributing to these gaps in the literature, the work of this thesis will improve our understanding of the issues influencing engagement in HIV care during and after pregnancy and will inform robust measures to evaluate engagement in care. The ultimate aim of this work is to inform the development, evaluation and implementation of interventions to improve long-term engagement in HIV care among pregnant and postpartum women.

Table 2-1. Summary of retention time reference periods, data sources and definitions used in the Option B+ literature

Author, year [ref] Trial name if applicable	Country	Study design	Reference period	Source of retention data	Facility-specific/ interlinked	Retention outcome definition
Cross-sectional						
Clouse, 2017 [53]	South Africa	Observational cohort	Up to 3.5 years on ART	National laboratory database	Interlinked	For evidence of engagement: At least one CD4 or viral load or a laboratory record from a named ART facility after being considered lost from clinic
Foster, 2017 [205] EPAZ	Zimbabwe	Cluster randomised trial	One year postpartum	Record review of facility registers and patient files Included PMTCT, ART as well as family planning and illness visits	Facility-specific	Visited the clinic at 12 months postpartum ±1 month
Koss, 2017 [55] PROMOTE-PIs	Uganda	Cross-sectional follow-up of a random sample of women in a randomised trial	Median 4 years since ART start	Review of patient records combined with patient interviews	Traced regardless of clinic	Attended the clinic in the 90 days preceding the interview
Miller, 2017 [206]	Uganda	Retrospective cohort	One year after pregnancy detection	Record review of facility registers and patient records	Facility-specific	At least one clinic visit ≥12 months after pregnancy detection
Myer, 2016 [207] MCH-ART	South Africa	Randomised control trial	One year postpartum	Combination of routine electronic HIV databases	Interlinked	Evidence of any HIV-care contact between 9 and 18 months postpartum
Longitudinal						
Woelk, 2016 [56]	Rwanda	Retrospective cohort	One year postpartum	Record review of facility registers and patient files	Facility-specific	At least one visit (any indication of ART dispensed) in each period 6wk, 3, 6, 9, 12 months postpartum

Author, year [ref] Trial name if applicable	Country	Study design	Reference period	Source of retention data	Facility-specific/ interlinked	Retention outcome definition
Kiweewa, 2013 [176]	Uganda	Randomised control trial	One year on ART	Record review of facility registers and patient files?	Facility-specific	Attendance of all scheduled visits in first 12 months on ART
Sam-agudu, 2017 [208] MoMent	Nigeria	Prospective cohort	Six months postpartum	Record review of facility registers and patient files	Facility-specific	≥3 (of expected 6) 30-day periods between delivery and 180 days postpartum with at least one clinical visit
Gaps after scheduled visit or with no drug in hand						
Atanga, 2017 [66]	Cameroon	Prospective cohort	Up to one year from ANC registration	Study collected facility level data on refill appointments	Facility-specific with active tracing of lost patients	No gap of ≥90 days after scheduled appointment missed
Schwartz, 2015 [209]	South Africa	Pilot intervention	One year postpartum	Record review of facility registers and patient files	Facility-specific	No gap of >6 weeks after scheduled appointment missed [210]
Van Lettow, 2014 [45]	Malawi	Observational cohort	Six and 12 months on ART	Routine facility cohort reports	Facility-specific	No gap with no ART for ≥2 months
Haas, 2016 [54]	Malawi	Observational cohort	One, two and three years on ART	Routine electronic medical records	Facility-specific	No gap of >60 days after scheduled appointment missed
Phiri, 2017 [211] PURE	Malawi	Randomised control trial	Two years on ART	Record review of facility registers and patient files	Facility-specific	No gap of ≥60 days after scheduled appointment missed
Auld, 2016 [212]	Mozambique	Observational cohort	Six months on ART	Routine electronic programme data	Facility-specific with active tracing of lost patients	≥60 days late for their next scheduled medication pick-up appointment
Chan, 2016 [67]	Malawi	Retrospective cohort	Six months on ART	Record review of facility registers and patient records	Facility-specific	Attending clinic within two months after the date that last dispensed antiretroviral drugs would run out

Author, year [ref] Trial name if applicable	Country	Study design	Reference period	Source of retention data	Facility-specific/ interlinked	Retention outcome definition
Kamuyango, 2014 [181]	Malawi	Retrospective cohort	One year on ART	Record review of facility registers and patient records	Facility-specific	No gap of ≥60 days after scheduled appointment missed
Koole, 2014 [213]	Malawi	Retrospective cohort	Six months on ART	Record review of facility registers and patient records plus patient interviews	Attempt to link to other clinics	No gap of ≥60 days after scheduled appointment missed
Landes, 2016 [69]	Malawi	Retrospective cohort	One year on ART	Review of standard ART monitoring tools captured through an ongoing observational cohort	Facility-specific	No gap of ≥60 days after scheduled appointment missed
Tenthani, 2014 [71]	Malawi	Retrospective cohort	Six months on ART	Review of facility records aggregated for routine monitoring and evaluation Routine electronic medical records	Facility-specific	No gap of ≥60 days after scheduled appointment missed
Tweya, 2014 [77]	Malawi	Retrospective cohort	Up to two years on ART	Routine electronic medical records	Facility-specific with active tracing of lost patients	No gap of ≥3 weeks after scheduled appointment missed
Gamell, 2017 [214] One-Stop clinic model	Tanzania	Prospective cohort	Median 17 months on ART	Routine electronic medical records	Facility-specific	No gap of ≥60 days after scheduled appointment missed

Author, year [ref] Trial name if applicable	Country	Study design	Reference period	Source of retention data	Facility-specific/ interlinked	Retention outcome definition
Hoffman, 2017 [215]	Malawi	Case-control	One year on ART	Review of facility records	Facility-specific with active tracing of lost patients	No gap of ≥60 days after scheduled appointment missed
Gaps with no visits						
Llenas-Garcia, 2016 [216]	Mozambique	Observational cohort	Up to one year on ART	Routine HIV programme data	Facility-specific	No gap in visits ≥180 days
Ford, 2017 [3] Lablite project	Zimbabwe	Retrospective cohort	One year on ART	Record review of facility registers and patient records	Facility-specific	No gap >90 days with no visit
Etoori, 2018 [68]	eSwatini	Prospective cohort	Up to two years on ART	Review of facility registers and patient records	Facility-specific with active tracing of lost patients	No gap in visits ≥4.5 months
Musomba, 2017 [57]	Uganda	Retrospective cohort	Up to two years on ART	Routine electronic medical records	Facility-specific	No gap in visits ≥3 months
Mitiku, 2016 [70]	Ethiopia	Retrospective cohort	From three months to two years on ART	Record review of facility registers and patient files	Facility-specific	No gap of ≥90 days with no visit
Combined						
Oyeledun, 2017 [198]	Nigeria	Cluster randomised trial	Six months postpartum	Record review of facility registers and patient files	Facility-specific	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

Author, year [ref] Trial name if applicable	Country	Study design	Reference period	Source of retention data	Facility-specific/ interlinked	Retention outcome definition
Mwapasa, 2017 [117] PRIME	Malawi	Cluster randomised trial	One year postpartum	Record review of facility registers and patient files	Facility-specific	Attends 12-month postpartum visit and all ARV drug refills no more than 14 days late Attends 12-month postpartum
Joseph, 2017 [73] E4E	Zimbabwe	Cluster randomised trial	One year on ART	Record review of facility registers and patient files	Facility-specific	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.
Not defined						
Dzangare, 2016 [51]	Zimbabwe	Retrospective cohort	Six months on ART	Record review of facility registers and patient records	Facility-specific (transfers out assumed retained)	Retention/LTF not defined in the paper (or in national guidelines)
Price, 2014 [217]	Malawi	Retrospective cohort	Median four months postpartum	Review of facility records and self-report	Searched across facilities	"on ART" at the time of the interview. Not further defined.

Abbreviations: ART – antiretroviral therapy

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Chapter 3: Self-reported side effects and adherence to antiretroviral therapy in HIV-infected pregnant women under option B+: a prospective study

Phillips TK, Cois A, Remien RH, Mellins CA, McIntyre JA, Petro G, Abrams EJ, Myer L. Self-reported side effects and adherence to antiretroviral therapy in HIV-infected pregnant women under option B+: A prospective study. PLoS One 2016; **11**:e0163079. doi:10.1371/journal.pone.0163079

Relevance of this paper to the thesis:

Side effects from antiretroviral therapy (ART) are frequently reported as barrier to adherence soon after starting ART and there are particular concerns about side effects with efavirenz-based regimens. However, little is known about patient perceived side effects to first-line efavirenz-based regimens and the association with treatment adherence during pregnancy. This paper presents a detailed analysis of the patterns of system-specific and overall self-reported side effects among women who started ART during pregnancy and explores the association between reported side effects and reported missed ART doses.

Contribution of the student and co-authors:

TP conceptualised the analysis with the guidance of LM, EJA, AC and JAM. AC conducted the latent class analysis. TP conducted all other analyes with support from AC and LM. TP wrote the initial manuscript draft and all co-authors reviewed it, providing conceptual and intellectual comment. All authors were involved in the final draft of the manuscipt.

3.1 Abstract

Antiretroviral therapy (ART) regimens containing efavirenz (EFV) are recommended as part of universal ART for pregnant and breastfeeding women. EFV may have appreciable side effects, and ART adherence in pregnancy is a major concern, but little is known about ART side effects and associations with adherence in pregnancy.

We investigated the distribution of patient-reported side effects (based on Division of AIDS categories) and the association of side effects with missed ART doses in a cohort of 517 women starting EFV+3TC/FTC+TDF during pregnancy. In analysis, side effects were considered in terms of their overall frequency, by systems category, and by latent classes.

Overall 97% of women reported experiencing at least one side effect after ART initiation, with 48% experiencing more than five side effects. Gastrointestinal, central nervous system, systemic and skin side effects were reported by 81%, 85%, 79% and 31% of women, respectively, with considerable overlap across groups. At least one missed dose was reported by 32% of women. In multivariable models, ART non-adherence was associated with systemic side effects compared to other systems categories, and measures of the overall burden of side effects experienced were most strongly associated with missed ART doses.

These data demonstrate very high levels of side effects in pregnant women initiating EFV-based ART and a strong association between side effect burden and ART adherence. ART regimens with reduced side effect profiles may enhance adherence, and as countries expand universal ART for all adult patients, counselling must include preparation for ART side effects.

3.2 Introduction

With the recent adoption of Option B+ for prevention to mother-to-child HIV transmission (PMTCT) there have been rapid increases globally in the use of antiretroviral therapy (ART) by HIV-infected pregnant and breastfeeding women [1]. Following initiation of ART, successful treatment implementation and continued adherence to lifelong therapy is a widespread concern, emerging as a particular issue for women initiating ART during the perinatal period [2,3]. In turn, understanding adherence under Option B+ and the determinants of non-adherence, is a major priority both for individual and programme level PMTCT outcomes.

Medication side effects are commonly thought to influence treatment adherence [4-6]. Efavirenz (EFV)-containing ART regimens are currently recommended by the World Health Organization (WHO) as first-line treatment. They are widely used in resource-limited settings and are generally considered to be better tolerated than previous Non-nucleoside reverse transcriptase inhibitor (NNRTI) regimens [7-10]. However, specific side effects associated with EFV are well known, particularly neuropsychiatric side effects such as dizziness and vivid dreams [11,12]. In general, side effects from current first-line therapy are thought to be relatively short lived and improve as patients continue on ART. However, these early side effects may disrupt initial implementation of the regimen, and there is some evidence that early treatment adherence is important to set the course of long-term adherence and treatment success [13]. Early adherence, particularly during pregnancy, is required to ensure rapid viral suppression, reduced transmission risk and improved maternal health outcomes.

Experience of side effects has been associated with non-adherence and discontinuation of ART in general adult populations using various regimens [12,15-20]. However, few studies focus specifically on EFV-containing regimens and treatment adherence. One study in a small general adult cohort in South Africa, the majority on EFV-based regimens, found that experience of symptoms was associated with lower self-reported adherence scores [18]. Fear and experiences of side effects have been mooted as threats to ART adherence and continued ART use both in general adult patients as well as in pregnant and postpartum women [3,16,21-26].

The role of side effects in ART adherence warrants special attention in pregnant and postpartum women. To date evaluations of side effects in pregnant populations have been mostly limited to clinician-reported adverse events, primarily in trial settings [27-30]. Yet

patients' experiences of side effects may differ from clinician-reported adverse events [7,19,31]. While data on side effects under Option B+ are few, country-level data show high rates of early loss to follow-up under Option B+, particularly among women with higher baseline CD4 cell counts, which may be attributable in part to ART side effects [32,33]. The experience and tolerance of ART side effects in relatively healthy individuals, commonly the case in pregnant women initiating ART under Option B+, may differ from that of individuals with more advanced HIV disease [31,34-36]. Also, in the context of pregnancy, ART initiation is frequently fast-tracked to maximize the chances of reaching viral suppression by delivery. There may be limited time to counsel patients on common side effects and their management, and lack of preparation for side effects has been suggested as a risk factor for poor adherence in the context of Option B+ [24].

Despite the importance of these issues, little is known about experience of side effects and the relationship with adherence after ART initiation in pregnancy, particularly with first-line EFV-containing regimens in the context of Option B+. We examined the occurrence and patterns of side effects during pregnancy among women initiating EFV-based ART and investigated the relationship between reported side effects and reported missed ART doses.

3.3 Methods

Population

This analysis draws on data from a large multi-phase trial evaluating strategies for delivering HIV care and treatment services during pregnancy and the postpartum period (The MCH-ART study, https://clinicaltrials.gov/ct2/show/NCT01933477) [37]. The study took place in a large public sector antenatal clinic in Gugulethu, Cape Town, South Africa. This setting is characterized by high levels of poverty and HIV with a local antenatal HIV seroprevalence of 33% [38]. Local public-sector health services have provided free ART services since 2004 and from 2012 ART was delivered together with antenatal care (ANC). From July 2013, all HIV-infected pregnant women were eligible to start lifelong ART regardless of CD4 cell count or clinical stage (Option B+).

Consecutive HIV-infected, ART-eligible pregnant women 18 years and older making their first ANC visit during the current pregnancy were enrolled into the MCH-ART study between April 2013 and June 2014. Overall, 526 women were enrolled under Option B+ which started on 1 July 2013. Women started a first-line regimen of EFV (600mg),

emtricitabine (FTC)/ lamivudine (3TC) (300mg) and tenofovir (TDF) (300mg) (EFV+FTC/3TC+TDF), provided as a fixed dose combination. ART initiation and follow-up was conducted by nurse-midwives within the ANC clinic. ART was usually initiated on the day of the first antenatal visit or within two weeks, with routine follow-up visits occurring monthly for the first four months on treatment and one to two monthly thereafter. ART counselling was provided by trained counsellors before initiation and at each follow-up visit.

The cohort was followed through study assessments conducted separately from routine care. Participants completed an interviewer-administered questionnaire at the time of enrolment, up to twice more during pregnancy, and once immediately after delivery. Each study assessment included structured questionnaires on ART use, and at the first postpartum study visit self-reported side effects experienced since ART initiation were assessed. This study was conducted in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments and was approved and conducted in accordance with the standards of the Human Research Ethics Committee of the University of Cape Town and the Columbia University Medical Centre Institutional Review Board. All participants provided written informed consent.

Measures

A structured questionnaire based on Division of AIDS (DAIDS) Tables for grading adverse events [39] was used to collect information on side effects experienced, including gastrointestinal tract (GIT) (nausea/vomiting, appetite change, diarrhoea, other GIT), central nervous system (CNS) (headache, dizziness, unusual dreaming, other CNS), skin (rash, other skin), systemic (fatigue, fever/sweats, non-specific pain, other systemic) side effects. The collected information was codified using a set of 14 binary variables for the reporting of each side effect from ART initiation through to the first postpartum study visit.

Missed doses in the preceding 30 days were reported at each visit. The average number of missed ART doses was calculated by summing the reported missed doses across all study visits between ART start and the first postpartum visit. The sum of missed doses was divided by the sum of the reference period (the maximum number of visits on ART completed was three, resulting in a maximum reference period of 90 days) and multiplied by 30 to obtain the average number of missed doses in a 30-day period. This was analysed as both a continuous and binary variable (any vs. no missed doses). A secondary outcome of a reported period of no treatment for 30 days or more at the time of the last assessment was also evaluated.

Analysis

This secondary analysis of data from the MCH-ART study excluded women enrolled under the Option A policy as well as women who did not have data available on side effects in pregnancy (n=9). Women were included regardless of mode of delivery. Data were analysed using Stata Version 12.0 (Stata Corporation, College Station, Texas, USA) and MPlus Version 7.3 (Muthén & Muthén, Los Angeles, CA). Variables were described using medians (with interquartile ranges, IQR) and proportions with (95% confidence intervals, CI). We used rank-sum and chi-square (replaced in the case of sparse data by Fisher's exact) tests to examine differences in central tendencies and proportions, respectively. Three different constructs were used to examine the patterns of side effects reported by participants and the associations with missed ART doses:

a) *Systems categories*: A classification based on DAIDS categories [39] was used to divide reported side effects into groups of GIT, CNS, skin and systemic side effects. Assignment to these categories was not mutually exclusive.
b) *Cumulative number of side effects*: Subjects were grouped according to the number of different types of side effects experienced since ART initiation (from no side effects reported to up to 14 different side effects).
c) *Latent side effects class*: Latent Class Analysis (LCA) was used to classify individuals into mutually exclusive groups (latent classes) characterized by different pattern of side effects, allowing for patterns that may not be solely systems-based (as assumed in *[a]* above). LCA, a statistical method for inferring unmeasured class membership using a set of measured variables as imperfect class indicators, has been used to identify underlying patterns of signs and symptoms in other contexts [40-43]. Here the binary variables representing presence/absence of different side effects since ART initiation were used as indicators, and the optimal number of latent classes was determined by comparing the fit of models with different number of classes according to statistical information criteria together with the results of the bootstrap likelihood ratio test [44]. Individuals were assigned to each class according to the maximum posterior probability. The LCA process is described in Supplementary Table 9-3-1 and Supplementary Table 9-3-2.

Multiple logistic regression was used to investigate adjusted associations between reported side effects (according to the three different classifications described above) and reported

missed ART doses. Covariates with associations at p≤0.10 in the bivariate models were included in the multivariable models. When analysing predictors of latent class membership, the probability of misclassification of individuals was taken into account in the estimation, using the three-step approach described by Asparouhov and Muthén [45].

3.4 Results

Overall, 517 women who initiated ART in pregnancy under Option B+ were included in this analysis (Table 3-1). The median age was 28 years, 74% of women had not completed secondary school and 63% were unemployed. At ART initiation, the median CD4 cell count was 361 cells/µL (IQR 244-539 cells/µL) and the median gestational age was 21 weeks (IQR 16-27 weeks). HIV diagnosis occurred during the current pregnancy for 55% of women and 28% had used some form of antiretroviral (ARV) previously (predominantly short-course PMTCT regimens). All women received folic acid, calcium carbonate and iron supplements during ANC, and 6 women were treated for tuberculosis during pregnancy. At the time of the side effects assessment postpartum (median, 7 days after delivery) the median duration of ART use was 19 weeks (IQR 12-23 weeks).

Prevalence of side effects

Overall, 97% of women (n=502) reported experiencing at least one side effect on ART during pregnancy. Only median duration on ART differed between women who did and did not report side effects (19 and 9 weeks, respectively; p=0.012) (Table 3-1). The median number of different side effects experienced was five (IQR 3-7; max 12) and 91% of women reported two or more different side effects. GIT, CNS, systemic and skin side effects were reported by 81%, 85%, 79% and 31% of women, respectively. There was considerable overlap in side effect reporting (Figure 3-1) with 22% of women (n=112) experiencing at least one side effect from all four categories, and 40% (n=208) reporting GIT, CNS and systemic side effects. The distributions of each SE construct by socio-demographic sub- groups are displayed in Supplementary Table 9-3-3.

Table 3-1 Demographic characteristics of 517 women initiating ART during pregnancy included in the study, by reported side effects. All cells are N (%) unless otherwise specified.

	All women	**Any side effects**	**>5 side effects**	**1-5 side effects**	**No side effects**	**p-value** (any vs none)
Number of women	517	502 (97)	250 (48)	252 (49)	15 (3)	-
Median age (IQR)	28 (24-32)	28 (25-32)	28 (24-32)	28 (25-32)	33 (23-34)	0.364
Socioeconomic status						
Lowest	197 (38)	190 (38)	103 (41)	87 (35)	7 (47)	0.758
Medium	152 (29)	149 (30)	68 (27)	81 (32)	3 (20)	
Highest	168 (33)	163 (32)	79 (32)	84 (33)	5 (33)	
Education level						
Finished secondary school	134 (26)	130 (26)	59 (24)	71 (28)	4 (27)	1.000
Did not finish secondary school	383 (74)	372 (74)	191 (76)	181 (72)	11 (73)	
Employment status						
Employed	193 (37)	187 (37)	91 (36)	96 (38)	6 (40)	0.794
Not employed	324 (63)	315 (63)	159 (64)	156 (62)	9 (60)	
Relationship status						
Married/cohabiting	198 (38)	194 (39)	88 (35)	106 (42)	4 (27)	0.427
Not married/cohabiting	319 (62)	308 (61)	164 (65)	144 (58)	11 (73)	
Median gravidity (IQR)	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)	3 (2-3)	0.183
Primigravida	93 (18)	91 (18)	50 (20)	41 (16)	2 (13)	1.000
Multigravida	424 (82)	411 (82)	200 (80)	211 (84)	13 (87)	
Timing of HIV diagnosis						
In the current pregnancy	286 (55)	278 (55)	135 (54)	143 (57)	8 (53)	1.000
Prior to this pregnancy	231 (45)	224 (45)	115 (46)	109 (43)	7 (47)	
ARV history						
ARV naïve	374 (72)	365 (73)	186 (74)	179 (71)	9 (60)	0.386
Previous PMTCT	126 (24)	120 (24)	53 (21)	67 (27)	6 (40)	
Previous ART	17 (3)	17 (3)	11 (4)	6 (2)	0 (0)	
Median CD4 cell count at ART initiation (IQR) [§]	361 (244-539)	359 (242-536)	337 (225-507)	390 (271-553)	502 (294-635)	0.104
CD4<200	85 (17)	85 (18)	52 (21)	33 (14)	0 (0)	0.200
CD4 200 - 349	150 (30)	145 (30)	76 (31)	69 (29)	5 (33)	
CD4≥350	265 (53)	255 (53)	115 (47)	140 (58)	10 (67)	
Median gestation(weeks) at ART initiation (IQR)	21 (16-27)	21 (16-27)	20 (15-25)	22 (17-29)	23 (13-21)	0.360
Median weeks on ART (IQR)	19 (12-23)	19 (12-23)	19 (15-24)	17 (10-23)	9 (4-21)	0.012

[§]17 missing CD4 count; ARV - antiretroviral

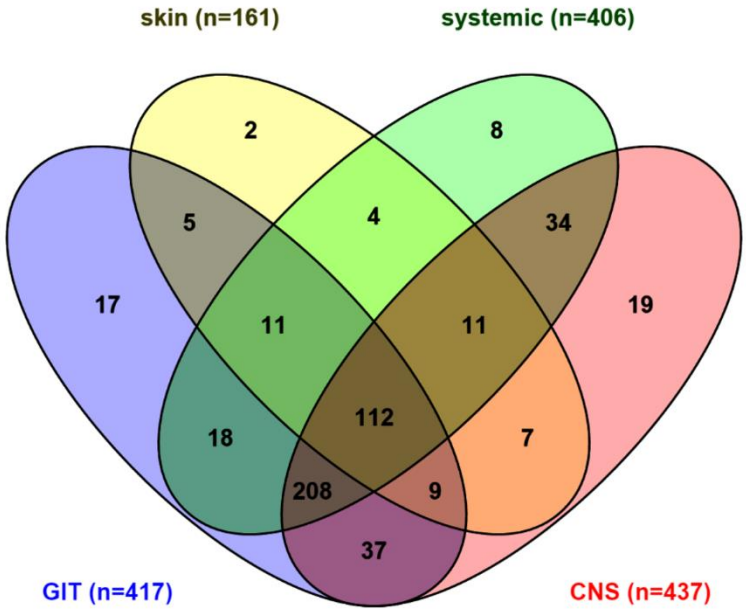

Figure 3-1 Venn diagram of number of women reporting each side effect by system category. (CNS – central nervous system; GIT – gastrointestinal tract).

Latent side effect classes

Four distinct patterns of side effects identified using LCA are shown in Figure 3-2 and described in Table 3-2. One group of women, comprising 26% of the cohort, reported experiencing most of the assessed side effects (here referred to as Class 1). A second group (Class 2, 17% of the cohort) frequently reported experiencing systemic side effects but reported experiencing CNS, GIT and skin side effects less commonly. Class 3 (30% of women) reported experiencing all types of side effects less commonly (including systemic side effects), while a fourth class (27% of women) reported experiencing few side effects.

In a multinomial logistic regression adjusted for age and number of weeks on ART, education, CD4 count and gestation at ART initiation were significantly associated with class membership (Supplementary Table 9-3-4). Women with lower CD4 counts at ART initiation were more likely to belong to Class 1 than other classes. Increased education predicted membership to Class 3, experiencing moderate levels of all side effects, compared to Class 1, experiencing most or all types of side effects. In addition, starting ART earlier in pregnancy was associated with higher probability of belonging to latent classes characterized by higher levels of side effects (Classes 1 and 2).

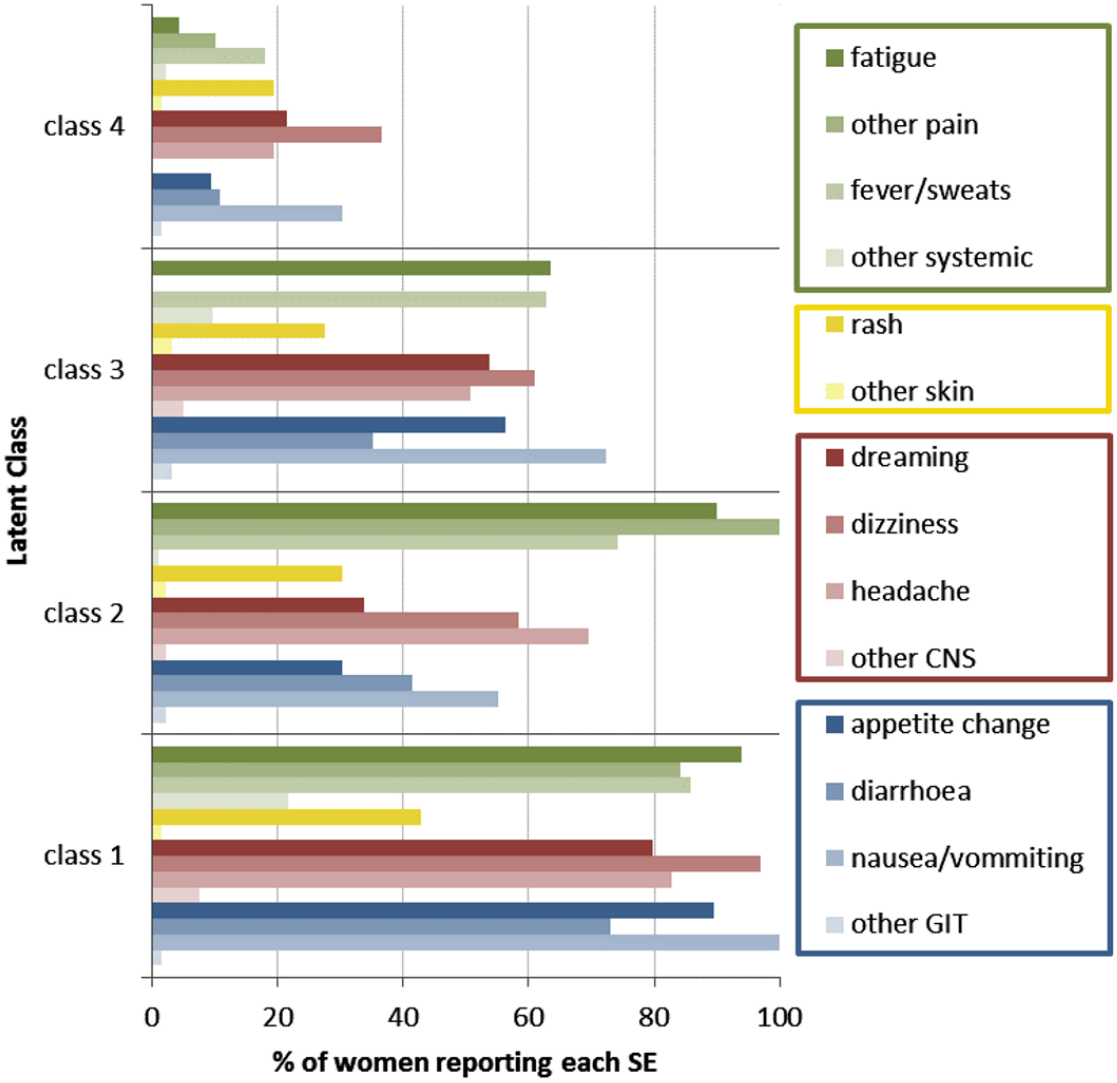

Figure 3-2 Proportion of women reporting each side effect by latent side effect classes; systems-based side effects categories are shown in green (systemic side effects), yellow (skin side effects), red (central nervous system [CNS] side effects) and blue (gastrointestinal tract [GIT] side effects).

Side effects and ART adherence

At least one missed ART dose during pregnancy was reported by 32% of women (n=166). Among these women, 87% (n=145) reported between one and three missed doses, and the remaining 13% (n=21) reported four or more missed doses, per 30 days on ART, respectively (Table 3-2). Women who experienced any side effects were significantly more likely to report any missed ART dose compared to those who reported no side effects (100% versus 96%, p=0.003). Women with any missed dose reported a marginally higher number of

individual side effects compared to women reporting no missed doses (median 5 versus 6 reported side effects, $p<0.001$).

Figure 3-3 shows the proportions of women reporting individual side effects grouped by reporting any versus no missed doses. For all systems side effects groups, the proportion of women reporting side effects was higher among those who missed any dose compared to those who reported no missed doses. These differences were statistically significant for all GIT, systemic and skin side effects, except for the "other" categories which were reported at very low frequencies. Of the CNS side effects, only dizziness was associated with reporting any missed ART doses. In the analysis of side effects as latent classes, missed doses were reported more frequently in classes where side effects reporting was more common: 36%, 21%, 31% and 13% of women who reported any missed ART during pregnancy were in Classes 1, 2, 3 and 4, respectively ($p<0.001$, Table 3-2).

The associations between each side effect construct (including frequency of side effects, systems classification and latent classes) and missed ART doses were considered separately in multivariable logistic regression models adjusted for participant age, marital status, parity and time on ART. In all models, side effects were consistently associated with missed ART doses (Supplementary Table 9-3-4). CD4 cell count, although associated with reporting side effects, was not associated with missed doses and did not appear to confound the association between reported side effects and missed ART doses. Higher numbers of different reported side effects were associated with increasing odds of a missed dose (OR 1.20, CI 1.12-1.29, for each additional type of side effects reported). Using systems side effects categories, having any GIT or any systemic side effects was associated with increased odds of reporting missed doses (OR 1.78 [CI 1.00-3.17] and OR 2.65 [CI 1.46-4.81], respectively). However, CNS and skin side effects were not associated with self-reported adherence. Compared to women in Class 1, women in Class 4 (with the lowest side effect profile) had significantly lower odds of reporting any missed dose (OR 0.25, CI 0.14-0.45). These associations did not change appreciably when mode of delivery was included in the final model.

Six women (1%) reported missing 30 or more ART doses and the time off ART at assessment ranged from 43 to 156 days. The reasons reported for missing more than 30 days of ART are shown in Supplementary Table 9-3-5. Five out of six women were in Classes 1 or 2 where the experience of side effects was highest, and four of the six women cited side effects among the reasons for stopping to take their treatment.

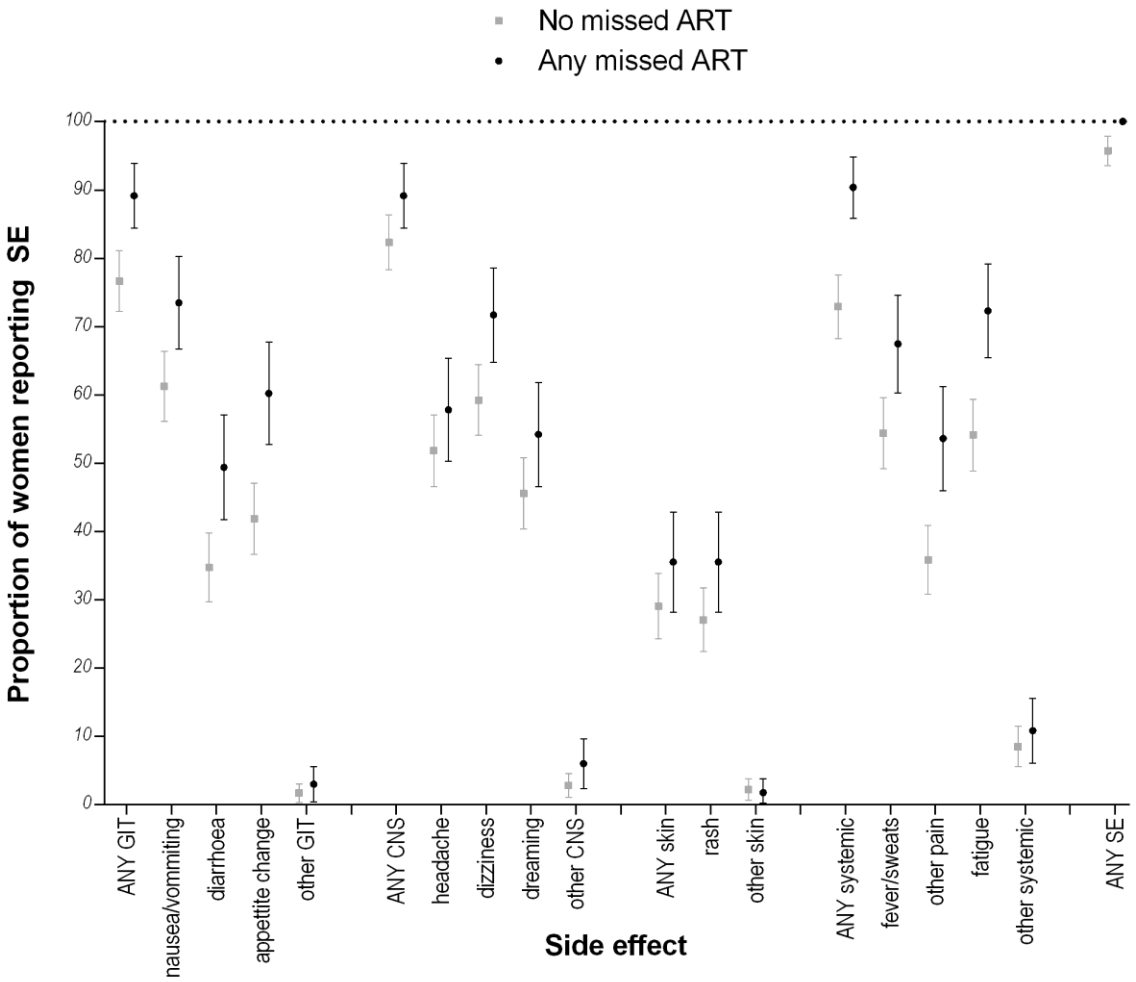

Figure 3-3 Proportions of women reporting each side effect with 95% confidence intervals, by any or no missed doses reported.

Table 3-2 Reported side effects among 517 women following ART initiation during pregnancy in Cape Town, South Africa. All cells are N (%) unless otherwise specified.

	All women	Missed doses in 30 days (on average)				Discontinued ART		p-value
		None	1-3	4 or more	Any missed	on ART	Stopped ART	(any vs. no missed dose)
Number of women	**517**	**351**	**145**	**21**	**166**	**511**	**6**	
Any side effect reported	**502 (97)**	**336 (96)**	**145 (100)**	**21 (100)**	**166 (100)**	**496 (97)**	**6 (100)**	**0.003**
Median number of reported side effects (IQR)	**5 (3-7)**	**5 (2-7)**	**6 (4-8)**	**8 (5-9)**	**6 (4-8)**	**5 (3-7)**	**8 (7-9)**	**<0.001**
No reported side effects	15 (3)	15 (4)	0 (0)	0 (0)	0 (0)	15 (3)	0	<0.001
Only 1 reported side effects	32 (6)	28 (8)	3 (2)	1 (5)	4 (2)	31 (6)	1 (17)	
More than 1 reported side effects	**470 (91)**	308 (88)	142 (98)	20 (95)	162 (98)	**465 (91)**	**5 (83)**	
Any GIT side effects	**417 (81)**	**269 (77)**	**131 (90)**	**17 (81)**	**148 (89)**	**412 (81)**	**5 (83)**	**0.001**
Nausea or vomiting	337 (65)	215 (61)	107 (74)	15 (71)	122 (73)	332 (65)	5 (83)	0.006
Diarrhoea	204 (39)	122 (35)	73 (50)	9 (43)	82 (49)	202 (40)	2 (33)	0.001
Appetite change	247 (48)	147 (42)	89 (61)	11 (52)	100 (60)	244 (48)	3 (50)	<0.001
Other GIT	11 (2)	6 (2)	4 (3)	1 (5)	5 (3)	11 (2)	0	0.272
Any CNS side effects	**437 (85)**	**289 (82)**	**128 (88)**	**20 (95)**	**148 (89)**	**431 (84)**	**6 (100)**	**0.045**
Dizziness	327 (63)	208 (59)	101 (70)	18 (86)	119 (72)	321 (63)	6 (100)	0.006
Unusual dreaming	250 (48)	160 (46)	75 (52)	15 (71)	90 (54)	246 (48)	4 (67)	0.067
Headache	278 (54)	182 (52)	82 (57)	14 (67)	96 (58)	273 (53)	5 (83)	0.203
All other CNS side effects	20 (4)	10 (3)	9 (6)	1 (5)	10 (6)	19 (4)	1 (17)	0.080
Any skin side effects	**161 (31)**	**102 (29)**	**48 (33)**	**11 (52)**	**59 (36)**	**158 (31)**	**3 (50)**	**0.137**
Rash	154 (30)	95 (27)	48 (33)	11 (52)	59 (36)	151 (30)	3 (50)	0.049
All other skin side effects	11 (2)	8 (2)	2 (1)	1 (5)	3 (2)	11 (2)	0	0.728
Any systemic side effects	**406 (79)**	**256 (73)**	**131 (90)**	**19 (91)**	**150 (90)**	**401 (78)**	**5 (83)**	**<0.001**
Fever or sweats	303 (59)	191 (54)	96 (66)	16 (76)	112 (67)	299 (59)	4 (67)	0.005
Other nonspecific pain	215 (42)	126 (36)	75 (52)	14 (67)	89 (54)	210 (41)	5 (83)	<0.001
Fatigue	310 (60)	190 (54)	104 (72)	16 (76)	120 (72)	305 (60)	5 (83)	<0.001
All other systemic side effects	48 (9)	30 (9)	14 (10)	4 (19)	18 (11)	48 (9)	0	0.401
Class 1 (high side effects)	133 (26)	74 (21)	31 (28)	28 (51)	59 (36)	130 (25)	3 (50)	<0.001
Class 2 (moderate side effects, high systemic)	89 (17)	55 (16)	26 (23)	8 (15)	34 (20)	87 (17)	2 (33)	
Class 3 (moderate side effects)	156 (30)	105 (30)	37 (33)	14 (25)	51 (31)	156 (31)	0 (0)	
Class 4 (low side effects)	139 (27)	117 (33)	17 (15)	5 (9)	22 (13)	138 (27)	1 (17)	

(GIT – gastrointestinal tract; CNS – central nervous system)

3.5 Discussion

Our study is the first to document very high levels of side effects experienced by women initiating efavirenz-based ART during pregnancy in sub-Saharan Africa and an association with self-reported missed ART doses. Missed doses were reported frequently. However, we found no persistent associations between specific side effects and missed doses; instead, the strongest associations with missed doses involved measures of the overall burden of side effects experienced by women. This finding adds an important new perspective to ART adherence in pregnancy under Option B+.

Overall, 97% of women reported at least one side effect and the vast majority of women reported multiple side effects. While there are few data on ART side effects reporting in pregnancy and methods of measurement vary, these levels appear substantially higher than in other studies of first-line, EFV-containing regimens in non-pregnant adults [7,18,46]. As in other analyses of medication side effects in pregnant women, it is not clear if the side effects reported here were related to the ARVs, routine supplements given in pregnancy (iron, folate and calcium), symptoms of pregnancy, or symptoms of HIV disease. Unfortunately, we did not collect data on additional supplements however, use of over the counter supplements in this setting is not common. Concurrent tuberculosis medication may also impact reported side effects however less than 1% of this cohort had a tuberculosis episode during pregnancy. GIT and systemic side effects may be related to physiologic changes of pregnancy, many of which typically occur early in pregnancy. The median gestation at ART start in this cohort was 21 weeks, meaning most women were well into the second trimester when they initiated ART. The finding that women with lower CD4 cell counts appeared to experience more diverse side effects in both the absolute count and latent class analysis suggests that some of this reporting may be linked to HIV disease rather than ART use directly. There are concerns that healthier individuals starting ART may have more adherence problems. However, our findings show that individuals with lower CD4 cell counts are likely to experience more side effects and therefore may also be at risk for poor adherence. These findings may have important implications for universal ART initiation in pregnancy as well as for adult “test and treat” approaches. Appropriate counselling and support for side effect management is required both to prepare healthy individuals for the effects of ART, as well as to prepare the individuals with more advanced disease for the effects of their HIV and ART.

In general, EFV side effects are thought to be relatively short-lived and improve over time. However, early side effects on ART have not been well documented in the literature. Our findings suggest that women who booked for ANC earlier, and therefore had a longer duration on ART, report more side effects than women with less time on ART. Further research on the timing and severity of ART side effects during pregnancy and in non-pregnant women and healthy adults will be valuable to better understand these side effect profiles and provide appropriate support in the early time on treatment.

Regardless of the underlying cause, all three constructs of reported side effects (number of different side effects reported, systems-based side effects categories, and latent side effects classes) were associated with reported missed ART doses. There was more imprecision around some associations between any side effects or specific side effects and missed doses observed in the logistic regression estimates in Supplementary Table 9-3-4, likely due to the very high proportions of women reporting side effects in this cohort. In all three of the side effects constructs used, effect sizes were relatively small and no specific side effects appeared to be driving missed doses in any of the analyses. Although this may in part be due to inability to detect small differences with relatively homogenous reports of side effects overall, this finding suggests that non-adherence may not be related to any one specific type or cluster of side effects (for example nausea or dizziness), but rather to the overall side effects burden.

This finding has several possible interpretations. The experience of multiple side effects may present a cumulative burden of physical symptoms, any one of which may not contribute to non-adherence in isolation. There is evidence that the experience of side effects is related to plasma ARV levels, including EFV, which in turn may be moderated by genetic polymorphisms influencing drug metabolism [47]. The polymorphism resulting in increased plasma EFV levels has been found to be relatively common in patients of African descent, and high EFV concentrations have been associated with experiencing EFV related side effects [47,48]. In addition to this physiologic explanation, it is important to note that the reporting of larger numbers of side effects may be more common in individuals with specific personality traits, such as neuroticism [49]. In this context it is plausible that mental health concerns may contribute to side effects reporting as well as to non-adherence. These and other possible interpretations warrant additional attention.

This is the first report of side effects experienced by pregnant women starting ART under Option B+ in South Africa. The data provide novel insights but are subject to important

limitations. All women in this analysis were on a regimen of EFV+FTC/3TC+TDF, the regimen initiated by the majority of HIV-infected pregnant women under current global policy. However, we were unable to examine how this regimen compares to others with respect to reported side effects and adherence. As individual ARV agents have different side effects profiles, the possibility that different ART regimens may have less side effects and contribute to better adherence in pregnancy is a pertinent consideration. The prevalence of reported CNS side effects, a specific concern in EFV-containing regimens, was very high and limited our ability to examine associations with non-adherence in this analysis [11]. More generally, all side effects and adherence data were based on patient self-report, and social desirability may have led to misreports of ART adherence and/or reported side effects, though we note the relatively high levels of missed dose reporting in this sample.

Despite these limitations, these findings have important implications for health services providing ART to pregnant women. Experiences of side effects and fear of side effects have been reported as barriers to adherence to ART in pregnancy [3,21,23,24]. The high level of reported side effects and the association with missed doses found in this cohort supports previous calls for specific counselling on ART side effects [6,50]. Antenatal ART initiation is often rapid to ensure maximum time on ART prior to delivery. Time for pre-ART counselling may be limited, however counselling to address possible ART side effects, as well as pregnancy symptoms which may be perceived as ART related, should be a focus both at treatment initiation as well as subsequent follow up visits. More generally, the high burden of side effects experienced in this cohort using EFV+FTC/3TC+TDF points to the ongoing need both to understand the causes of side effects in context of pregnancy, and to identify new agents that minimize experience of side effects.

3.6 Conclusion

In summary, these novel data are important in demonstrating a high level of side effects experienced in this population of pregnant women initiating a first-line EFV-containing regimen under Option B+. The overall burden of side effects experience, rather than specific side effects, appears persistently associated with self-reported missed ART doses. Although the reported side effects may not be directly related to ARV regimen, these data highlight that patient reported side effects in the early time on ART may impact treatment adherence and there is a clear need to include counselling on expected ART side effects at ART initiation and follow-up visits. In this analysis we did not find an association between CD4 cell count

and missed ART doses which is reassuring for universal ART policies. As many countries move towards a "test and treat" approach, providing ART for all HIV-infected adults, the lessons we have learned from rapid universal ART initiation in pregnancy should be carefully considered. Managing experience and perception of ART side effects may play an important role in optimizing adherence behaviour during this early treatment period, which could in turn improve long term treatment outcomes.

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Chapter 4: A comparison of plasma efavirenz and tenofovir, dried blood spot tenofovir-diphosphate, and self-reported adherence to predict virologic suppression among South African women

Phillips TK, Sinxadi P, Abrams EJ, Zerbe A, Orrell C, Hu N-C, Brittain K, Gomba Y, Norman J, Wiesner L, Myer L. A comparison of plasma efavirenz and tenofovir, dried blood spot tenofovir-diphosphate, and self-reported adherence to predict virologic suppression among South African women. *J Acquir Immune Defic Syndr* 2019;81(3):311-318. doi: 10.1097/QAI.0000000000002032.

Relevance of this paper to the thesis:

There is an urgent need for robust measures of ART adherence to flag patients at risk for treatment failure and prompt appropriate intervention, particularly in the high risk periods of pregnancy and breastfeeding. Tenofovir-Diphosphate in dried blood spots is one possible measure but it has not been evaluated among African women living with HIV. There are also no data comparing this measure to other less expensive and more simple adherence measures that may be more appropriate for settings with limited resources. This paper compares the performance of self-reported adherence, plasma efavirenz, plasma tenofovir and tenofovir-diphosphate in dried blood spots to predict virologic suppression. A limitation of this chapter is that these data were only available at a single postpartum time point. These results therefore cannot speak directly to the utility of these measures during pregnancy, a time when pharmacokinetics may shift considerably.

Contribution of the student and co-authors:

TP conceptualised the analysis with the guidance of LM, GM, PS and EA. YG, NCH, AZ, KB and myself implemented the study. JN and LW ran all the antiretroviral assays. TP conducted all analyses and wrote the initial manuscript draft. All co-authors reviewed it, providing conceptual and intellectual comment. All authors were involved in the final manuscript.

4.1 Abstract

Background: Tenofovir-diphosphate (TFV-DP) in dried blood spots (DBS) is an objective long-term adherence measure but data are limited on its ability to predict virologic suppression (VS) among people on antiretroviral (ARV) treatment. There are also no data comparing DBS TFV-DP with plasma ARV concentrations as predictors of VS.

Methods: Women who were on a first-line regimen of tenofovir, emtricitabine, and efavirenz (EFV) were enrolled in a cross-sectional study. Plasma EFV and tenofovir (TFV), DBS TFV-DP assays, and 30-day self-reported adherence were evaluated as predictors of VS (<50 copies/mL) with area under the curve (AUC) of receiver operating characteristics (ROC) and logistic regression.

Results: We enrolled 137 women; mean age 33 years; median 4 years on ART; 88 (64%) had VS. In ROC analyses: DBS TFV-DP (0.926 [95%CI 0.876-0.976]) had a higher AUC than plasma TFV (0.864 [0.797-0.932]; p=0.006), while plasma EFV (0.903 [0.839-0.967]) was not significantly different from DBS TFV-DP (p=0.138) or plasma TFV (p=0.140); all ARV assays performed better than self-report. The association of TFV-DP in DBS with VS strengthened with increasing concentrations (reference <350 fmol/punch: 350-699 fmol/punch aOR 37 [8-178]; 700-1249 fmol/punch aOR 47 [13-175]; ≥1250 fmol/punch aOR 175 [20-1539]). "White coat adherence" (defined as DBS TFV-DP <350 fmol/punch with detectable plasma TFV) was only detected in 4 women.

Conclusions: Plasma EFV, TFV and DBS TFV-DP were all strong predictors of VS. Plasma EFV and TFV concentrations, which are much simpler and cheaper than DBS TFV-DP, may warrant consideration as adherence measures in low-resource settings.

4.2 Introduction

Good adherence to antiretroviral therapy (ART) is required to achieve and sustain virologic suppression [1]. A multitude of adherence measures exist but there is no gold standard and measuring ART adherence in both routine care and research settings is a major challenge [2]. Self-reported adherence frequently overestimates actual treatment adherence [3] while HIV viral load, which is often used as a marker of ART adherence, does not capture patterns of adherence or discriminate between poor adherence and resistance as causes of virologic failure [2].

Measuring antiretroviral (ARV) drug concentrations has limitations but is an objective way to assess ART adherence [2]. Plasma concentrations of the ARVs tenofovir (TFV) and efavirenz (EFV), which are used in first-line ART regimens, are only informative about dosing in the past 4-5 days [4,5]. Plasma TFV has a half-life of approximately 14 hours [6] while EFV concentrations and half-life vary with *CYP2B6* metaboliser genotype making interpretation of plasma EFV concentrations as an adherence measure difficult [4,7,8]. Recently, an assay has been developed to measure tenofovir-diphosphate (TFV-DP) concentrations in dried blood spots (DBS) [9]. TFV-DP in DBS has a half-life of 17 days and can be detected for up to 12 weeks after stopping, a major benefit for assessing long-term adherence [10–12]. However, TFV-DP in DBS is measured using a complex and expensive laboratory assay that is not feasible outside of the context of clinical trials, and certainly not possible for routine care in resource limited settings.

To date, most data on DBS TFV-DP as an adherence measure have been obtained from HIV-negative individuals in pre-exposure prophylaxis (PrEP) studies. There are very few studies reporting TFV-DP DBS concentrations or therapeutic thresholds for ART adherence among people living with HIV (PLWH). Two small studies compared DBS TFV-DP with other adherence measures: pharmacy refill adherence among 35 women in the United States [10] and electronic drug monitoring in South Africa (n=29) [13]. Only one study has reported on the ability of TFV-DP in DBS to predict virologic suppression [11]. In addition, little is known about how TFV-DP in DBS compares with plasma ARV drug concentrations or other more affordable adherence measures that could be used in low-resource settings. Existing data on TFV-DP concentrations in DBS indicate that concentrations are up to 19% lower in males than females [12] and that there appear to be differences across populations with lower concentrations among Black compared with White or Hispanic individuals [11]. African women bear the largest burden of the HIV epidemic but to date there is just one unpublished

report on TFV-DP in DBS in an African cohort on ART [13] and there are no data on the ability of TFV-DP in DBS to predict virologic suppression among African women. Here we describe plasma EFV, plasma TFV and DBS TFV-DP concentrations, and self-reported adherence, in a cohort of women living with HIV who are on ART in Cape Town, South Africa, and assess their relationship with HIV viral load.

4.3 Methods

Design, participants and setting

Women who were enrolled during pregnancy in a large implementation science study (the MCH-ART study) in Gugulethu, Cape Town were approached between 36 and 60 months postpartum and invited to participate in this cross-sectional sub-study. The MCH-ART study methods and results have been described previously [14,15]. All women had initiated the first-line regimen of tenofovir disoproxil fumarate (TDF) 300mg, emtricitabine 200mg or lamivudine 300mg (XTC), and EFV 600mg, provided as a once daily fixed-dose combination. For this sub study, the first 150 women who agreed to participate were recruited and had blood drawn for ARV assays. Women who were pregnant or had switched to second line ART were excluded.

Procedures

During the study visit, all women completed structured face-to-face interviews in the predominant local language, isiXhosa. Self-reported medication adherence in the past 30 days was measured using a simple, three-item scale that has been described previously [16,17]. Women reported on their current ART use and which regimens they were taking. ART regimen history was reviewed using the provincial electronic pharmacy records. Women were asked to report their current pregnancy status and their height and weight were measured by study staff who were trained in anthropometric techniques. Weight was measured using a standing scale and height using a stadiometer with equipment calibrated regularly.

Antiretroviral drug assays and viral loads

Venous EDTA blood samples were drawn from each participant and kept cold until processing. The majority of specimens were collected in the mid-dose interval (12-18 hours post-dose). For the TFV-DP DBS assay, 50 µL of whole blood was pipetted onto Whatman

903 Proteinsaver® cards, allowed to dry overnight at room temperature and then stored desiccated in airtight freezer-safe bags at -80°C. Samples were then centrifuged at 3500 rpm and plasma decanted into cryovials, before being frozen at -80°C.

EFV, TFV and TFV-DP were analysed with validated liquid chromatography tandem mass spectrometry assays by the Clinical PK Laboratory, Division of Clinical Pharmacology, University of Cape Town. EFV plasma concentrations were determined as described by Bienczak et al [18]. TFV concentrations were determined using a protein precipitation extraction method, with tenofovir-d6 as internal standard, followed by high performance liquid chromatography with MS/MS detection using an AB SCIEX API 3000 instrument. Gradient chromatography was performed on a Waters Atlantis T3 (C18, 3µm, 100 X 2.1 mm) analytical column. The mobile phase consisted of 0.1% formic acid in water and 0.1% formic acid in acetonitrile and was delivered at a flow-rate of 300 µl per minute. The analyte and internal standard were monitored at mass transitions of the protonated precursor ions m/z 288.1 and m/z 294.1 to the product ions m/z 176.2 and m/z 182.2 for tenofovir and tenofovir-d6, respectively. The calibration curve fitted a quadratic (weighted by 1/concentration) regression over the ranges 10 to 1600 ng/ml. TFV-DP in DBS was indirectly measured using a slightly modified LC-MS/MS assay as described by Castillo-Mancilla *et al* [9].

An additional venous sample was sent to the National Health Laboratory Services (NHLS) for viral load testing (Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 assay; Roche Diagnostics, Branchburg, New Jersey, US).

Routine medical records

In addition to data collected from participants during the study visit, routine electronic health records were requested from the Western Cape Provincial Health Data Centre. This included data from the NHLS (for serum creatine and CD4 cell count measures) and pharmacy databases (to validate ARV regimens), all of which are linked by a unique patient identifier and include all public health facilities in the Western Cape Province. Serum creatinine concentrations and CD4 cell counts measured within six months before or after the study visit were abstracted from the laboratory records. Less than 25% of women had CD4 cell counts available so these data were not included.

Analysis

All analyses were performed in Stata (Stata Corporation, College Station, TX). Means with standard deviations, medians with interquartile ranges, or proportions were used to describe the characteristics of the cohort and the adherence measures. Drug concentrations were also log-transformed and back-transformed to report geometric means with 95% confidence intervals (CI). Concentrations below the lower limit of quantification for each assay (LLOQ; 0.0195 µg/mL for plasma EFV, 10 ng/mL for plasma TFV and 16.6 fmol/punch for DBS TFV-DP) were assigned a value half that of the LLOQ (0.00975 µg/mL for plasma EFV, 5 ng/mL for plasma TFV and 8.3 fmol/punch for DBS TFV-DP) [10].

Logistic regression models were used to evaluate the relationship between continuous adherence measures and virologic suppression. Virologic suppression was defined as viral load <50 copies/mL with sensitivity analyses using thresholds of <400 and <1000 copies/mL. Area under the curves (AUC) of receiver operating characteristics (ROC) were used to assess discrimination of the adherence measures to predict virologic suppression. ROC AUCs for each drug concentration and self-reported adherence were compared in STATA using chi-squared tests for equality of AUCs proposed by De Long *et al* [19]. We estimated sensitivity, specificity and positive and negative predictive values (PPV and NPV) using established drug concentration thresholds: ≥0.7µg/mL for plasma EFV [20,21], ≥35.5ng/mL for plasma TFV [22], and five adherence thresholds (<350, 350-699, 700-1249, 1250-1849 and ≥1850 fmol/punch) for TFV-DP from DBS that were determined in a healthy volunteer study [11,12]. We also examined which thresholds of each of the continuous drug concentrations would maximise both sensitivity and specificity to detect women with and without virologic suppression. Sensitivity analyses were conducted excluding women who reported taking no ART in the past 30 days, a group in whom drug concentrations may not be measured in a routine care setting.

Ethics

All participants completed written informed consent, including consent for specimen storage and drug assays, prior to completing any study procedures. This study was reviewed and approved by the University of Cape Town Human Research Ethics Committee and the Columbia University Institutional Review Board.

4.4 Results

Thirteen of the 150 consecutive women screened were excluded (seven were pregnant [23] and six had switched to second line ART regimens). The characteristics of 137 women enrolled into the study are displayed in Table 4-1. At the study visit the median time on ART was 3.9 years (IQR 3.7-4.0) and 88 women (64%) were virologically suppressed (<50 copies/mL).

Table 4-1 Characteristics of 137 non-pregnant women on first-line ART at the time of the study visit.

	All women
Mean age (SD)	33 (5)
Median (IQR) years on ART	3.9 (3.7-4.0)
Median (IQR) weight (kg)	81 (65-93)
Median (IQR) body mass index (BMI, kg/m^2)	32 (26-36)
BMI <18.5 kg/m^2	3 (2)
BMI ≥18.5 and <25 kg/m^2	26 (19)
BMI ≥25 and <30 kg/m^2	33 (24)
BMI ≥30 kg/m^2	75 (56)
Serum creatinine available, n (%)	74 (54)
Median (IQR) serum creatinine[1] (n=74)	55 (51-60)
Median (IQR) log_{10} viral load	1.30 (1.30-3.56)
Viral load <50 copies/mL, n (%)	88 (64)
Viral load ≥50 and <400 copies/mL, n (%)	8 (6)
Viral load ≥400 and <1000 copies/mL, n (%)	2 (1)
Viral load ≥1000 copies/mL, n (%)	39 (28)

[1]Creatine measures were abstracted from routine laboratory records within six months before or after the study visit

The distribution of plasma EFV, TFV and DBS TFV-DP concentrations are presented in Table 4-2 and Supplementary Figure 9-4-1. Specimens were collected at a median of 15 hours after last dosing (IQR 14-16). In total, 84%, 76% and 86% of women had any detectable plasma EFV, plasma TFV and DBS TFV-DP, respectively. There were 38 women (28%) who had drug concentrations below the LLOQ for all three ARV assays; two of these 38 women were virologically suppressed. These two women both reported that they were no longer taking ART, which was confirmed in medical records, and their HIV diagnosis was confirmed on ELISA. Both were thought to be elite controllers. Most women had high self-reported adherence scores with 56% of women (n=77) reporting 100% adherence in the last 30 days on the three-item scale; 62 of whom (81%) were virologically suppressed.

Table 4-2 Concentrations of TFV-DP in DBS, TFV plasma and EFV plasma as well as self-reported adherence among 137 women, grouped by viral load <50, <400 and <1000 copies/mL. Results presented as n (%) unless specified.

	Viral load <50 copies/mL	**Viral load ≥50 copies/mL**	**Viral load <400 copies/mL**	**Viral load ≥400 copies/mL**	**Viral load <1000 copies/mL**	**Viral load ≥1000 copies/mL**	**All women**
Number of women	88 (64)	49 (36)	96 (70)	41 (30)	98 (72)	39 (28)	137
EFV plasma (µg/mL)							
Median (range)	1.9 (0.00975, 19.5)	0.00975 (0.00975, 4.8)	1.91 (0.00975, 19.5)	0.00975 (0.00975, 4.8)	1.87 (0.00975, 19.5)	0.00975 (0.00975, 4.8)	1.52 (0.00975, 19.5)
Geometric mean (95% CI)	1.8 (1.4-2.3)	0.03 (0.02-0.06)	1.6 (1.2-2.1)	0.02 (0.01-0.03)	1.5 (1.1-2.0)	0.02 (0.01-0.03)	0.4 (0.3-0.6)
LLOQ to <0.7	9 (10)	39 (80)	11 (11)	37 (90)	13 (13)	35 (90)	48 (35)
0.7 to <4	66 (75)	8 (16)	71 (74)	3 (7)	71 (72)	3 (8)	74 (54)
≥4	13 (15)	2 (4)	14 (15)	1 (2)	14 (14)	1 (3)	15 (11)
TFV plasma (ng/mL)							
Median (range)	44.3 (5.0, 120)	5.0 (5.0, 90.1)	44.2 (5.0, 120)	5.0 (5.0, 90.1)	44.0 (5.0, 120)	5.0 (5.0, 90.1)	32.90 (5.0, 120)
Geometric mean (95% CI)	35 (30-42)	8 (6-11)	34 (29-41)	7 (5-8)	33 (28-39)	7 (5-9)	21 (17-25)
LLOQ to <35.5	31 (35)	42 (86)	35 (36)	38 (93)	37 (38)	36 (92)	73 (53)
≥35.5	57 (65)	7 (14)	61 (64)	3 (7)	61 (62)	3 (8)	64 (47)
TFV-DP DBS (fmol/punch)							
Median (range)	961.5 (8.3, 2402)	8.3 (8.3, 1359)	952.5 (8.3, 2402)	8.3 (8.3, 930)	940.5 (8.3, 2402)	8.3 (8.3, 930)	701 (8.3, 2402)
Geometric mean (95% CI)	815 (670-992)	25 (14-43)	740 (591-926)	16 (10-25)	700 (551-889)	15 (9-24)	241 (163-336)
LLOQ to <350	7 (8)	40 (81)	10 (10)	37 (90)	12 (12)	35 (90)	47 (35)
350 to <700	16 (18)	3 (6)	17 (18)	2 (5)	17 (17)	2 (5)	19 (14)
700 to <1250	36 (41)	5 (10)	39 (41)	2 (5)	39 (40)	2 (5)	41 (30)
1250 to <1850	23 (26)	1 (3)	24 (25)	0 (0)	24 (24)	0 (0)	24 (18)
≥1850	6 (7)	0 (0)	6 (6)	0 (0)	6 (6)	0 (0)	6 (4)
Self-reported adherence in past 30 days							
Median (range)	100 (0-100)	92 (0-100)	100 (0-100)	83 (0-100)	100 (0-100)	83 (0-100)	100 (0-100)
Score ≤80	3 (3)	20 (41)	4 (4)	19 (46)	5 (5)	18 (46)	23 (17)
Score >80 and ≤100	23 (26)	14 (29)	27 (28)	10 (24)	28 (29)	9 (23)	37 (27)
Score=100	62 (70)	15 (31)	65 (68)	12 (29)	65 (66)	12 (31)	77 (56)

In ROC analyses to evaluate how well each adherence marker predicted virologic suppression, DBS TFV-DP had the highest AUC of 0.926 (95% CI 0.876-0.976) after adjusting for age and duration on ART (Figure 4-1; unadjusted ROC curves shown in Supplementary Figure 9-4-2). This was significantly better than plasma TFV (AUC=0.864 95% CI 0.797-0.932, p=0.006) but not significantly different from plasma EFV (AUC=0.903 95% CI 0.839-0.967, p=0.138). All drug concentrations performed better than 30-day self-reported adherence (AUC=0.756 95% CI 0.660-0.852, p<0.05 for each assay).

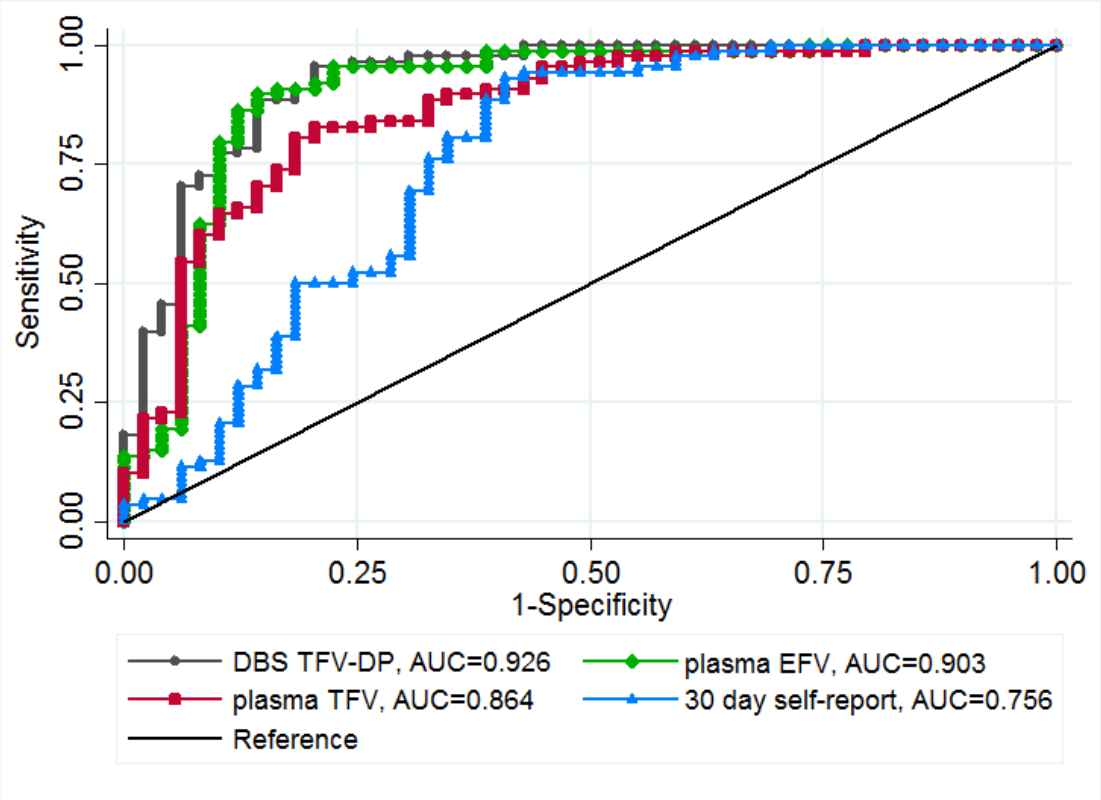

Figure 4-1 Adjusted area under the receiver operating characteristics (ROC) curves of DBS TFV-DP (grey), plasma EFV (green), plasma TFV (maroon), and self-reported adherence (blue) to predict viral suppression; n=137 (adjusted for age and duration on ART).

Using drug concentrations to predict virologic suppression, we used ROC analyses to examine the diagnostic characteristics of different drug concentration cut-off points, including established thresholds for TFV-DP in DBS [11], plasma TFV [22] and plasma EFV [20,21] (Table 4-3). Having any detectable drug concentration on any of the three assays was highly predictive of virologic suppression. Almost 90% of the cohort were correctly classified based on any detectable TFV-DP in DBS or any plasma EFV; 85% were correctly classified by any detectable plasma TFV. Higher drug concentration cut-offs resulted in higher positive predictive values.

Table 4-3 Diagnostic characteristics of different binary drug concentration thresholds to predict virologic suppression (<50 copies/mL) using both established drug concentration cut-off values and alternative cut-off values (indicated by *) that maximised sensitivity and specificity in ROC analyses.

Tenofovir-diphosphate (TFV-DP) in DBS						
Select TFV-DP cut-off values	**Probability of virologic suppression[1]**	**Sensitivity[2] (%)**	**Specificity[3] (%)**	**PPV[4] (%)**	**NPV[5] (%)**	**Correctly classified[6] (%)**
>LLOQ	>0.190	97.7	73.5	86.9	94.7	89.1
≥350	≥0.464	92.1	81.6	90.0	85.1	88.3
≥399*	≥0.515	92.1	83.7	91.0	85.4	89.1
≥700	≥0.787	73.9	87.8	91.5	65.2	78.8
≥1250	≥0.975	33.0	98.0	96.7	44.9	56.2
≥1850	≥0.998	6.8	100.0	100.0	37.4	40.2
Plasma tenofovir (TFV)						
Select plasma TFV cut-off values	**Probability of virologic suppression[1]**	**Sensitivity[2] (%)**	**Specificity[3] (%)**	**PPV[4] (%)**	**NPV[5] (%)**	**Correctly classified[6] (%)**
>LLOQ	≥0.411	88.6	77.6	87.6	79.2	84.7
≥23.5*	≥0.586	78.4	79.6	87.3	67.2	78.8
≥35.5	≥0.750	64.8	85.7	89.1	57.5	72.3
Plasma efavirenz (EFV)						
Select plasma EFV cut-off values	**Probability of virologic suppression[1]**	**Sensitivity[2] (%)**	**Specificity[3] (%)**	**PPV[4] (%)**	**NPV[5] (%)**	**Correctly classified[6] (%)**
>LLOQ	≥0.253	97.7	75.5	87.8	94.9	89.8
≥0.70	≥0.483	89.8	79.6	88.8	81.3	86.1
≥1.00	≥0.605	85.2	81.6	89.3	75.5	83.9
≥1.13*	≥0.636	81.8	83.7	90.0	71.9	82.5
≥4.00	≥0.995	14.8	95.9	86.7	38.5	43.8

[1]Probability estimated from logistic regression models.

[2]Proportion of subjects with a viral load <50 copies/mL who were detected using this cut-off

[3]Proportion of subjects with a viral load ≥50 copies/mL who were detected using this cut-off

[4]Positive Predictive Value: proportion of those who were detected with this drug concentration cut-off who had a viral load <50 copies/mL

[5]Negative Predictive Value: proportion of those who were not detected with this drug concentration cut-off who had a viral load ≥50 copies/mL

[6]Overall proportion of those above and below the cut-off who were correctly classified. Note that this proportion is always biased towards the larger group.

Thresholds of DBS TFV-DP have been shown to relate back to doses taken per week in healthy volunteers [11]. Table 4-4 examines in more detail the viral load distribution and association between virologic suppression and DBS TFV-DP in our cohort within these established thresholds. In our cohort 97% of women (n=29) who had a DBS TFV-DP concentration ≥1250 fmol/punch were virologically suppressed (defined as <50 copies/mL). This threshold also perfectly predicted viral loads <400 and <1000 copies/mL. Seven of the 47 women (15%) in the lowest TFV-DP category, <350 fmol/punch, remained suppressed

despite none or very low drug concentrations. A dose-response relationship was observed between virologic suppression and increasing concentrations of TFV-DP in DBS; this was not observed for increasing concentrations of plasma EFV or TFV (data not shown). Similar associations were observed in sensitivity analyses excluding women who self-reported not taking any ART in the past 30 days (Supplementary Table 9-4-1). Increasing years of age (aOR 1.12 95% CI 1.01-1.25) and increasing years on ART (aOR 1.56 95% CI 0.13-18.07) were associated with virologic suppression, although the association with duration on ART was not statistically significant (crude models in Supplementary Table 9-4-2). Serum creatinine concentrations were not measured at the time of the drug concentration testing and only 74 women had available serum creatinine concentrations in the six months before or after the study visit. In this group, serum creatinine was not associated with virologic suppression. Neither serum creatinine nor body mass index (BMI) changed the associations between drug concentrations and viral load and were therefore not included in adjusted models.

To examine improved short-term ART adherence related to the study visit among participants (so called “white coat” adherence [2,24]), we compared adherence in plasma TFV (half-life approximately 14 hours [6]) with TFV-DP (half-life of up to 17 days [12]). Concentrations of TFV-DP in DBS correlated well with plasma TFV concentrations (r=0.700, Supplementary Figure 9-4-3). There were four women with any detectable plasma TFV but DBS TFV-DP concentrations below 350 fmol/punch. All four women also had detectable plasma EFV concentrations and only two women had viral loads above 50 copies/mL (Supplementary Table 9-4-3).

Table 4-4 Viral load characteristics within established DBS TFV-DP thresholds among 137 women. Odds ratios (OR) predicting viral load <50, <400 and <1000 copies/mL are presented.

TFV-DP threshold (approximate doses per week[1])	**<350 (<2)**	**350-699 (2-3)**	**700-1249 (4-6)**	**≥1250 (7)**
Total number of women	47	19	41	30
Median viral load log_{10} copies/mL (IQR)	3.7 (2.8-4.6)	1.3 (1.3-1.3)	1.3 (1.3-1.3)	1.3 (1.3-1.3)
Median viral load copies/mL (IQR)	12200 (618-40027)	20 (20-20)	20 (20-20)	20 (20-20)
Viral load <50 copies/mL				
Viral load <50 copies/mL, n (%)	7 (15)	16 (84)	36 (88)	29 (97)
OR (95% CI)	Ref	30 (7-133)	41 (12-141)	166 (19-1421)
aOR[2] (95% CI)	Ref	37 (8-178)	47 (13-175)	175 (20-1539)
Viral load <400 copies/mL				
Viral load <400 copies/mL, n (%)	12 (26)	17 (89)	39 (95)	30 (100)
OR (95% CI)	Ref	31 (6-159)	72 (15-352)	Omitted
aOR[2] (95% CI)	Ref	47 (8-287)	100 (17-579)	Omitted
Viral load <1000 copies/mL				
Viral load <1000 copies/mL, n (%)	10 (21)	17 (89)	39 (95)	30 (100)
OR (95% CI)	Ref	25 (5-123)	57 (12-272)	Omitted
aOR[2] (95% CI)	Ref	31 (6-167)	64 (12-330)	Omitted

[1]As previously described by Castillo-Mancilla *et al* (CID, 2018)

[2]Adjusted for age and duration on ART

4.5 Discussion

Our findings from a cohort of South African women show that concentrations of TFV-DP in DBS, plasma EFV and plasma TFV were all strongly associated with virologic suppression and all performed better than self-reported adherence. The strength of association between DBS TFV-DP and virologic suppression increased with increasing drug concentrations and remained consistent after adjustment for covariates and in sensitivity analyses, confirming recent findings in a US cohort [11]. This study is the first to compare TFV-DP in DBS with plasma ARV concentrations and HIV viral load for measuring ART adherence in an African population and adds novel insights for the potential use of TFV-DP in DBS and plasma EFV or TFV to measure adherence among PLWH.

Plasma EFV and DBS TFV-DP concentrations above the LLOQ both had sensitivities approaching 100% and correctly identified 89% of women with virologic suppression. We found a stronger association between plasma EFV concentrations and virologic suppression than previously reported in a similar population up to one year on ART [7]. Adherence is

known to change over time and there may be less intermittent adherence in our cohort at 3-4 years after ART start compared with the first year on ART. However, there are mixed results in the literature regarding the association between increasing duration on ART and adherence [25]. Although we were not able to measure the genes relevant to EFV metabolism in this study, it is likely that women with EFV concentrations above 4 µg/mL (11% of our cohort) possess the *CYP2B6* slow metaboliser genotype resulting in a longer EFV half-life [8]. The longer DBS TFV-DP half-life and possibly longer EFV half-life compared to plasma TFV may explain why, even when administered in a fixed dose combination, plasma TFV concentrations performed slightly worse than plasma EFV and TFV-DP in DBS at predicting virologic suppression.

TFV-DP concentrations in DBS among suppressed women in our cohort (geometric mean 815 fmol/punch, median 961 fmol/punch) were equivalent to values reported in another South African cohort of predominantly women (median 939 fmol/punch) [13]. However, they were lower than observed among suppressed Black PLWH in the US (geometric mean 1453 fmol/punch) [11] and higher than observed among non-pregnant HIV-negative women on PrEP in Uganda and Kenya (mean 637 fmol/punch) [23]. This supports recent findings that virologically suppressed PLWH have higher DBS TFV-DP concentrations than HIV-negative individuals [11] and suggests therapeutic thresholds of DBS TFV-DP may be lower among Black African PLWH. Although we observed lower TFV-DP concentrations in DBS than Castillo-Mancilla and colleagues [11], we found a similar dose-response relationship between virologic suppression and increasing TFV-DP concentrations in DBS. In contrast to their findings, we found no association between TFV-DP in DBS and BMI which may be due to most women in our cohort having BMI $\geq$25kg/m^2. Other individual characteristics such as comorbidities and concomitant medication may also influence TFV-DP concentrations in DBS [11] but we were not able to evaluate these in our study. We were also unable to assess variability in TFV-DP concentrations in DBS due to ARV regimen, race or gender as our cohort was restricted to non-pregnant women on a first-line fixed-dose combination regimen of TDF+XTC+EFV. Pregnancy status has also recently been shown to influence TFV-DP concentrations in DBS among African women on PrEP [23] and this requires further evaluation in the context of HIV infection.

Our findings should be interpreted with the following additional limitations in mind. Previous studies have accounted for CD4 cell count and kidney function in their analyses, however these data were not collected by the study and, although effort was made to abstract

information from routine medical records, few women had available measures within six months before or after the study visit. We ascertained ART regimen by self-report and through triangulation with routine pharmacy dispensing data, but errors may have occurred. In this cross-sectional study, we were also unable to assess daily dosing or to match drug concentration thresholds to actual ART dosing prior to the study visit as the last dose was not observed. Given the observed differences in TFV-DP concentrations in DBS among people living with and without HIV, as well as the lower concentrations reported among Black individuals, further research is needed to evaluate adherence thresholds in African populations living with HIV.

In both research and routine care there is often concern about improved adherence shortly before a scheduled research or clinical visit, or "white coat" adherence [2,24]. We found little evidence of this in our cohort with only four women with therapeutic plasma TFV but TFV-DP in DBS below 350 fmol/punch. The long half-life of TFV-DP in DBS and the dose-response relationship with virologic suppression show that measuring TFV-DP in DBS provides a more nuanced measure of adherence than plasma EFV or TFV concentrations. However, our findings suggest that plasma EFV and TFV, both less expensive and complex assays, can also be strong predictors of virologic suppression and these assays may warrant consideration as adherence measures in resource-limited settings.

4.6 Conclusion

In summary, our data add to the evidence on the use of TFV-DP in DBS for monitoring ART adherence in PLWH, providing new insights from a cohort of African women. TFV-DP in DBS and plasma EFV and TFV concentrations were strongly associated with virologic suppression and are superior to self-reported adherence. Further research is needed to assess the added value of these drug concentration assays in the context of viral load monitoring and screening for ART resistance.

4.7 References

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Chapter 5: Decreases in self-reported antiretroviral therapy adherence predict HIV viremia among pregnant and postpartum South African women

Phillips TK, Wilson IB, Brittain K, Zerbe A, Mellins CA, Remien RH, Orrell C, Abrams EJ, Myer L. Decreases in self-reported ART adherence predict HIV viremia in a longitudinal cohort of pregnant and postpartum women in Cape Town, South Africa. *J Acquir Immune Defic Syndr* 2018; 80(3):247-254. doi:10.1097/QAI.0000000000001909

Relevance of this paper to the thesis:

Following on from Chapter 4, where drug concentration assays all outperformed the cross-sectional self-reported adherence measure, this paper presents a novel approach to the use of self-reported adherence. Self-report is known to be prone to bias and frequently overestimates adherence but is still a widely used in routine care and research. This paper examine whether decreases in self-reported adherence over consecutive measurement times is associated with risk of viremia and provides a proof of concept for future work using longitudinal self-reported adherence in low-resource settings.

Contribution of the student and co-authors:

TP conceptualised the analysis with techinical advise from LM and IW. TP conducted all analyses and wrote the initial manuscript draft. All co-authors reviewed the manuscript and provided conceptual and intellectual comment. All authors were involved in the final draft of the manuscipt.

5.1 Abstract

Introduction: Routine HIV viral load (VL) monitoring is recommended for patients on antiretroviral therapy (ART) but frequent VL testing, required in pregnant and postpartum women, is often not feasible. Self-reported adherence can be valuable, but little is known about its longitudinal characteristics.

Methods: We followed women living with HIV from ART initiation in pregnancy through 18 months postpartum in Cape Town, South Africa, with repeated measurement of VL and self-reported adherence using a three-item scale. We used generalized estimating equations (with results presented as odds ratios [OR] with 95% confidence intervals [CI]) to investigate the association between viremia and change in adherence over pairs of consecutive visits.

Results: Among 2085 visit pairs from 433 women, a decrease in self-reported adherence relative to the previous visit on any of three self-report items, or the combined scale, was associated with VL >50 and >1000 copies/mL. The best performing thresholds to predict VL >50 copies/mL were a single level decrease on the Likert response item "how good a job did you do at taking your HIV medicines in the way that you were supposed to?" (OR 2.08 95% CI 1.48-2.91), and a decrease equivalent to ≥5 missed doses or a one level decrease in score on either of two Likert items (OR 1.34 95% CI 1.06-1.69).

Conclusion: Longitudinal changes in self-reported adherence can help identify patients with viremia. This approach warrants consideration in settings where frequent viral load monitoring or other objective adherence measures are not possible.

5.2 Introduction

Antiretroviral therapy (ART) is the cornerstone of HIV treatment and prevention efforts. Current global guidelines recommend that all individuals living with HIV start lifelong ART as soon as they are diagnosed, thereby improving their long-term health outcomes [1]. HIV transmission during pregnancy, labour and delivery, and breastfeeding can be reduced to below 1% in the presence of suppressive ART [2]. However, optimal ART adherence is essential to achieve sustained viral suppression and to realize the treatment and prevention benefits.

Routine HIV viral load monitoring is being rolled out globally [3]. Viral load offers an objective marker of treatment success and a signal for poor adherence and antiretroviral resistance but, even with the push to scale up routine viral load monitoring, numerous challenges persist [3,4]. During pregnancy and postpartum, ART adherence is a particular concern due to the added risk of vertical HIV transmission [5,6]. An increased frequency of viral load testing is recommended during these periods, but this is not always feasible [7,8]. In low-resource settings where viral loads are infrequent or unavailable, other methods of assessing ART adherence are still required [9].

Self-reported adherence – which is inexpensive, immediate and easy to administer – is often used to assess ART adherence in both routine care and research settings. Although validated self-reported adherence measures exist, finding an optimal measure has been a focus of much research [10–13]. Self-reported adherence, which can often overestimate individual medication taking behaviour, measures an individual's perception of their treatment adherence [10]. It may be influenced by various biases such as social desirability or recall bias, and this may vary between individuals depending on their own reference points regarding their medication-taking practices [11,14,15]. Despite these issues, self-reported adherence has often shown a reasonable correlation with viral load and other objective markers of adherence, including in low-resource settings [9,11,16].

Although there have been calls for longitudinal adherence measures to assess changes in ART adherence [17,18], the vast majority of studies have only evaluated the association between adherence and viral load at a single time point. Longitudinal measures provide an opportunity to examine relative changes in reported adherence which could help to account for individual reporting patterns. Predictors of changes in reported adherence have been explored but few studies have assessed whether changes in reported adherence are associated

with an objective marker such as viral load [19–24]. Here we examined self-reported adherence and viral load among women living with HIV over multiple measurement points during and after pregnancy and investigate the association between changes in self-reported adherence and viremia.

5.3 Methods

We conducted a longitudinal analysis of women enrolled into a multi-phase implementation science study (the MCH-ART study, ClinicalTrials.gov NCT01933477) which has been described previously [25]. Women were followed from ART initiation during pregnancy for up to 18 months postpartum. Study visits occurred 2-3 times during pregnancy (depending on gestational age), once shortly after delivery and approximately every three months thereafter.

Setting

Women were recruited into the parent study between April 2013 and June 2014 when they presented for antenatal care (ANC) at a large primary care antenatal and obstetric care clinic in Gugulethu, Cape Town, with follow-up through January 2016. This setting is characterized by high levels of poverty and unemployment, and a very high burden of HIV [26]. The local antenatal HIV prevalence was estimated to be 22% in 2015 [27] and all women starting ART received a fixed dose combination of efavirenz, tenofovir and emtricitabine [28].

Measures

Data were collected at study visits which occurred independently of routine HIV and ANC. Interviews were conducted by trained interviewers in the predominant local language, isiXhosa. Demographic characteristics including age, marital status, employment and timing of HIV diagnosis were collected at the time of enrolment. CD4 cell count and gestational age at presentation for ANC were abstracted from routine medical records.

Self-reported adherence was measured using a simple three-item adherence scale that was developed through a process of rigorous cognitive interviewing and has been validated in the United States [29–31]. It was translated into isiXhosa for use in South Africa and the cross-sectional validity of the translated individual scale items and the overall scale score were evaluated previously in this setting (Cronbach α=0.79) [32]. The three items in the scale (Table 5-1) include a quantification of missed doses as well as two Likert response scales that ask patients “how good a job did you do taking your medications in the way you were

supposed to" and "how often did you take your medications in the way that you were supposed to," all with reference to the past 30 days. To analyse the combined scale score, these three items were aggregated based on a re-coding of each item with equal weighting, to create a score ranging from 0 to 100, with the latter representing the best possible self-reported adherence.

HIV RNA viral load, the "gold standard" in our analyses, was measured at each study visit on the same day as the self-reported adherence scale was administered. Separate from routine HIV care services, venous blood was collected, and batch tested by the National Health Laboratory Services (Abbott RealTime HIV-1 assay, Abbott Laboratories, Illinois, USA), with results only available at the end of the study period.

Table 5-1 Description of items in the three-item self-reported adherence scale and the thresholds used to assess change in adherence across visits.

Item	Threshold
1. E: In the last 30 days, on how many days did you miss at least one dose of any of your HIV medicines? **X: Kwintsuku ezi-30 ezidlulileyo, zimini ezingaphi okhe walibala ukutya amchiza akho entsholongwana?** ***Range 0-30***	Stayed the same Increased by ≥1 missed dose Decreased by ≥1 missed dose
2. E: In the last 30 days, how good a job did you do at taking your HIV medicines in the way that you were supposed to? **X: Kwezi ntsuku zi-30 zidlulileyo uwatye kakuhle kanjani amachiza akho entsholongwane njengohlobo omele ukuwatya ngalo?** ***Range "very poor" to "excellent" (1-6)***	Stayed the same Increased by ≥1 level Decreased by ≥1 level
3. E: In the last 30 days how often did you take your HIV medicines in the way that you were supposed to? **X: Kwezi ntsuku zi-30 zidlulileyo,kukangaphi usitya amachiza akho entsholongwane ngendlela omele kuwatya ngayo?** ***Range "never" to "always" (1-6)***	Stayed the same Increased by ≥1 level Decreased by ≥1 level
Combined three-item scale ***Range 0-100***	Change ≤1 missed dose, both Likert items stayed the same Score increased ≥2 missed doses Score decreased ≥2 missed doses Change ≤4 missed doses, both Likert items stayed the same Increased by ≥1 level or ≥5 missed doses on any item Decreased by ≥1 level or ≥5 missed doses on any item Change ≤9 missed doses or 1 level change in either Likert item Increased by ≥2 levels or ≥10 missed doses on any item Decreased by ≥2 levels or ≥10 missed doses on any item

E – English; X – isiXhosa

Visits

Women were included in analyses from their first suppressed viral load after ART initiation (V0). To minimize potential bias introduced by attrition from the study, we included only women who had at least four consecutive study visits after V0 in primary analyses of self-reported adherence and viral load over time (n=363). Data on trends over time for all women where at least one visit with both an adherence and a viral load measure was available after V0 are presented in supplementary material (n=434). We examined changes in self-reported adherence from each visit (Vi) to the next visit (Vi+1) among all available visit pairs from initial viral suppression (or from 16 weeks on ART in sensitivity analyses). Vi+1 was defined as the first visit occurring 1-6 months after Vi. Figure 5-1 summarizes A) the women and visits included in each analysis and B) the visit pair structure.

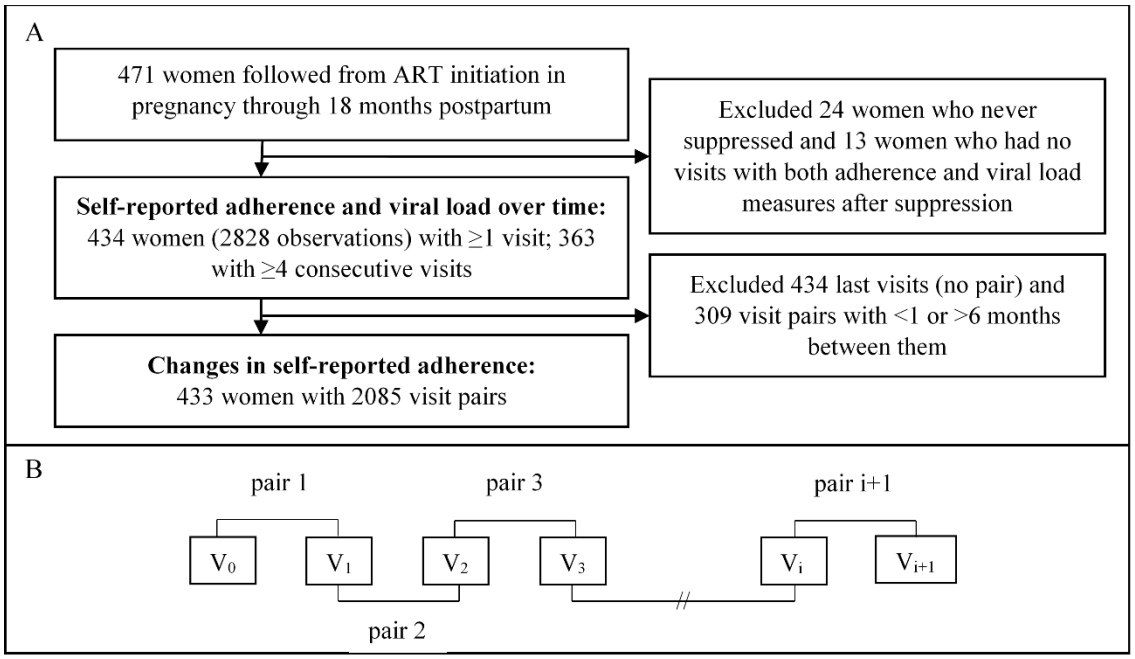

Figure 5-1 A) Flow diagram of patient and visit inclusion and B) schematic of visit pairs where the first visit (V_0) is the first suppressed visit after ART initiation in pregnancy.

Adherence and viral load thresholds

To describe the adherence scale score over time, thresholds of 100 versus <100 and ≥80 versus <80 were used. In prior work these cut-offs produced a reasonable balance between sensitivity and specificity [32]. To analyse changes in adherence score from Vi to Vi+1, we used a simple approach that could potentially be applied in routine care. We determined thresholds based on the minimum possible change in each self-reported adherence item. For

item 1, reporting missed doses during the past 30 days, we examined a change of a single missed dose. For the other two items, 6-level Likert-type responses, a one-level change in response was examined. Larger changes in reported adherence were explored in sensitivity analyses, however there were very few visit pairs with larger changes and thus these data are not presented. For the combined scale score, we examined changes ranging from a single missed dose change in item 1 or a one level change in either of the Likert rating items, through to a change of ≥10 missed doses or ≥2 level change in either of the Likert rating items. All the change thresholds are outlined in Table 5-1. Viral load thresholds of >50 and >1000 copies/mL were examined based on the South African National ART guideline definitions of suppression and flags for treatment failure [33].

Analyses

Data were analysed in Stata v14.0 (Stata Corporation, College Station, Texas, USA). Means with standard deviation (SD) or medians with interquartile ranges (IQR) were used to describe continuous variables. Frequencies and proportions were used to describe categorical variables. Regression coefficients (as slopes) with standard error (SE) and chi-squared tests for trend were used to assess trends in reported adherence and viral load over time.

Generalized estimating equations (GEE) with robust SE and exchangeable correlation structures were used to explore the association between changes in reported adherence from Vi to Vi+1 and viral load at Vi+1 [13,34]. Quasi-likelihood under the independence model criterion (QIC), a modification of the Akaike information criterion (AIC), was used for model selection [35]. We included baseline self-reported adherence, viral load at Vi and time between Vi and Vi+1 in all models and examined additional baseline covariates (maternal age, marital status, education, employment, gravidity, gestational age at presentation for ANC, timing of diagnosis and CD4 cell count) that are often available in routine care and have previously been found to be associated with poor adherence or loss to follow-up [36]. We then selected the final adjusted model based on the lowest QIC. Model results were reported as crude (OR) and adjusted odds ratios (aOR) with 95% confidence intervals (CI).

Primary analyses included all women who achieved viral suppression after ART initiation and who had at least one visit with both adherence and viral load data available following initial suppression (n=434; 92% of the total cohort of 471). Sensitivity analyses were conducted including an additional 17 women who did not achieve viral suppression but had

adherence and viral load measurements after 16 weeks on ART. These results were very similar and are presented in supplementary material.

Ethics

All women included in this analysis provided written informed consent on enrolment into the parent study. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Columbia University Institutional Review Board and the University of Cape Town Human Research Ethics Committee.

5.4 Results

Among 471 women followed in the parent cohort, 37 women were excluded from analyses either because they were never observed to reach viral suppression (n=24) or they did not have at least one visit with adherence and viral load measured after achieving suppression (n=13). A total of 2828 visits were available from 434 included women (mean 4 visits per woman after initial viral suppression [range 1-9]). The median age was 28 years (IQR 25-33), 41% were married or cohabiting and 56% had been diagnosed with HIV in the incident pregnancy (Table 5-2). Only 18% were in their first pregnancy and median gestational age at presentation for ANC was 21 weeks (IQR 16-26). Adherence and viral load over time were examined among women who had at least four consecutive visits after initial suppression (n=363) to minimize the impact of attrition, as well as among all 434 women. Women excluded were younger, more likely to be in their first pregnancy, presented later for ANC and had slightly lower baseline CD4 cell counts compared to the women included (Table 5-2).

Table 5-2 Descriptive characteristics of women at the time of presentation for antenatal care, presented as n (%) unless otherwise stated.

	≥4 consecutive visits after first viral suppression		≥1 visit after first viral suppression		All women in the parent cohort
	Included	**Excluded**	**Included**	**Excluded**	
Number of women	363 (77)	108 (33)	434 (92)	37 (8)	471
Median age (IQR)	28 (25-33)	27 (23-31)	28 (25-33)	26 (23-30)	28 (24-32)
Age ≤25	95 (26)	42 (39)	121 (28)	16 (43)	137 (29)
Married/cohabiting	152 (42)	41 (38)	178 (41)	15 (41)	193 (41)
Completed secondary school	87 (24)	30 (28)	104 (24)	13 (35)	117 (25)
Employed	143 (39)	41 (38)	169 (39)	15 (41)	184 (39)
First pregnancy	60 (17)	27 (25)	78 (18)	9 (24)	87 (18)
Diagnosed with HIV in this pregnancy	199 (55)	69 (64)	245 (56)	23 (62)	268 (57)
Median CD4 (IQR)	355 (254-544)	327 (214-469)	354 (251-534)	284 (173-456)	354 (248-517)
Median weeks gestation (IQR)	20 (16-25)	24 (19-30)	21 (16-26)	25 (21-31)	21 (16-26)
Median adherence score at first visit on ART	89 (78-94)	89 (78-94)	89 (78-94)	93 (78-94)	

Self-reported adherence and viral load over time

Among women with at least four visits after initial suppression (n=363), the proportion reporting adherence scores ≥80 increased slightly over time (slope 0.024, SE 0.004; chi-squared for trend p<0.001) while the proportion with viral loads ≤1000 copies/mL decreased (slope -0.028, SE 0.003; chi-squared for trend p<0.001) (Figure 5-2). These patterns were consistent when including all 434 women (Supplementary Figure 9-5-1) and in sensitivity analyses including women who did not suppress after ART initiation (Supplementary Figure 9-5-2). Although individual fluctuations in reported adherence were observed (Supplementary Figure 9-5-3), the median reported adherence remained stable over time (Supplementary Table 9-5-1).

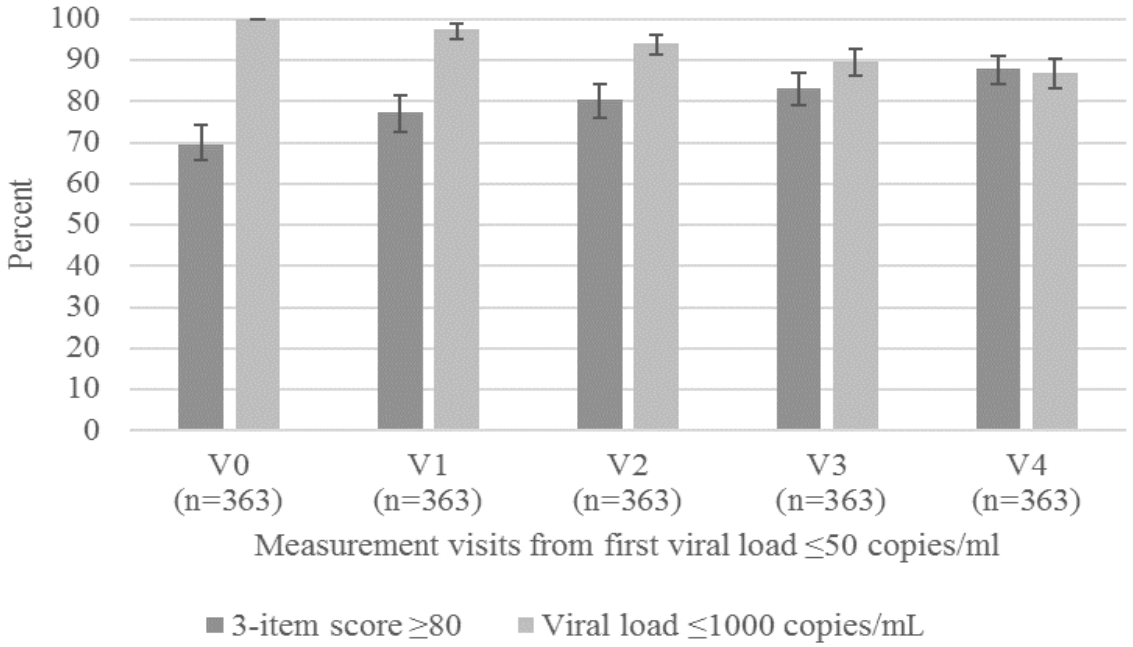

Figure 5-2 Proportion of women with adherence scores ≥80 and HIV viral loads ≤1000 copies/mL among 363 women with at least four study visits after V_0 (first visit with a viral load ≤50 copies/mL after ART initiation during pregnancy). Data are shown from V_0 through 4 additional visits (V_1-V_4).

Association between changes in self-reported adherence score and viral load

To analyse changes in reported adherence, 2085 visit pairs were available for 433 women (mean 3 visit pairs per woman [range 1-8]). The average time between Vi and Vi+1 was 2.4 months (SD 1.1). An adherence score ≥80 was reported at Vi in 81% and at Vi+1 in 83% of visit pairs. Viral load at Vi and Vi+1 was ≤50 copies/mL in 89% and 84% of visit pairs, and ≤1000 copies/mL in 93% and 89% of visit pairs, respectively. Overall, viral load remained below 50 copies/mL in most visit pairs. Viral load declined from >50 to ≤50 copies/mL in only 1% of visit pairs and increased from ≤50 to >50 copies/mL in 5% of pairs (Supplementary Table 9-5-2).

The results of univariable GEE models predicting viral load >50 and >1000 copies/mL at Vi+1, independent of the viral load measure at Vi, are presented in Table 5-3. Using the change thresholds outlined in Table 5-1 for a minimum change in each individual item and three different change thresholds on the combined scale score, a decrease in score was associated with viral load >50 and >1000 copies/mL. These results persisted in sensitivity analyses that included women who had never suppressed but who had at least 16 weeks on

ART (Supplementary Table 9-5-3). In stratified analyses restricted to visit pairs where the viral load at the first visit of the pair (Vi) was ≤50 copies/mL (1852 visit pairs), the strength of association increased. However, when restricted to women who already had a raised viral load at Vi (126 visit pairs), a change in reported adherence was no longer predictive of having a raised viral load at Vi+1 (Table 5-3).

Multivariable models were examined for the two thresholds with the strongest associations: Item 2 "How good a job did you do at taking your HIV medicines in the way that you were supposed to?", and the combined three-item scale threshold of a change of one level on either of the Likert items or ≥5 missed doses. A single level decrease in reported adherence on item 2 remained predictive of having a viral load >50 and >1000 copies/mL (aOR 2.62 95% CI 1.57-4.30 and aOR 1.91 95% CI 1.15-3.17, respectively) in adjusted models (Supplementary Table 9-5-4). Similarly, a decrease in self-reported adherence score equivalent to ≥5 missed doses or a one level decrease in score on either item 2 or 3 also remained predictive of viral load >50 and >1000 copies/mL (aOR 1.62 95% CI 1.11-2.38 and aOR 1.42 95% CI 1.00-2.03, respectively). Again, these results were consistent in sensitivity analyses (Supplementary Table 9-5-5). In all analyses, there was no association between an improvement in reported adherence and odds of viral suppression at Vi+1. Increasing age, being married/cohabiting and being employed all independently reduced the odds of having a raised viral load, while increasing months on ART, presenting later for ANC, having a viral load >50 or >1000 copies/mL at Vi, and increasing time between Vi and Vi+1, increased the odds of having a viral load >50 and >1000 copies/mL at Vi+1 (Supplementary Table 9-5-4; univariable associations presented in Supplementary Table 9-5-6).

Table 5-3 Univariable GEE models for change in each reported adherence from V_i to V_{i+1} to predict viremia >50 and >1000 copies/mL at V_{i+1} in all visit pairs and stratified by viral load ≤50 or >50 copies/mL at V_i. Results are presented as odds ratios with 95% confidence intervals; statistically significant associations are in bold.

	All visit pairs			**Pairs with V_i viral load ≤50 copies/mL**		**Pairs with V_i viral load >50 copies/mL**	
Number of women	**433**			**428**		**126**	
Number of visit pairs	**2085**			**1852**		**233**	
	Number of visit pairs, N (%)	**To predict viral load >50 copies/mL**	**To predict viral load >1000 copies/mL**	**To predict viral load >50 copies/mL**	**To predict viral load >1000 copies/mL**	**To predict viral load >50 copies/mL**	**To predict viral load >1000 copies/mL**
Change in item 1 (missed dose)							
No change in missed doses	1621 (78)	Ref	Ref	Ref	Ref	Ref	Ref
Increased ≥1 missed dose	223 (11)	0.95 (0.65-1.40)	0.97 (0.62-1.23)	0.96 (0.54-1.71)	1.37 (0.71-2.65)	1.28 (0.51-3.21)	0.85 (0.41-1.76)
Decreased ≥1 missed dose	241 (12)	**1.45 (1.07-1.97)**	**1.41 (1.04-1.93)**	**1.72 (1.11-2.66)**	1.54 (0.84-2.81)	1.87 (0.71-4.92)	1.64 (0.87-3.07)
Change in item 2 (good job)							
No change	1824 (87)	Ref	Ref	Ref	Ref	Ref	Ref
Increased ≥1 level	139 (7)	1.07 (0.70-1.64)	0.93 (0.55-1.58)	0.98 (0.49-1.94)	0.72 (0.26-1.97)	2.36 (0.53-10.52)	1.83 (0.88-3.78)
Decreased ≥1 level	122 (6)	**2.08 (1.48-2.91)**	**1.89 (1.33-2.68)**	**2.30 (1.32-3.99)**	**2.09 (1.03-4.25)**	5.57 (0.80-38.64)	1.85 (0.67-3.93)
Change in item 3 (how often)							
No change	1600 (77)	Ref	Ref	Ref	Ref	Ref	Ref
Increased ≥1 level	240 (12)	0.98 (0.72-1.33)	0.76 (0.51-1.34)	1.23 (0.75-2.00)	1.09 (0.55-2.16)	0.83 (0.33-2.12)	0.61 (0.30-1.23)
Decreased ≥1 level	245 (12)	1.34 (0.98-1.83)	1.10 (0.79-1.54)	**1.72 (1.09-2.71)**	1.73 (0.97-3.09)	1.73 (0.63-4.75)	0.82 (0.43-1.57)
Change in combined score							
No change in missed doses	565 (27)	Ref	Ref	Ref	Ref	Ref	Ref
Increased ≥1 missed dose	784 (38)	1.00 (0.78-1.27)	0.96 (0.73-1.25)	1.08 (0.70-0.66)	1.05 (0.58-1.89)	1.04 (0.45-2.40)	0.94 (0.51-1.76)
Decreased ≥1 missed dose	736 (35)	1.23 (0.98-1.54)	1.22 (0.96-1.55)	**1.53 (1.01-2.31)**	1.72 (0.99-2.97)	1.00 (0.43-2.32)	1.03 (0.57-1.87)
Change ≤4 missed doses	1209 (58)	Ref	Ref	Ref	Ref	Ref	Ref
Increased ≥1 level or ≥5 missed doses	447 (21)	1.02 (0.78-1.34)	0.95 (0.69-1.30)	1.19 (0.78-1.81)	1.23 (0.42-2.12)	1.21 (0.54-2.72)	1.08 (0.60-1.93)
Decreased ≥1 level or ≥5 missed doses	429 (21)	**1.34 (1.06-1.69)**	**1.32 (1.05-1.68)**	**1.69 (1.16-2.47)**	**1.71 (1.05-2.78)**	1.19 (0.55-2.57)	1.37 (0.79-2.36)
Change ≤9 missed doses or 1 level	1321 (63)	Ref	Ref	Ref	Ref	Ref	Ref
Increased ≥2 levels or ≥10 missed doses	387 (19)	0.94 (0.72-1.24)	0.87 (0.63-1.21)	1.19 (0.78-1.82)	1.24 (0.71-2.16)	1.28 (0.53-3.11)	1.09 (0.61-1.92)
Decreased ≥2 levels or ≥10 missed doses	377 (18)	**1.29 (1.02-1.63)**	1.28 (0.99-1.65)	**1.65 (1.11-2.45)**	**1.76 (1.07-2.90)**	1.25 (0.56-2.77)	1.22 (0.66-2.24)

5.5 Discussion

In this cohort of women living with HIV who were followed from ART initiation during pregnancy through 18 months postpartum, decreases in self-reported adherence relative to the previous visit were independently predictive of raised viral load. Self-reported adherence remained high over repeated follow-up visits and, despite decreases in the proportion of women with viral suppression over time, over 80% of women attending each visit were virally suppressed.

With a rapidly growing population on ART, routine viral load monitoring is recommended at least annually with increased frequency during pregnancy and breastfeeding, but not all settings are able to implement such frequent viral load testing [3,8]. Assessing change in reported adherence may provide an interim assessment to flag patients requiring additional intervention between viral load measures. The association between reporting decreased adherence and having a raised viral load in our cohort was most marked when restricted to visits where the viral load at the previous visit was suppressed. When participants had an unsuppressed viral load at the first visit of the pair, a decline in reported adherence did not predict viremia. However, in this adherent cohort there were relatively few such cases, which reduced statistical power to detect these differences. In routine practice this may be less of a concern as women with any raised viral loads should already be flagged for further intervention. One possible application may be to measure change in reported adherence following a suppressed viral load as an interim screening tool to prompt adherence counselling or viral load testing only among women reporting worse adherence. Further exploration of the utility and application of this approach is warranted in routine care settings where resources limit the frequency of viral load testing or other objective adherence measures.

Self-reported adherence measures, although subject to well-documented biases, present the patient's perception of their own adherence behaviour, e.g. some patients may miss a few doses and report excellent adherence while others may miss the same number of doses and report very poor adherence. Assessing a change in reported adherence in an individual over two consecutive visits could be a straightforward way for providers to flag emerging adherence problems, relative to each patient's individual reporting. We found that, on average, women with viremia >50 or >1000 copies/mL, had increased odds of reporting worsening adherence across two visits on one or more of the three adherence scale items.

These findings persisted after adjusting for duration between visits, viral load at the previous visit, and other covariates. Previous studies have used similar methods to assess the predictors of changes in reported adherence, but few have linked this change to a biological or objective adherence marker [21,22,24]. The three individual scale items examined independently did not all perform equally. The second item, a Likert rating scale of how good a job you did taking your medication in the last 30 days, had the highest point estimates (OR 2.08 95% CI 1.48-2.91 to detect viral load >50 copies/mL). An additional benefit of this change in adherence approach is that no adherence score conversions would be required. A provider could, for example, plot a patient's response to each of the three questions at each visit. A patient reporting a poorer score on any or a combination of the questions could be flagged for further evaluation and appropriate interventions. Whether longitudinal changes in adherence could be assessed in this way, or even using a single item, merits testing in other populations and in routine care settings.

Although a strength of this study is the very well-characterized cohort contributing over 2800 visits, it is important to note that there was attrition over time. Women excluded from these analyses were younger, more likely to be in their first pregnancy, presented later for ANC and had lower CD4 cell counts compared to the overall cohort. These characteristics are all potential risk factors for loss to follow-up and poor ART adherence [36]. In pregnant and postpartum women, younger age in particular has been consistently found to predict loss to follow-up and poor adherence [36,37]. By including only the available data, selection bias was introduced and women at higher risk of poor adherence or viremia are likely to have been excluded. While this is a limitation, it is equivalent to the selection bias that would be present in the monitoring of ART services in routine care settings. This emphasizes the importance of comprehensive efforts to retain all people living with HIV in ART services.

The longitudinal relationships between changes in self-reported adherence and viral load will likely vary depending on the distribution of reported adherence and viral load levels in the population being examined, the population sampled (e.g. pregnant and postpartum women), and other contextual factors. Here we studied pregnant and postpartum women from a single site in Cape Town, South Africa. This is likely representative of other urban sites in South Africa and sub-Saharan Africa but generalizability to other settings and populations should be considered with caution. All adherence and viral load measures were taken as part of research study visits, independent of routine HIV care, which may have reduced socially desirable response bias. Language and context translation are complex issues that may have impacted

these results. The self-report scale was translated into isiXhosa directly from the questions designed and validated in the United States and translation could partly explain the differences observed between the individual adherence items. Results may be strengthened by exploring cognitive interviewing approaches in the local language. We studied a population with excellent adherence and high rates of viral suppression for whom, in most cases, adherence could only decrease. It would be important to repeat this analysis in less adherent populations for whom adherence could both increase and decrease. Lastly, we were unable to assess the association between changes in self-reported adherence and an objective adherence marker, such as electronic drug monitoring or drug-level monitoring, which may be better "gold standard" measures of adherence behaviours than viral load.

5.6 Conclusion

In this cohort of South African women who initiated ART during pregnancy as part of routine care, self-reporting worse adherence relative to the previous visit on any of three simple adherence questions, and specifically the Likert item asking how good a job you did taking your medications in the way you were supposed to, was consistently associated with viremia. These results show that changes in self-reported adherence could provide a simple flag for women at risk for raised viral loads. This approach warrants further consideration in the context of monitoring ART adherence in settings with limited access to viral load and objective adherence monitoring.

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Chapter 6: Estimating retention in HIV care: data sources and definitions in a South African cohort of pregnant and postpartum women

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Relevance of this paper to the thesis:

This thesis focuses on engagement in maternal ART care which includes both adherence to ART (the focus of Chapters 3 through 5) as well as retention in HIV care. In the general adult ART literature, as well as among pregnant and postpartum women, there is major variability in definitions and approaches to measuring retention and most studies use facility-specific data sources. This paper focuses on the use of interlinked routine electronic medical records to measure retention in HIV care and explores the impact of using different definitions and routine data sources to estimate retention.

Contribution of the student and co-authors:

TP conceptualised the analysis with guidance from LM, CO and EJA. TP conducted all analyses and wrote the initial manuscript draft. All co-authors reviewed the manuscript and provided conceptual and intellectual comment. All authors have been involved in the draft manuscipt which is currently being prepared for submission to the American Journal of Epidemiology.

6.1 Abstract

Retention in HIV care is required to achieve viral suppression and is measured to support patient care and to monitor HIV programs. A variety of data sources and definitions are used to estimate retention and most estimates are facility-specific. We examined the impact of different definitions and routine data sources (clinic visit, laboratory test and pharmacy dispensing data), linked across facilities, on estimates of retention, consistency of associations with risk factors for non-retention, and associations between retention and viral load, in a cohort of women who started antiretroviral therapy (ART) in pregnancy in South Africa. Different data sources and definitions yielded markedly different retention estimates. However, regardless of data source or definition, the proportion of women retained declined through 24 months on ART and associations with known risk factors for non-retention remained consistent. Clinic visit data identified over 80% of women considered retained in all definitions and provided a robust data source for measuring retention. Researchers must carefully consider the most appropriate retention definition depending on the available data sources and presentation of more than one approach may be warranted to obtain both context-appropriate and comparable estimates. Unique patient identifiers and linking existing data sources should be prioritised to improve retention estimates for patient care and program monitoring.

6.2 Introduction

Sustained retention on lifelong antiretroviral therapy (ART) for all people living with HIV, the second 90 in the UNAIDS 90-90-90 targets [1] remains a significant challenge globally [1,2]. Pregnant and postpartum women were the first to receive universal ART and over 80% of women with known HIV infection in sub-Saharan Africa received antiretrovirals during pregnancy in 2017 [3,4]. However, almost a quarter of women starting ART during pregnancy in Africa are estimated to be lost from HIV care by 12 months on treatment [5] and concerns about retention in care abound [6,7]. Retention in care is a necessary precursor to viral suppression and treatment success, thus monitoring postpartum retention in care, as well as developing and evaluating interventions to improve postpartum retention, has been a focus of much research [5,8–10].

Over the past decade there have been a number of calls for a more standardized approach to measuring retention in HIV care [11–13]. Despite this, the methods used to estimate retention in HIV care remain variable. In the existing literature reporting on postpartum retention since the start of universal ART for pregnant and breastfeeding women, a variety of data sources and many different definitions have been used [5,8,9,13]. Most studies use facility-specific clinic visit data, sometimes including pharmacy dispensing, either from physical record review of patient folders and clinic registers or from electronic records. In addition, a few studies of postpartum women and adult ART cohorts have used laboratory test data to estimate retention [14,15]. There is also variation in the literature on definitions of retention. Commonly used definitions can be grouped broadly into cross-sectional (evidence of accessing care in one specified window of time [16–18]), longitudinal (evidence of accessing care in multiple windows of time [19–21]), and gaps in care (assessing time between attended visits [22–26] or time with no ART in hand [27–30]), or a combination of the three [31–33]. The need for longitudinal definitions that can capture continuity of care, particularly in the context of pregnancy and postpartum, was raised by Rollins *et al* [13]. Visit constancy is one commonly used longitudinal measure while the Health Resources and Services Administration (HRSA) HIV/AIDS Bureau (HAB) definition is frequently used in the United States [34,35]. Both measures use an accumulation of cross-sectional retention measures over multiple time points to estimate continuity of care.

Another key element of estimating retention is whether attempts are made to ascertain care engagement beyond a single facility of interest. Pregnant and postpartum women are often required to transfer care, either to start ART during pregnancy or to continue treatment at a

general ART clinic postpartum [36,37]. It is well documented that patients who transfer out of one facility do not always link to care at a new facility, while many patients who are considered lost are accessing care elsewhere [14,37,38]. To successfully monitor outcomes on ART among pregnant and postpartum women who are required to transfer, and to intervene when women have been lost from care, there is a need to ascertain retention beyond the facility of ART initiation. Interlinked routine health information systems are currently recommended by the World Health Organisation (WHO) for patient monitoring to allow assessment of continuity of care across programs and facilities [39], yet much of the retention literature, in both maternal and adult ART cohorts, relies on single facility-specific data sources.

To systematically investigate the impact of variation in data sources and definitions used to estimate retention using interlinked data, we used routine electronic clinic visit, pharmacy refill and laboratory test data, linked across clinics, for an existing cohort of women who initiated ART in pregnancy in South Africa. First, we examined the impact of data sources and retention definitions on estimates of retention in care through 24 months on ART. Second, we explored the contribution of individual and combined data sources to retention estimates. Third, we investigated the consistency of associations between known risk factors and different retention estimates, and lastly, we compared the association between different estimates of retention and HIV viral load, a key biological marker of treatment success.

6.3 Methods

Study participants

This is a secondary analysis of data collected during the MCH-ART study, a large implementation science trial that aimed to optimize ART services for postpartum women in Gugulethu, Cape Town, South Africa. The full study methods and the primary results have been reported [18,40]. Briefly, the study consecutively enrolled 628 pregnant women living with HIV who were eligible to initiate ART (April 2013-April 2014). All women were prospectively followed through delivery; a subset of breastfeeding women were followed through 18 months postpartum. Study data included demographics, date and gestation at ART initiation, delivery details and batched study viral load measures roughly every three months. Routinely collected electronic health data were obtained retrospectively for all women from presentation for antenatal care (ANC) through 30 months on ART.

Setting

Gugulethu is characterised by high levels of poverty and the antenatal HIV seroprevalence in 2015 was approximately 30% [41]. Health services are provided free of charge at all public primary health care facilities. In this setting, women receive integrated ANC and ART services during pregnancy and are required to transfer to general ART clinics to continue care postpartum. During the MCH-ART trial, women were randomly assigned to be transferred our per standard of care (6-10 weeks postpartum) or at cessation of breastfeeding [18]. During the study period, 1-4 months of ART was dispensed at each clinic visit depending on the facility and model of care. Routine viral load tests were expected every 3-6 months during pregnancy and breastfeeding and annually thereafter [42,43].

Routine data sources

Routine electronic health data (summarised in Supplementary Table 9-6-1) were obtained from the Provincial Health Data Centre (PHDC) of the Western Cape Department of Health and the National Health Laboratory Services (NHLS) database. The PHDC structure has been described in detail elsewhere [44]. In brief, the PHDC receives data from all public health facilities in the Western Cape including clinic visits (routinely captured by clerks at each facility into the local clerical information systems and electronic registers) [45] and pharmacy dispensing data from the local pharmacy administrative databases. All patients receiving care in the province are allocated a unique patient identifier which is used to link records for patients across facilities. Data on HIV-related laboratory testing (CD4 cell counts and HIV viral loads) were abstracted from the NHLS database using patient identifiers collected at study enrolment. Where possible to differentiate, acute health care contacts and contacts with non-routine services were excluded. Although data on ART refills were frequently available within the clinic visit data, the data directly from the pharmacy dispensing databases was less consistently available across facilities, thus this data source was not considered alone but only as an additional source.

Retention definitions

Definitions of retention that have been frequently used in the adult or maternal ART literature were compared (Table 6-1). These included cross-sections, 6- and 12-month visit constancy (binarized at 100% visit constancy over all 6-month windows in the 24-month period), the HRSA-HAB definition and gaps in care. Data on next appointments and quantity of ART

dispensed were not reliably available and thus definitions using gaps without treatment and missed visits were not considered. We examined retention from ART initiation to 24 months on ART. All databases were closed on 31 December 2016, allowing a minimum of 30 months on ART for all women. This provided 180 days after the primary point of interest, 24 months on ART, so all women had the potential to experience the outcome of interest by 24 months when using the definition of a 180-day gap in care [12].

Table 6-1 Retention definitions included in analyses and examples from the literature.

Retention definition	Description of retention	Examples from the literature
Cross-sections		
6-month window	Any single HIV-specific contact within a 6-month window (e.g. 0-6 months on ART)	- Visited the clinic at 12 months postpartum ±1 month [16]
12-month window	Any single HIV-specific contact within a 12-month window (e.g. 0-12 months on ART)	- Evidence of any HIV-care contact between 9 and 18 months postpartum [18]
Longitudinal		
100% 6-month visit constancy	At least one HIV-specific contact in each 6-month period: 0-6, 6-12, 12-18 and 18-24 months on ART	- Visit constancy example: At least one visit within one month of 6 weeks, 3, 6, 9 and 12 months [19]
100% 12-month visit constancy	At least one HIV-specific contact in each 12-month period: 0-12 and 12-24 months on ART	- HRSA-HAB example: Whether a patient had 2 kept visits separated by >90 days during the 12-month observation period [35]
100% HRSA-HAB	Two HIV-specific contacts separated by 90 days or more within each 12-month period: 0-12 and 12-24 months on ART	
Gap in care		
180-day visit gap	No gap of >180 days without a visit through 30 months after ART start	- No gap in visits ≥180 days [22] - No gap in visits ≥3 months [26]
150-day visit gap	No gap of >150 days without a visit through 30 months after ART start	

Covariates associated with retention estimates

Using a combination of all data sources, we examined the consistency of associations between different estimates of retention 0-24 months on ART and three covariates. The covariates were based on consistent risk factors for non-retention reported in a recent systematic review of postpartum retention [5]: younger age (<25 years), being newly diagnosed with HIV at ART start, and late gestation at presentation for ANC (≥20 weeks gestation).

Association of retention estimates with viral load

Lastly, we examined the association between retention estimates and viral load ≥1000 copies/mL, in line with the initial flag for treatment failure in the South African National ART Guidelines [46]. Viral load is a key marker of treatment success, thus we wanted to investigate the impact of differences in retention estimates on the association between retention in the first 24 months on ART and viral suppression near the end of this period. We combined viral load results from the routine laboratory data with viral loads taken as part of the parent MCH-ART study and selected the viral load nearest to 18 months on ART within a window of 12 to 24 months on ART. Viral loads conducted during the study were batch tested by the NHLS using the same assays as routine care viral loads (Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 assay; Roche Diagnostics, Branchburg, New Jersey, US). Study viral loads were conducted independently from routine HIV care and therefore allow insight into viral loads among women retained and not retained in HIV care.

Statistical analyses

All analyses were conducted in Stata (StataCorp, College Station, Texas, US) or R (R Foundation for Statistical Computing, Vienna, Austria). Characteristics of the cohort are described using frequencies and proportions, means with standard deviations (SD) and medians with interquartile ranges (IQR) as appropriate. Retention estimates for each data source and definition were described as proportions with 95% confidence intervals (CI). Chi-squared tests were used to compare estimates using different data sources and definitions and chi-squared tests for trend were used to assess change in retention estimates over time. Venn diagrams created using *BioVenn* [47] were used to describe the contribution of each data source to retention estimates using all sources. Associations between covariates at the time of ART initiation and each retention estimate were examined using univariable logistic

regression models presented as odds ratios (OR) with 95% confidence intervals (CI). Among women with a viral load available between 12-24 months on ART, diagnostic characteristics including sensitivity, specificity, positive (PPV) and negative predictive values (NPV), positive and negative likelihood ratios (LR) as well as area under the curve (AUC) from Receiver Operating Characteristics (ROC) analyses were used to describe the ability of each retention estimate to discriminate between women with and without viral load ≥1000 copies/mL. Sensitivity analyses were conducted assuming women with no available viral load were ≥1000 copies/mL.

Ethical considerations

The parent study was approved by the Columbia University Institutional Review Board and the University of Cape Town Human Research Ethics Committee (UCT HREC). All women completed written informed consent prior to enrolment which included consent to link to and abstract their paper and electronic routine medical records. This secondary analysis was approved by UCT HREC.

6.4 Results

Of 628 ART eligible pregnant women enrolled in the MCH-ART study, eight were known to have died and three relocated out of South Africa, thus 617 were included (Supplementary Table 9-6-2). Follow-up data were included for all women up to 30 months on ART (median 26 [IQR 25-27] months postpartum at database closure). At the time of presentation for ANC, the mean age was 29 years (SD 5), 54% of women were newly diagnosed with HIV and 48% presented for ANC before 20 weeks gestation.

Data sources and definitions

Estimates of retention in care varied substantially by data source and definition (Figure 6-1). The lowest estimates for all definitions were observed when using only the laboratory test data: using a 12-month constancy definition and only laboratory data, 55% of women had 100% constancy compared to 62% using the clinic visit data alone and 72% combining all sources ($p<0.001$). Combining the clinic visit and laboratory test data slightly increased the proportion of women considered retained compared to clinic visit data alone, as did the addition of data from pharmacy dispensing databases, but all confidence intervals overlapped.

Using a combination of all available data sources through 24 months on ART, retention estimates ranged from 41% (no gap of >180 days) to 72% (100% 12-month visit constancy, described above). Retention declined over time in all definitions. Using a 100% 6-month constancy definition and all data sources, retention estimates decreased from 100% in the first 6 months to 77%, 65% and 58% in months 6-12, 12-18 and 18-24, respectively (chi-squared for trend $p<0.001$). There were similar significant declines in retention from 0-12 to 12-24 months on ART in both the 12-month constancy and HRSA-HAB definitions (both $p<0.001$ on chi-squared for trend).

The contribution of each data source to retention estimates

The contribution of each data source to the estimate of retention using a combination of all data sources was investigated for each definition of retention from 0-24 months on ART (Figure 6-2). Over 80% of women considered retained in each definition were identified in the clinic visit data. Of the 72% of women who were estimated as retained using the 100% 12-month constancy definition, 87% had evidence of retention using the clinic visit data alone. An additional 12% were identified using the laboratory test data and only 1% of women were identified in the pharmacy databases alone. The laboratory and pharmacy databases alone contributed a very small proportion of the women considered retained using all databases and the 6-month constancy or HRSA-HAB definitions. When using a retention definition of experiencing no gap in care >180 days, the pharmacy databases made a slightly larger contribution, accounting for 17% of the estimated retention using all data sources.

Covariaties associated with estimates of retention in HIV care using different definitions

Using univariable logistic regression models, we examined crude associations between different definitions of retention 0-24 months on ART (using a combination of all available data sources) and three simple covariates [5]. Although point estimates varied slightly, there were consistent associations with all three covariates (Figure 6-3). Retained women had lower odds of being <25 years old and being newly diagnosed with HIV. They also had consistently higher odds of having presented for ANC before 20 weeks gestation.

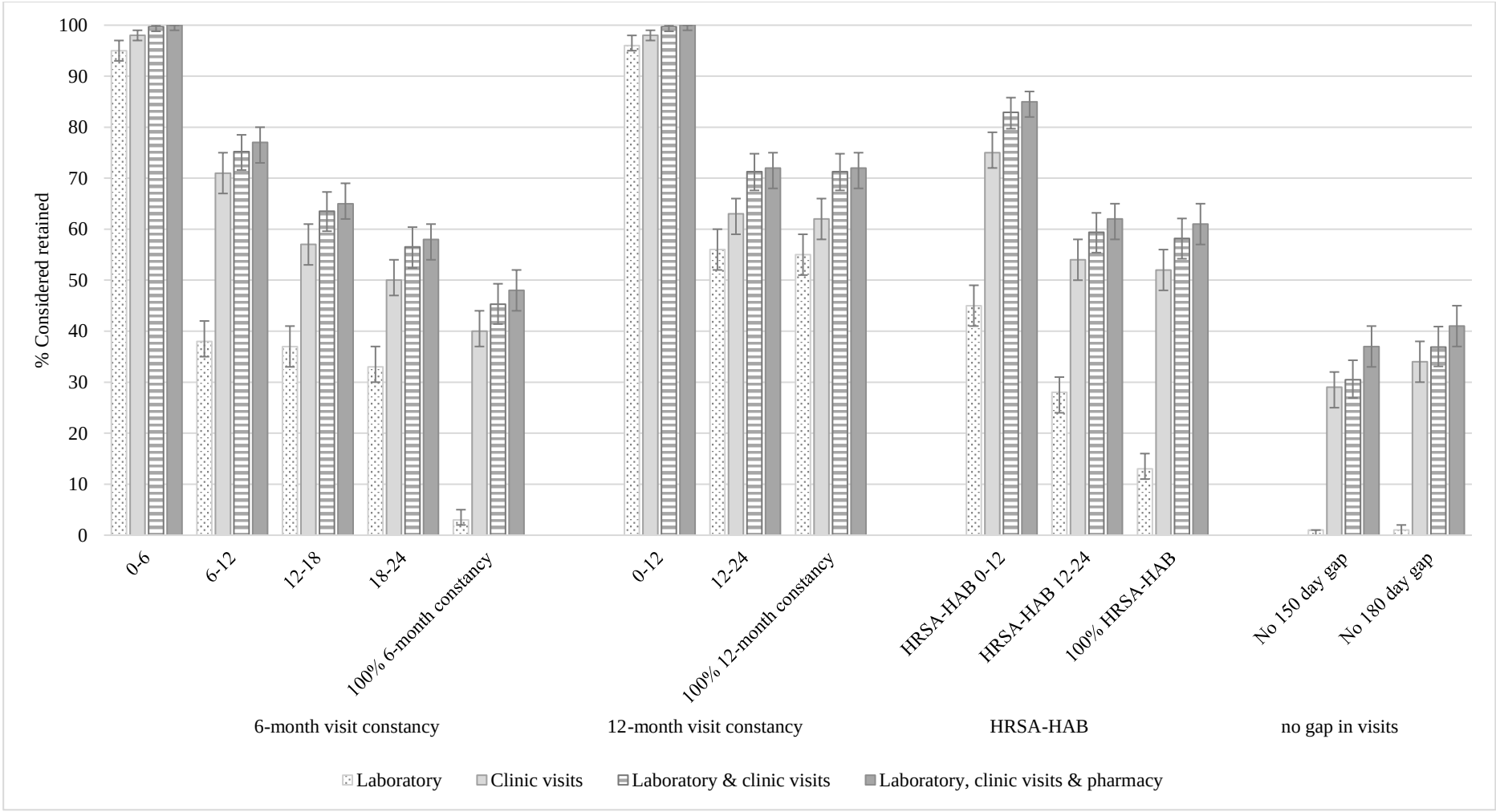

Figure 6-1 The proportion of 617 women considered fully retained in HIV care using different individual and combination data sources across retention definitions in the first 24 months on ART.

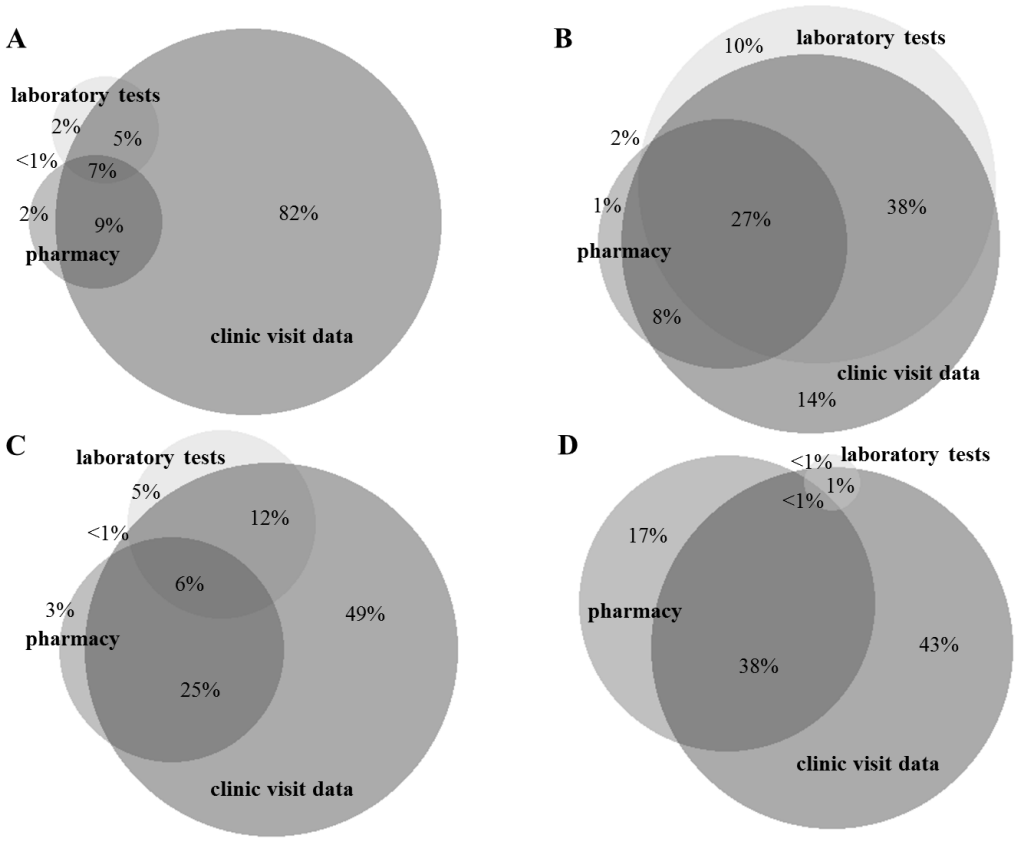

Figure 6-2 Overlap of retention in HIV care using each of laboratory tests, clinic visit data or pharmacy databases. Retention was measured from ART initiation through 24 months on ART using the following definitions: A) 100% 6-month visit constancy (n=298 retained using all data sources), B) 100% 12-month visit constancy (n=446 retained using all data sources),C) 100% HRSA-HAB definition (n=378 retained using all data sources) and D) never experiencing a 180-day gap in care (n=256 retained using all data sources).

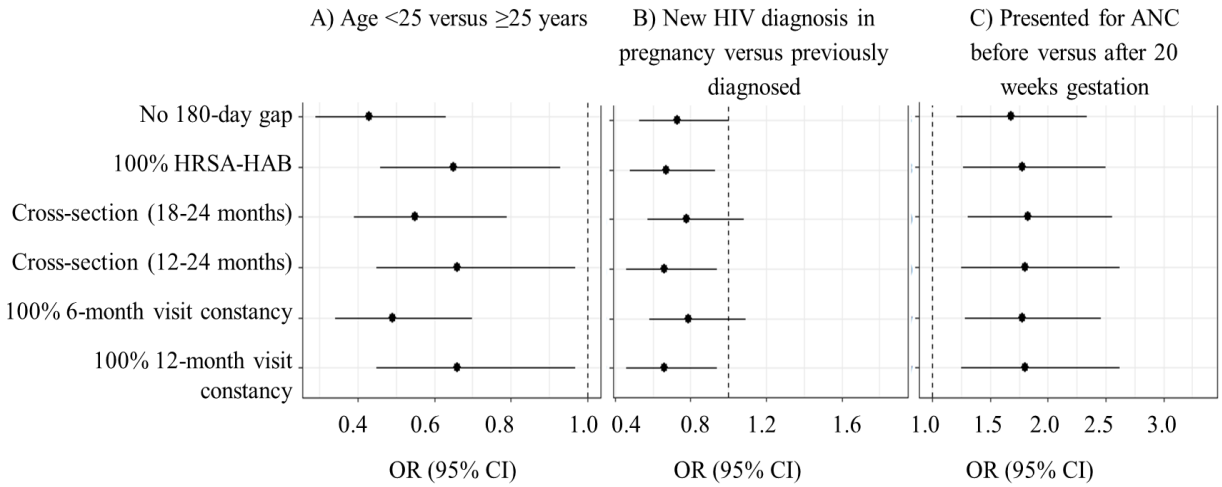

Figure 6-3 Univariable associations of characteristics at ART start with retention in care through 24 months on ART using different definitions based on all available data sources. Results are presented as odds ratios (OR) with 95% confidence intervals (CI); n=617 except for C where n=613. (ANC – antenatal care).

Relationship between retention estimates and viral load

Of the 617 women included, 475 (77%) had a viral load result available between 12 and 24 months on ART (median 17 months on ART, IQR 16-19). Overall, 75% of viral loads came from the MCH-ART study (Supplementary Table 9-6-2). Women with no viral load available were more likely to be <25 years old and newly diagnosed with HIV at entry into ANC. A higher proportion of those with viral loads available were estimated to be retained in care compared to those with no available viral load, regardless of retention definition and data source. Analyses predicting viral load ≥1000 copies/mL were conducted using complete cases (Supplementary Table 9-6-3) and in sensitivity analyses assuming all women with no viral load were ≥1000 copies/mL (Supplementary Table 9-6-4).

When assessing the performance of each retention definition using a combination of all data sources to predict viral load <1000 copies/mL, any 180-day gap in care had the highest sensitivity (93% [95% CI 86-97%]) and AUC (0.792 [95% CI 0.757-0.826]). It also had a very low LR- (0.1 [95% CI 0.1-0.2) indicating good ability to rule out viral load ≥1000 copies/mL. This was very similar when using only the clinic visit data (sensitivity 93% [95% CI 86-97%], AUC 0.732 [95% CI 0.696-0.767]). NPVs were above 80% for all definitions except for the 100% 6-month visit constancy using laboratory data, but a substantial proportion of those who were not considered retained had viral loads <1000 copies/mL with

PPVs ranging from 25 to 64%. The findings remained similar in sensitivity analyses assuming missing viral loads were ≥1000 copies/mL, although PPVs and AUCs all improved slightly (Supplementary Table 9-6-4).

6.5 Discussion

These results highlight that careful consideration is required to select the most appropriate retention definition depending on the available data sources. Different data sources and definitions of retention result in marked variation in the estimates of the proportion of patients retained in care over time. However regardless of data source or definition, the proportion of women retained declined over time and associations with known risk factors for non-retention remained consistent. Experiencing any 180-day gap in care had the strongest association with the clinical outcome of HIV viral load, although relatively strong associations were observed for all definitions using clinic visit data alone, or in combination with additional data sourcesClinic visit data, which is the most frequently used data source to measure retention in HIV care, identified over 80% of women estimated to be retained regardless of the definition used. These data are aligned to local visit schedules and allow for measurement of the local care cascade. Clinic visit data are usually available to programs and researchers in some format, but they are not always electronic and seldom linked across facilities. This makes it difficult to account for transfers and clinic switching, important considerations in maternal ART cohorts who are often required to transfer from integrated antenatal ART services to general ART clinics postpartum [14,37]. The use of interlinked clinic visit data in this cohort, where everyone had to transfer clinics, was a robust data source for estimating retention. If interlinked data sources are not available, active tracing of at least a sample of women would be critical to verify transfer and ascertain retention elsewhere [48–50].

Laboratory testing alone has been used as a surrogate marker for retention in care [14,15]. In high-income settings, laboratory testing often closely follows the schedule of clinic visits, and in that context using laboratory markers rather than clinic visits has been shown to slightly overestimate retention in care [51]. However, in most low-resource settings routine HIV laboratory tests are conducted far less frequently than clinic visits or ART dispensing [52,53]. In our cohort of women who started ART in pregnancy, viral load tests were expected at least every six months during pregnancy and breastfeeding, yet laboratory tests alone resulted in much lower estimates of retention than clinic visits suggesting that testing is not always done

as scheduled. Despite this, laboratory test data may be more likely than clinic visit data to be managed centrally and have the potential to link across clinics [15].

Regardless of data source or definition, retention in HIV care appeared to worsen over time and retention estimates through 24 months on ART using a combination of all data sources ranged from 41% to 72%. This is well below the UNAIDS target of 90% of those diagnosed with HIV being on ART [1], but in line with estimates of the second 90 in South Africa [3,54]. Retention in HIV care is a necessary precursor to viral suppression which is required to prevent perinatal, postnatal and sexual transmission, as well as to optimize maternal health. The low estimates of retention observed here present a threat to the success of ART programmes and emphasise the need for continued research into interventions to support sustained retention in HIV care.

A major strength of this study was the ability to link routine health data for patients across facilities and therefore include women who had transferred or switched clinics (all women in this setting). Although similar data sources are often available in other low- and middle-income countries, the availability of these data in electronic databases and linked across facilities is unique and may impact the translation of these findings to other settings. The findings using clinic visit data and laboratory test data are likely to be generalizable to other settings where mobility and transfer are less common, in so far as there is robust paper or electronic routine data collection. Routine health data is always subject to error and the completeness and quality of the data may have varied over time and by facility. Even in this setting, women attending private clinics or clinics outside of the Western Cape could not have been linked and would be considered not retained. Complex linking algorithms are used to ensure best linkage and prevent duplication, however women may have presented to a clinic using different identifying information and preventing linkage. Facility-recorded deaths were ascertained through the PHDC, but additional deaths that were not recorded in a health facility or occurred outside of the Western Cape may have resulted in overestimation of non-retention in all data sources.

We were unable to evaluate definitions based on scheduled visits or time without ART as data on next appointments and quantity of ART dispensed were not consistently available. Pharmacy refill data has shown great promise as a marker of both retention in HIV care and adherence to treatment. Central pharmacy dispensing databases, where available, may also provide data linked across facilities [55–57]. A previous study found little difference in estimates of retention when counting loss from last attended visit or from a missed scheduled

visit [58]. This is particularly reassuring when looking at retention across clinics where, if scheduled visits or dispensing quantities are not available electronically, abstracting these data from multiple health facilities would likely not be feasible. However, the fact that we could not investigate these data is an important limitation as these definitions are recommended by the WHO and frequently used by routine ART programs [46].

In an era of lifelong ART, and particularly where models of care require transfer between ART clinics as in the case of maternal ART, measures that allow ascertainment of retention beyond a single facility are critical. Within this framework, there is still need for careful consideration of the most appropriate retention definition to use based on available data sources, local models of care and intended use. Active tracing of women to ascertain retention status beyond the facility of interest is very resource-intensive. Resources should be invested into the establishment of unique patient identifiers and leveraging existing clinical, clerical and administrative data systems to form interlinked data sources with important uses for improving patient care as well as program monitoring and research.

The tension between a need for context-specific measures, needed to inform local services and intervene in patient care, and comparable estimates of retention, needed for program monitoring, has been the subject of much discussion [10–13,58] and is highlighted again in this work. Alongside clear descriptions of the local context and available data sources, presentation of sensitivity analyses using different measurement approaches should be encouraged. Clinic visit data appears to be a robust source for measuring retention in care as it includes the granularity of data required for context-specific retention estimates as well as the breadth of data for more generalisable definitions. We suggest that researchers make use of a combination of both an ideal context-appropriate retention definition as well a more generalisable definition, such as any 180-day gap in care [11], to allow comparison within and between programs and research studies.

6.6 Conclusion

Using different interlinked data sources yielded markedly different findings with respect to definitions of retention in HIV care in this cohort of women who started ART in pregnancy. Benefits and challenges exist for each data source and research should consider the nature of the data source used as a critical factor in studies measuring retention. Clinic visit data that is linked across facilities provides a robust data source for measuring retention in HIV care. Resources should be prioritised to implement unique patient identifiers and leverage these

existing data sources to form interlinked health information systems to improve patient care and program monitoring.

6.7 References

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Chapter 7: Linkage to care, mobility and retention of HIV-positive postpartum women in antiretroviral therapy services in South Africa

Phillips TK, Clouse K, Zerbe A, Orrell C, Abrams EJ, Myer L. Linkage to care, mobility and retention of HIV-positive postpartum women in antiretroviral therapy services in South Africa. *J Int AIDS Soc*. 2018;**21**:e25114.

Relevance of this paper to the thesis:

This manuscript addresses issues of measuring retention as well as understanding factors that impact on retention in care postpartum. In particular it focuses on retention in care and mobility to access HIV care after leaving integrated antenatal and ART services after delivery. The paper highlights high levels of loss from care both at the initial transfer step and further along the cascade postpartum. It also shows that women access care in a wide geographic area and this clinic switching is not uncommon. This movement appears to be related to an increased risk of viraemia and this chapter highlights the need to support mobile patients in their HIV care and for data sources that are linked across health facilities to better monitor outcomes and intervene where needed.

Contribution of the student and co-authors:

TP conceived the design, conducted the analysis and drafted the manuscript. KC contributed to the study design and spatial analysis. All co-authors reviewed the manuscript and provided conceptual and intellectual comment. All authors were involved in the final draft of the manuscipt.

7.1 Abstract

Introduction: Linkage to care and mobility postpartum present challenges to long-term retention after initiating antiretroviral therapy (ART) in pregnancy, but there are few insights from sub-Saharan Africa. We aimed to describe postpartum linkage to care, mobility, retention and viral suppression after ART initiation in pregnancy.

Methods: Using routine electronic data we assessed HIV-specific health contacts and clinic movements among women initiating ART in an integrated antenatal care (ANC) and ART clinic in Cape Town, South Africa. The local care model includes mandatory transfer to general ART clinics postpartum. We investigated *linkage to care* after leaving the integrated clinic and *mobility* to new clinics until 30 months on ART. We used Poisson regression to explore predictors of linkage, *retention* (accessing care at least once at both 12 [6 to <18] and 24 [18 to <30] months on ART), and *viral suppression* (HIV viral load [VL] ≤50 and ≤1000 copies/mL after 12 months on ART).

Results: Among 617 women, 23% never linked to care; 71% and 65% were retained at 12 and 24 months on ART, respectively, with 59% retained in care at both times. Those who linked (n=485) accessed HIV care at 98 different clinics and 21% attended ≥2 clinics. Women >25 years, married/cohabiting or presenting early for ANC were more likely to link. Younger and unemployed women were more likely to attend ≥2 clinics (adjusted risk ratio [aRR] 1.10 95% confidence interval [CI] 1.02-1.18 and aRR 1.06 95% CI 0.99-1.12, respectively). Age >25 years (aRR 1.17 95% CI 1.02-1.33) and planned pregnancy (aRR 1.20 95% CI 1.09-1.33) were associated with being retained. Among 338 retained women with VL available, attending ≥2 clinics reduced the likelihood of viral suppression when defined as ≤50 copies/mL (aRR 0.81 95% CI 0.69-0.95). Distance moved was not associated with VL.

Conclusions: These data show that a substantial proportion of women do not link to postpartum ART care in this setting and, among those that do, long-term retention remains a challenge. Women move to a variety of clinics and young women appear particularly vulnerable to attrition. Interventions promoting linkage and continued retention for women initiating ART during pregnancy warrant urgent consideration.

7.2 Introduction

Population movement has received much attention in the context of the HIV epidemic [1,2]. Migration and mobility may be associated with HIV acquisition and providing HIV care to mobile populations presents particular challenges [3–6]. In South Africa, movement between rural and urban areas for employment, education, healthcare, cultural and family reasons occurs frequently, involving all demographic groups, including women of reproductive age [7–9].

Antiretroviral therapy (ART) during pregnancy and breastfeeding, and associated viral suppression, reduces mother-to-child transmission (MTCT), improves maternal health, and reduces sexual transmission [10]. However, these benefits hinge on women initiating ART, adhering to treatment, and remaining in care in the long term. Postpartum retention is a major challenge and there is an urgent need to understand how mobility may contribute to this [11–15].

In urban South Africa as well as other settings in sub-Saharan Africa, pregnant HIV-positive women who are not yet on ART start treatment during pregnancy in integrated clinics providing antenatal care (ANC) and HIV care including ART. Time in the integrated clinic after delivery varies, but ultimately women must transfer their HIV care and link to general ART clinics postpartum. Additional movement between healthcare facilities also occur due to relocation and patient choice. These movements may introduce challenges to the continuum of HIV care and maternal health services [3,4,16]. In South Africa, a recent analysis found that 38% of postpartum women who were considered lost to follow-up (LTFU) at the clinic of ART initiation were in care elsewhere, and 33% received care outside of the province where they started ART [13]. However, there are few data on the mobility of women with mandatory movement of ART care postpartum, and there is a need to understand the specific challenges related to linkage to care and mobility after delivery in these settings.

To address this, we explored continuity of care including linkage, geographic mobility and retention in care in a cohort of women who initiated ART in an integrated ANC-ART clinic. The objectives were i) to describe linkage to care after leaving the integrated clinic and additional mobility after linking and ii) to explore whether frequency or distance of clinic movement were associated with outcomes of retention in care and, in a subset of women, viral suppression.

7.3 Methods

Setting

This is a secondary analysis of women enrolled into the Maternal & Child Health – Antiretroviral Therapy (MCH-ART) study, which investigated optimal ART services for pregnant and postpartum women (ClinicalTrials.gov NCT01933477). This study was conducted at a large primary healthcare clinic in Cape Town, South Africa in an area with high rates of unemployment and poverty [17]. ANC coverage is high (~95%) and the antenatal HIV seroprevalence is approximately 30% [18]. The clinic serves over 4000 women annually from a wide catchment area. Women from neighbouring areas of Cape Town as well as from other provinces are known to access services here [19].

ART initiation and follow-up are provided with ANC by nurse-midwives throughout pregnancy. During the study period, ART eligibility was based on local public-sector guidelines (WHO stage III/IV disease or CD4 count ≤350 cells/μl until June 2013, and thereafter universal ART for pregnant women regardless of disease stage). All women initiated a fixed-dose combination of efavirenz, emtricitabine and tenofovir, and initiation usually occurred within a week of presentation for ANC. Per local standard of care, all women were transferred out to general ART services after delivery. They were provided with up to 3 months' supply of ART and a transfer letter to their new clinic, chosen based on preference or proximity to where a woman lived. Women were instructed to attend the new clinic before the end of her ART supply but no additional support for linkage occurs in this setting.

Data sources

Data for this analysis came from multiple sources. Retrospective data from available routine electronic data sources were assembled for all enrolled women through a minimum of 30 months on ART. Additional baseline data for all women, and for a subset of women additional prospectively collected data, were obtained from the parent study. The data sources are described in detail below.

The parent study methods have been described previously [20]. Briefly, between April 2013 and June 2014, 628 ART-eligible pregnant women were consecutively enrolled when they presented for ANC at the integrated clinic. Study measurement visits occurred prospectively through one month postpartum in all women and through 18 months postpartum in a subset

of breastfeeding women (n=471). Mandatory transfer out of the integrated clinic occurred at 6 weeks postpartum for most women per local standard of care. By study design, 233 women remained in the integrated clinic for up to 12 months postpartum (median 7 months, IQR 2-12). Data from the parent study provided details on baseline demographics, timing of ART initiation, delivery outcomes and last visit in the integrated clinic.

As part of the parent study, routine electronic health data were abstracted retrospectively through at least 30 months after ART initiation for all women (final data point December 2016). Data were abstracted from the National Health Laboratory Services (NHLS) database, which provides laboratory data for public health facilities in all provinces of South Africa. In addition, electronic data on pharmacy dispensing and clinic contacts, including facility recorded deaths were obtained from the Provincial Health Data Centre (PHDC) of the Western Cape Department of Health. These data are linked with a unique patient identifier and include all public health facilities in the Western Cape Province. Contacts at hospitals and other non-HIV services were excluded.

Measures

We brought together the above data sources to measure the following constructs. First, we defined *linkage to care* after leaving the integrated clinic based on evidence of at least one HIV-specific contact (routine ART clinic visit, antiretroviral (ARV) pharmacy refill or a CD4 cell count or HIV VL laboratory test) between the last visit at the integrated clinic and 30 months after ART initiation. Second, we assessed *mobility*, by determining the location and counting each clinic attended after leaving the integrated clinic. This was analysed as a binary variable of one versus ≥2 different clinics. Third, we created a global measure of *retention in HIV care* based on evidence of at least one HIV-specific contact at both 12 (6 to <18) and 24 (18 to <30) months after ART initiation at any clinic (including the integrated clinic for any women who linked to care prior to 30 months on ART but had not been transferred out of the integrated clinic by 12 months on ART). In sensitivity analyses we also examined evidence of HIV-specific contact at only 24 (18 to <30) months after ART initiation and at 18 (12 to <24) months postpartum. A 12-month window was used in all definitions as, although routine ART visits and ARV dispensing are expected more regularly, routine HIV laboratory results (our only nationally available data source) are only expected annually in this setting. Fourth, among women considered to be retained in HIV care, we investigated HIV *viral suppression* based on any HIV RNA VL taken nearest to 24 months on ART and at least 12 months after

ART initiation. These were primarily routine care VL results from the NHLS database. However, if no routine VL was found, available VL results from the MCH-ART study were used. VLs were found for 338 women; 61% from NHLS. VL thresholds of ≤50 and ≤1000 copies/mL were used to define suppression based on definitions of suppression and flags for treatment failure in the South African National ART guidelines [21].

Analysis

Analyses were conducted in STATA 14 (STATA Corporation, College Station, TX). Descriptive analysis used frequencies and proportions, means with standard deviations (SD) or medians with interquartile ranges (IQR) with chi-squared tests, Fisher's exact test, t-tests or rank sum tests as appropriate. ArcMap 10.3.1 (Esri, Inc., Redlands, CA, USA) was used to describe the spatial distribution of continued care after the integrated clinic. Multivariable Poisson regression models with robust standard errors were used to estimate the relative risk of each outcome [22]. Covariates that reached $p<0.10$ in bivariate analyses were included in model building using a step-wise approach. Although the parent MCH-ART trial intervention was not the focus of this analysis, the MCH-ART intervention did impact retention in HIV care at 12 months postpartum in the primary trial analysis [23] and some differences were seen for the retention outcomes in this analysis (Supplementary Table 9-7-6). To account for differences in subgroups of women who received continued prospective follow-up and/or delayed transfer out of the integrated clinic as part of the MCH-ART study, all multivariable models were adjusted for design status in the MCH-ART study in. Results are presented as crude or adjusted risk ratios (RR or aRR) with 95% confidence intervals (CI). In this exploratory secondary analysis which may not have had sufficient power to detect small associations, all associations reaching $p<0.10$ were discussed.

Ethics

All women included in this analysis completed written informed consent that included consent to review their routine medical records. Ethical approval was obtained from both the University of Cape Town Human Research Ethics Committee and the Columbia University Medical Centre Institutional Review Board.

7.4 Results

Among 628 women who initiated ART in pregnancy, eight women were found to have died and three to have relocated out of South Africa during the study period (up to 30 months on ART). These women were excluded from further analysis. Of the remaining 617 women, the mean age was 29 years (SD 5.3), 41% were married/cohabiting, 38% were employed and 26% had completed secondary school (Table 7-1). More than half the women (54%) were newly diagnosed with HIV in the incident pregnancy and 45% presented for ANC at ≤20 weeks gestation.

Linkage to care

Figure 7-1 describes the flow of access to HIV care after leaving the integrated clinic and Table 7-1 describes the characteristics among women who did and did not link to a new clinic after their last visit in the integrated clinic. There were 132 women (21%) with no evidence of linking to HIV care during the follow-up period. Of these, nine women were not seen after their first ANC visit. Among the 485 women who did link to care, 384 (79%) had evidence of attending one clinic, 85 (18%) linked to two and 16 (3%) linked to three different clinics (Figure 7-1). There were 20 women who moved and linked to a new ART clinic while still pregnant, while the remaining 465 women linked to a new clinic after delivery.

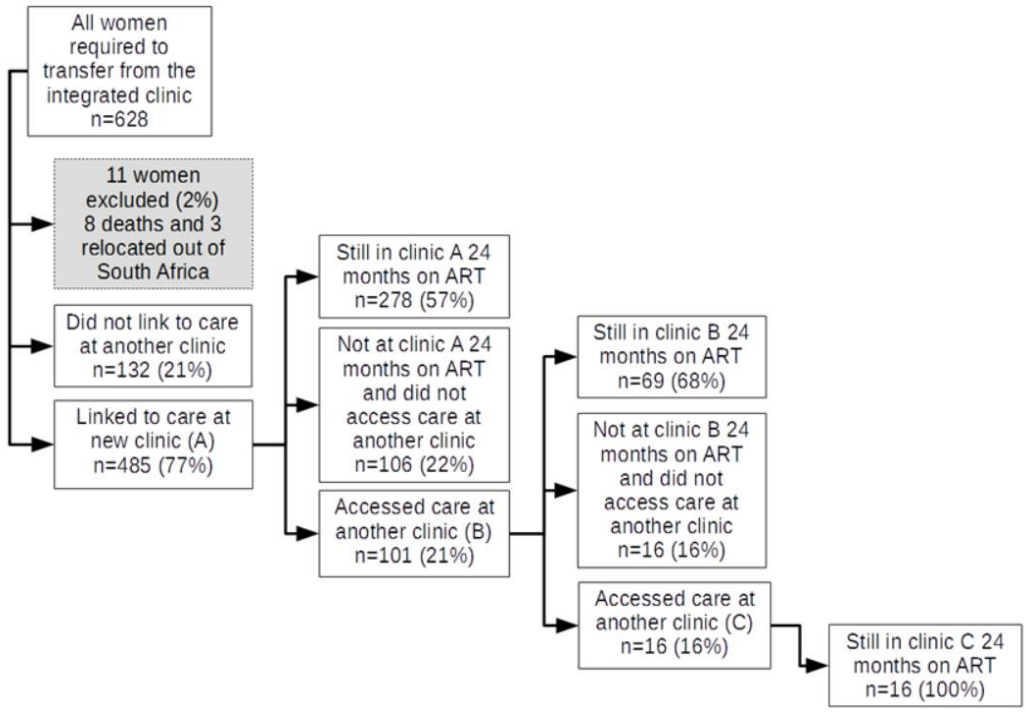

Figure 7-1 Flow of mobility for routine HIV care after leaving the integrated clinic through to 30 months after ART initiation.

Women who did not link to care during the follow-up period were slightly younger (mean age 28 versus 29), less likely to be married/cohabiting (28% versus 45%) and more often diagnosed with HIV in this pregnancy (61% versus 53%), compared to women who did link to care (Table 7-1). They also presented for ANC later (mean gestation 23 versus 21 weeks). The associations between successful linkage and age >25 years (aRR 1.11 95% CI 1.00-1.23), being married/cohabiting (aRR 1.13 95% CI 1.04-1.23) and presentation for ANC ≤20 weeks gestation (aRR 1.11 95% CI 1.02-1.20) persisted in multivariable models (Table 7-2).

Table 7-1 Description of 617 HIV-positive women who initiated ART during pregnancy, by linkage to HIV care after leaving the integrated clinic. Presented as n (%) unless specified.

	Linked to care	**Did not link to care**	**All women**	**p-value**
Number of women	485 (79)	132 (21)	617 (100)	
Median (IQR) months from ART initiation until last evidence of accessing care	28 (22-29)	4 (2-8)	26 (12-29)	<0.001
Characteristics at enrolment				
Mean age (SD)	29 (5.4)	28 (5.3)	29 (5.3)	0.015
Age ≤25	122 (25)	48 (37)	170 (28)	0.011
Married/cohabiting	216 (45)	37 (28)	253 (41)	0.001
Completed secondary school	124 (26)	39 (30)	163 (26)	0.358
Employed	182 (38)	52 (39)	234 (38)	0.695
First pregnancy	83 (17)	29 (22)	112 (18)	0.199
Intended pregnancy	146 (30)	35 (27)	181 (29)	0.422
Diagnosed with HIV in this pregnancy	255 (53)	81 (61)	336 (54)	0.072
Mean weeks gestation(SD)	21 (7.4)	23 (7.8)	21 (7.5)	0.005
Presented for ANC before 20 weeks gestation	231 (48)	47 (36)	278 (45)	0.014
Median (IQR) CD4 cell count at presentation for ANC (n=601)	342 (235-509)	386 (253-555)	345 (236-513)	0.110
Characteristics at delivery				
Place of delivery (n=597)				
Delivered in primary care	190 (41)	56 (43)	246 (41)	0.624
Delivered at tertiary hospital	277 (59)	74 (57)	351 (59)	
Delivery outcome				
Live birth	464 (96)	131 (99)	595 (96)	0.253
Stillbirth	11 (2)	1 (1)	12 (2)	
Miscarriage	6 (1)	0 (0)	6 (1)	
Unknown	4 (1)	0 (0)	4 (1)	

Table 7-2 Poisson regression model (n=617) predicting whether a woman linked to HIV care at any other clinic after the integrated clinic. Presented as unadjusted (RR) and adjusted (aRR) risk ratios with 95% confidence intervals (CI).

	Crude		**Adjusted**	
	RR	**95% CI**	**aRR**	**95% CI**
Age >25	1.13	1.02-1.26	1.11	1.00-1.23
Married/cohabiting	1.16	1.07-1.25	1.13	1.04-1.23
Diagnosed with HIV in this pregnancy	0.93	0.85-1.01	-	
Presented for ANC ≤20 weeks	1.11	1.02-1.20	1.11	1.02-1.20

Mobility

After leaving the integrated clinic, women accessed care at 98 different clinics across South Africa, excluding the integrated clinic. The median distance moved for initial linkage was 1 kilometre (km) (IQR <1-3, maximum 1271 km) and 95% of clinics initially linked to were in the Western Cape Province. After linkage, an additional 117 movements were observed and the distance between clinics increased with additional moves. The median distance of second (n=101) and third (n=16) move was 3 km (IQR 1-108) and 413 km (IQR 1-945) respectively, with 23% of the second and 25% of the third move being out of the Western Cape Province.

7.4.1 Overall, 270 women (56%) remained within the integrated clinic health district (clinics <5 km away), 157 (32%) moved out of the district but stayed in the Cape Town Metropole, 12 (2%) moved out of the region but stayed in the Western Cape, and 46 (9%) accessed care in other provinces (Supplementary Table 9-7-1Chapter 7

Supplementary Table 9-7-1). Figure 7-2 shows the geographic spread of clinics accessed A) within the Cape Town Metropole, and B) across South Africa.

Of 485 women who successfully linked to care after the integrated clinic, 101 women (21%) moved to ≥2 clinics (maximum 3) during 30 months of follow-up (Figure 7-1,Supplementary Table 9-7-1). Younger age and being unemployed were associated with moving to ≥2 clinics (aRR 1.10 95% CI 1.02-1.18 and aRR 1.06 95% CI 0.99-1.12, respectively; Supplementary Table 9-7-2). Total follow-up time from ART initiation to the last available clinic visit did not differ by movement frequency (median 28 months in both groups, p=0.787). However, women found at ≥2 clinics were more likely to ever access care outside of Cape Town (38% versus 5%) and had a greater maximum distance between clinics (median 4km versus 1km) compared to women who did not move again after linking.

Figure 7-2 Maps of clinics attended for HIV care after leaving the integrated clinic (A) within the Cape Town Metropole and (B) within South Africa.

Mobility, retention and HIV viral load

Of the 485 women who did have evidence of successfully linking after the integrated clinic, 438 (90%) and 398 (82%) women had evidence of being retained at 12 (6 to <18) and 24 (18 to <30) months after ART initiation, respectively (Supplementary Table 9-7-1). Evidence of retention at both 12 and 24 months was found for 363 women (75% of women who linked) (Table 7-3). When combining those who did not link to care after transfer (n=132) and those who linked but were subsequently LTFU (n=122), 71% (n=438) and 65% (n=398) of women were retained at 12 and 24 months after ART initiation, respectively; 59% (n=363) of women were retained in care at both time points.

Retention in care at both 12 and 24 months after ART initiation was associated with attending only one clinic, being >25 years old, being married, being employed, being multigravida, having a planned pregnancy and early presentation for ANC. The association with having a planned pregnancy (aRR 1.20 95% CI 1.09-1.33), age >25 years (aRR 1.17 95% CI 1.02-1.33) and presenting for ANC ≤20 weeks (aRR 1.10 95% CI 0.99-1.21) persisted in multivariable models (Supplementary Table 9-7-3). In sensitivity analyses, having a planned pregnancy was similarly predictive of retention at 24 months after ART initiation and at 18 months postpartum, and the association between being multigravida and being retained

maintained a similar effect size but reached statistical significance (Supplementary Table 9-7-3). Distance moved was not associated with being retained in care.

Table 7-3 Description of 485 HIV-positive women who linked to care after leaving the integrated clinic, by whether they were retained in HIV care at both 12 and 24 months after ART initiation. Presented as n (%) unless specified.

	Retained	**Not retained**	**All women**	**p-value**
Number of women	363 (75)	122 (25)	485 (100)	
Characteristics at enrolment				
Mean age (SD)	29 (5.4)	28 (5.2)	29 (5.4)	0.025
Age ≤25	81 (22)	41 (34)	122 (25)	0.013
Married/cohabiting	173 (48)	43 (35)	216 (45)	0.017
Completed secondary school	93 (26)	31 (25)	124 (26)	0.963
Employed	144 (40)	38 (31)	182 (38)	0.093
First pregnancy	56 (15)	27 (22)	83 (17)	0.089
Intended pregnancy	124 (34)	22 (18)	146 (30)	0.001
Diagnosed with HIV in this pregnancy	184 (51)	71 (58)	255 (53)	0.151
Mean weeks gestation (SD)	20 (7.2)	23 (2.6)	21 (4.4)	0.001
Presented for ANC ≤20 weeks	184 (51)	47 (39)	231 (48)	0.020
Median (IQR) CD4 cell count at presentation for ANC (n=474)	336 (235-499)	346 (242-537)	342 (235-509)	0.269
Characteristics at delivery				
Place of delivery (n=467)				
Delivered in primary care	141 (40)	49 (42)	190 (41)	0.694
Delivered at tertiary hospital	210 (60)	67 (58)	277 (59)	
Delivery outcome				
Live birth	349 (96)	115 (94)	464 (96)	0.042
Stillbirth	7 (2)	4 (3)	11 (2)	
Miscarriage	6 (2)	0 (0)	6 (1)	
Unknown	1 (<1)	3 (2)	4 (1)	
Characteristics postpartum				
Median (IQR) months from ART initiation until last evidence of accessing care	29 (27-29)	15 (9-22)	28 (21-29)	<0.001
Number of clinics after the integrated clinic				
Attended 1 clinic	278 (77)	106 (87)	384 (79)	0.015
Attended ≥ 2 clinics	85 (23)	16 (13)	101 (21)	
Median furthest distance (km) moved between clinics	1.07 (0.69-3.23)	1.07 (0.01-7.87)	1.07 (0.69-3.23)	0.868
Area moved after integrated clinic				
Same health district	207 (57)	63 (52)	270 (56)	0.252
Cape Town Metropole	117 (32)	40 (33)	157 (32)	
Western Cape Province	10 (3)	2 (2)	12 (2)	
Out of the Western Cape Province	29 (8)	17 (14)	46 (9)	

VL measures at least 12 months after ART initiation were available for 338 of 363 women (93%) who were retained in HIV care at both 12 and 24 months after ART initiation (Supplementary Table 9-7-4). There were 273 (81%) and 294 (87%) women who were virally suppressed ≤50 and ≤1000 copies/mL, respectively (Supplementary Table 9-7-4 and Supplementary Table 9-7-5). Attending ≥2 clinics reduced the likelihood of having a VL ≤50 copies/mL in multivariable models (aRR 0.81 95% CI 0.69-0.95); this association was not statistically significant for VL ≤1000 copies/mL (Table 7-4). Being diagnosed with HIV in the current pregnancy was associated with having a VL ≤50 and ≤1000 copies/mL at least 12 months after ART initiation. Age >25 years predicted VL ≤50 copies/mL and being married/cohabiting or employed were predictive of having a VL ≤1000 copies/mL in multivariable models (Table 7-4).

Table 7-4 Poisson regression model among 338 women who were retained in care and had a VL available at least 12 months after ART initiation, predicting A) VL ≤50 copies/mL at least 12 months after ART initiation, and B) VL ≤1000 copies/mL at least 12 months after ART initiation (n=325 with data complete). Presented as unadjusted (RR) and adjusted (aRR) risk ratios with 95% confidence intervals (CI).

	Crude		**Adjusted**	
A: VL ≤50 copies/mL at least 12 months after ART initiation				
	RR	**95% CI**	**aRR**	**95% CI**
Attended ≥2 clinics after the integrated clinic	0.80	0.68-0.94	0.81	0.69-0.95
Age >25	1.18	1.01-1.38	1.17	1.01-1.36
Completed secondary school	1.11	1.00-1.23	-	
Married/cohabiting	1.10	0.99-1.21	-	
Planned pregnancy	1.09	0.99-1.21	1.10	0.99-1.21
Presented for ANC <20 weeks gestation	1.06	0.96-1.18	-	
Diagnosed with HIV in this pregnancy	1.15	1.03-1.27	1.15	1.04-1.28
Employed	1.13	1.02-1.25	1.08	0.98-1.19
B: VL ≤1000 copies/mL at least 12 months after ART initiation				
	RR	**95% CI**	**aRR**	**95% CI**
Attended ≥2 clinics after the integrated clinic	0.91	0.81-1.02	0.92	0.82-1.03
Age >25	1.14	1.00-1.29	1.10	0.97-1.24
Completed secondary school	1.08	0.99-1.17	-	
Married/cohabiting	1.14	1.05-1.23	1.14	1.06-1.24
Planned pregnancy	1.10	1.02-1.19	-	
Presented for ANC <20 weeks gestation	1.08	0.99-1.17	-	
Diagnosed with HIV in this pregnancy	1.08	0.99-1.17	1.10	1.01-1.19
Employed	1.13	1.04-1.22	1.12	1.04-1.21

7.5 Discussion

This unique study describes outcomes over 30 months of follow-up for a cohort of women who initiated ART in an integrated ANC and ART clinic and who were required to transfer ART clinics after delivery. Overall, 20% of women did not link to a new clinic within 30 months of ART initiation and an additional 21% were subsequently LTFU after linking. Cumulatively, 41% of women were not retained in care at both 12 and 24 months after ART initiation. Younger women emerged as consistently at risk for not linking to care, non-retention, non-suppression and attending ≥2 different clinics.

Our findings add to the limited literature on retention of postpartum women in Africa beyond 12 months on ART [15]. Overall retention at 12 and 24 months after ART initiation (71% and 65%, respectively) were broadly comparable to reports from other parts of sub-Saharan Africa. A recent study from Malawi, using a more stringent definition of retention, found that 77% and 71% of women were retained at 12 and 24 months on ART, respectively [11]. In data from Zimbabwe and Mozambique, only 68% and 42% of women were still receiving ART 12 months after ART initiation [24,25]. A recent systematic review found a pooled estimate of 76% retained at 12 months on ART in African cohorts [15]. Reported retention in HIV care is often facility specific. Individuals who are transferred to new clinics are often considered retained in care, censored at the time of transfer or excluded from analyses [26,27]. In contrast, our results are from a cohort where all women were required to transfer care and access to HIV care was traced to any routine primary healthcare clinic in South Africa. It is of concern that, even after tracing women's movement to different clinics, 41% of women were not retained through 12 and 24 months after ART initiation. Importantly, women who never linked to care after the integrated clinic accounted for half the LTFU seen in our cohort. This highlights the need to incorporate support for linkage to care where movement between ART clinics after delivery is required.

Current infant feeding guidelines recommend that HIV-positive women breastfeed their children for up to 24 months postpartum, making continued postpartum retention critical not only for maternal health and sexual transmission, but also to prevent MTCT in the breastfeeding period [21,28]. Breastfeeding status and access to routine child health services, although not indicators readily available in routine data systems, may impact maternal mobility and engagement in HIV care. In addition, routine child health services are very well attended in many settings and could provide opportunities to re-engage mothers who fail to link or are LTFU from HIV care.

Despite concerning retention levels, these results showed reassuring levels of viral suppression among women who were retained in care in this cohort. Our results suggest that increased clinic movement could be associated with increased risk of viremia. However, we were unable to ascertain viral load outcomes for women who were not retained in care and therefore cannot conclusively determine the impact of mobility on HIV viral load. Younger age was a shared risk factor for not linking to care, more frequent mobility, non-retention and raised VL. This adds to the substantial evidence indicating that younger HIV-positive women are often at increased risk for poor treatment outcomes [15,29–33]. Although associations were small, younger age, timing of presentation for ANC and relationship status could flag women requiring additional support to link to care postpartum. Primigravity and unplanned pregnancy, previously linked to adverse maternal and child outcomes [34,35], may also flag women requiring targeted retention interventions. Although the impact of pregnancy intention on long-term ART outcomes is not clear, optimizing family planning services for both HIV-positive and negative women remains a vital component of strategies to prevent MTCT and improve maternal and child health. Importantly, interventions are needed not only at ART initiation facilities but also beyond the facility to promote continued retention in care when mobility is necessary.

Women accessed care at a variety of different clinics. Although some clinics provide combined appointments for HIV-positive mothers and their children, many require different appointments for maternal ART and routine child health and quite often these services are offered at different clinics. We were unable to systematically assess each model of care, but this should be a consideration in future work. The clinic movement seen in this analysis has further implications for linking mother-child pairs and monitoring long-term child and maternal outcomes. In both routine programmes and research cohorts, retention in ART care is frequently based on whether an individual is still receiving care from the clinic at which they started treatment [36–38]. A review of studies in low- and middle-income countries that actively traced patients to ascertain their status, showed a pooled estimate of 19% of adults considered LTFU were continuing care at other clinics [39]. Although the most recent World Health Organisation recommendations for monitoring include using unique patient identifiers to allow linkage across health services, this is not a reality in many settings [40]. Availability of facility-linked data and the choice of data sources used will impact the ability to monitor long-term outcomes of women on lifelong ART and their children [41].

The results of this analysis should be interpreted with the following additional caveats in mind. Although a strength of this study is the availability of diverse data sources throughout the Western Cape Province and nationally for evaluating evidence of engagement in care, not all contacts with the health system are captured into routine electronic databases which could lead to underestimation of retention. Attempts were made to ascertain vital status using clinic records, but unknown deaths may contribute to non-linkage and non-retention. Both a strength and limitation is that these results are applicable to a cohort of women required to transfer their ART care after delivery. We were unable to classify additional mobility after linkage and outcomes may vary between formal clinic transfers and patient-initiated mobility.

Another important limitation of this analysis is that the same data sources were used to define mobility and retention in care and the mobility patterns among women who were not observed to be in care cannot be known. Surprisingly, employment was not strongly associated with mobility or any of the outcomes in this study [2,42]. This is likely a limitation of the measure which only assessed employment status at entry into ANC. Women may have returned to or started work after delivery with possible impacts on both mobility and HIV care access. Studies which can assess mobility independently from access to routine health services and which can assess changing risk factors such as employment and relationship status over time, will be required to further understand postpartum mobility and the impact on ART outcomes.

These data add important insights regarding mobility and retention in care in postpartum women up to 30 months after ART initiation in pregnancy. The step of moving care between clinics is a vulnerable step in the HIV care continuum and even women who manage to link successfully, particularly younger, unmarried women and those who present late for ANC, remain vulnerable to subsequent LTFU and viremia. Models of care to provide ART to pregnant and postpartum women need to accommodate women's mobility and where they choose to access care. Facility-based interventions may not be sufficient to support postpartum retention. For example, South African differentiated models of care and mobile health (mHealth) interventions are starting to provide non-facility-based support for mothers [43,44]. Further consideration is needed on how continuous support for engagement in care can be provided as mothers living with HIV continue with their daily lives after delivery.

7.6 Conclusions

We found that less than two thirds of women who started ART in an integrated ANC-ART clinic were retained in care at both 12 and 24 months after ART initiation. Losses occurred at the initial mandatory postpartum transfer and after successful linkage to care. Women who linked to care attended a wide range of facilities creating challenges for monitoring postpartum outcomes. Based on these data there is a clear and urgent need for interventions that extend outside of health facilities to help support postpartum women, and young mothers in particular, to remain engaged in lifelong ART care.

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Chapter 8: Discussion and recommendations

8.1 Synopsis of key findings

8.1.1 Introduction

This chapter provides a synopsis of the key findings of this thesis as a combined body of work, the overarching limitations, and recommendations for policy and future research. The results included in this thesis come from a cohort of women living with HIV who initiated antiretroviral therapy (ART) during pregnancy in Gugulethu, South Africa in 2013 and 2014. Most of the cohort started ART under Option B+, the policy of universal ART for pregnant and breastfeeding women. That makes this one of the first universal ART cohorts in the South African public sector and the findings offer novel insights into engagement in care following ART initiation in pregnancy under this policy. Some of the results that have been presented are also applicable to other populations on ART and provide lessons that can be extended to universal ART for all people living with HIV.

To avoid repetition, presented here are the discussion points raised when considering the whole body of work included in this thesis, placing these in the context of relevant publications on maternal engagement in HIV care in sub-Saharan Africa (SSA). The discussion will focus on five themes that emerge across the results chapters: i) substantial disengagement from HIV care after ART initiation in pregnancy, ii) specific considerations among women starting ART in pregnancy around ART side effects, mobility and transfer of HIV care, iii) approaches to measuring ART adherence, iv) considerations for measuring retention in HIV care, and v) opportunities to support long-term engagement in HIV care.

8.1.2 Substantial disengagement from HIV care after ART initiation in pregnancy

The UNAIDS 90-90-90 targets aim to have 90% of people living with HIV know their status, 90% of those who know their status remaining on ART, and 90% of those on ART virologically suppressed [1]. In 2017, it was estimated that 79% of people who knew their HIV status globally were on treatment; in South Africa, 68% of those who know their status are estimated to be on ART and 78% of those on ART are suppressed [2]. The gap to achieving the second 90, remaining on ART, is made up of both people who do not link to care after diagnosis and people who successfully start ART but are lost from care. Successful linkage to treatment following an HIV diagnosis, combined with improved HIV testing, is a

critical focus for achieving the 90-90-90 targets and has been identified as a key weak point [3]. However, given the scale-up of testing and treatment with universal ART and high rates of loss to follow-up (LTFU) reported in all populations, the proportion of those who start ART but are not retained in care is likely to be substantial [4,5]. This group has received less attention than linkage to treatment in the context of the UNAIDS targets and these two components are usually not disaggregated in 90-90-90 estimates [3,6]. Similarly, the gap to reach the third 90, viral suppression, also has multiple components including poor medication adherence, viral loads not completed and ART resistance. The components of retention in care and adherence to ART, together termed engagement in HIV care, were the focus of this thesis.

The combined results of this thesis highlight substantial disengagement from care, both in the form of poor medication adherence as well as non-retention. In Chapter 3, almost a third of women reported at least one missed ART dose during pregnancy [7]. In the validation of the three-item self-reported adherence scale among pregnant and early postpartum women (Appendix 9.3), over 90% of women were virologically suppressed but almost all women reported some adherence difficulty [8]. In Chapter 5 we observed declining proportions of viral suppression over time, mirroring the trend in retention observed using 6-month visit constancy in Chapter 6. Results from Chapter 7 showed that only 59% of women had evidence of accessing routine HIV care around both 12 and 24 months on ART [9] and in the subset of women in Chapter 4 (median four years on ART), 30% of women had no detectable antiretrovirals (ARVs) and 28% had viral loads above 1000 copies/mL. Viral load data from the same cohort restricted to women who had ever suppressed showed that only 70% of women maintained viral suppression through one year postpartum (Figure 8-1) [10]. These combined findings align with data from other settings demonstrating high rates of LTFU and viremia after ART initiation in pregnancy [5,11–13].

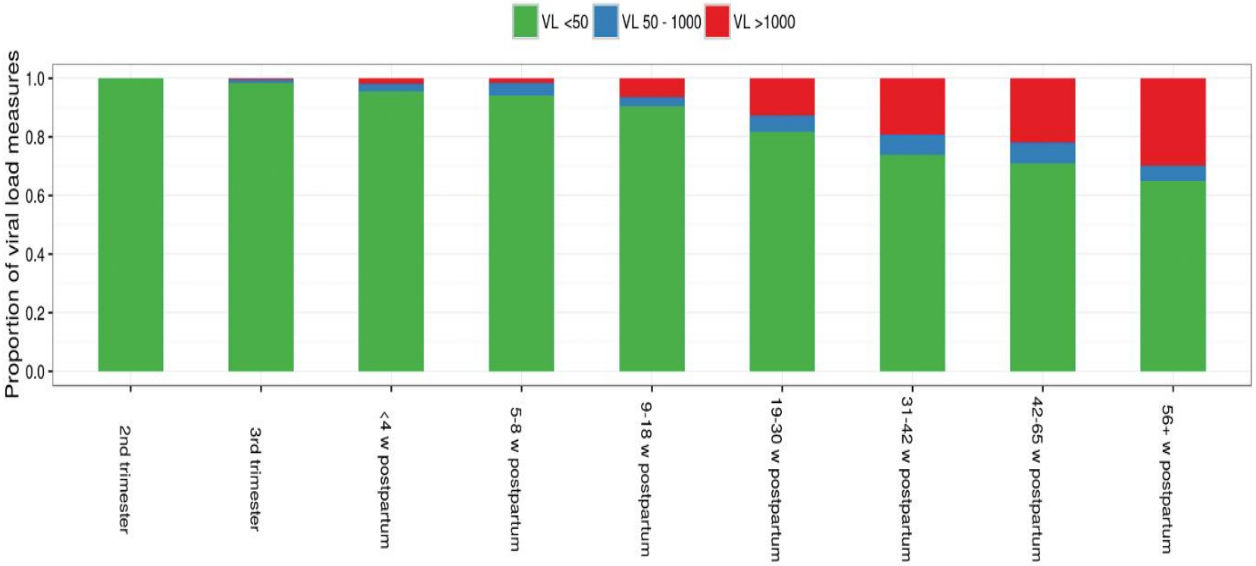

Figure 8-1 The distribution of viral loads <50, 50-1000 and >1000 showing an increasing proportion of viremia over time among women in the MCH-ART cohort who ever suppressed in pregnancy, from Myer *et al* [14].

The data presented in this thesis add to a small but growing literature reporting on longer-term outcomes of women who initiated ART in pregnancy. In Chapter 2, seven studies were identified that reported on adherence or retention at or after two years on ART [12,13,15–19]. Retention at around 24 months on ART was estimated in six studies. All studies used facility-specific data sources although some actively traced patients considered LTFU to ascertain their outcomes. All studies used gap in care definitions and time-to-event analyses with the proportion retained as follows: 53% in eSwatini (not retained if ≥4.5 months with no visit) [15]; 59%, 71% and 74% in Malawi (lost if >60 days late for a visit) [12,13,20]; 78% in Ethiopia (lost if >90 days with no visit) [16]; 91% in Uganda (lost if >3 months with no visit) [17]. Retention through 24 months on ART in this thesis was 37% (95% CI 33-41) when non-retained was defined as 150 days (or five months) with no visit (Chapter 6). This is lower than reported in eSwatini with a similar definition but where women were censored if they transferred to a new clinic [15]. In Chapter 7, using a more conservative, cross-sectional retention definition of any routine HIV contact between 18 and 30 months on ART, 65% of women were considered retained [9]. Only one published study has reported on ART adherence through 24 months on ART or longer in this patient population: in an observational

cohort in Malawi with adherence measured using pharmacy refill data, only 67% of women who started ART in pregnancy had ≥90% medication coverage over the two year period [12]. It was not possible to measure medication coverage in this thesis due to inconsistency in the availability of pharmacy refill data, but only 48% of women had evidence of any routine HIV care contact at least once in every 6-month window from ART start to 24 months on ART (Chapter 6). Moreover, in the subset of women with drug concentrations at 3-4 years postpartum (median four years on ART), only 70% had any detectable antiretrovirals (Chapter 4).

According to modelling estimates, reaching the 90-90-90 targets by 2020 will result in the end of the HIV epidemic by 2030 [1], but these targets require people not only to test for HIV and link to treatment services, but to stay retained in HIV care and adherent to ART to ensure sustained virologic suppression. Thus, the observed level of disengagement from care is concerning for several reasons. First, there is ongoing risk of HIV transmission during pregnancy and postpartum through breastfeeding in the incident and future pregnancies. Over the past decade, with the phenomenal success of ART for PMTCT, the incidence of new HIV infections in children has dropped substantially [21], but an increasing proportion of all new infections in children are now due to postpartum transmission through breastfeeding [22]. Second, disengagement results in increased risk of transmission of HIV to HIV-uninfected partners, removing the benefit of reduced HIV incidence at a population level. Finally, and importantly, sustained engagement in ART services is crucial to optimize maternal health. This is necessary to ensure that mothers live long healthy lives and can support their families. In these ways, poor engagement in HIV care threatens the potential individual-, family- and population-level benefits of lifelong ART [23].

The results of this thesis also provide some additional insight into the timing of loss from care. Chapter 7 showed considerable LTFU after transferring out of the integrated antenatal care (ANC) and ART clinic [9]. Previously the literature has shown that many women are lost from care shortly after delivery or cessation of breastfeeding [16,24–26] which may be due to a shift in motivation to remain engaged in care when transmission to the child is no longer a risk [26–28]. The results from this thesis suggest that the structure of the health service and the timing of transfer out of integrated antenatal and ART services may also have an impact on the timing of loss from care. Integration of services presents an opportunity to sustain engagement in care during pregnancy and breastfeeding [29–32], but may delay disengagement to a later point in time [33–35]. Careful consideration of the approach to and

impact of transferring care into and out of integrated maternal and child health services is required.

Disengagement from care during pregnancy and postpartum presents a risk for perinatal or postnatal transmission and, as noted above, most research and interventions to date have focused on this period [5,36]. However, in order to ensure that the benefits of lifelong ART are sustained for subsequent pregnancies, for maternal health and for prevention of sexual transmission, support strategies can no longer focus only on the immediate outcomes of vertical transmission of HIV during pregnancy, delivery and breastfeeding [37]. Rather it will be essential to shift focus to sustained engagement in lifelong ART services.

8.1.3 Specific considerations among women starting ART in pregnancy around ART side effects, mobility and transfer of HIV care

Many barriers to engagement in HIV care exist across population groups: experience of and fear of experiencing ART side effects are known barriers to ART adherence in adult and adolescent cohorts [38,39]; mobility has historically been investigated as it relates to HIV transmission [40] but movement and travel are increasingly being recognised as barriers to continued engagement in ART services [41–44]; transferring the location of HIV care was found to be a barrier to ART uptake in pregnancy prior to a move towards integrated ANC and ART services [45] and has been noted as a vulnerable time for disengagement when transitioning young people from paediatric to adult ART services [46]. Each of these considerations have also been posited as barriers to ongoing maternal adherence and retention in HIV care, yet at the time of starting this thesis, quantitative analyses of these risk factors in maternal ART cohorts were lacking. Different populations may experience or respond to similar risk factors differently. The results of this thesis highlight some of the ways women who start ART in pregnancy may be particularly vulnerable to these factors and their effects.

ARV regimens and side effects

Results of Chapter 3 aligned with existing evidence that ART side effects are associated with poor medication adherence [27,47–50]. At the time this thesis was conceived, efavirenz (EFV)-based first-line ART regimens were recommended for all adults, including pregnant and breastfeeding women [51]. Side effects from first-line ART regimens are usually thought to be short-lived, however for women starting ART in pregnancy, these early side effects may be exacerbated by or experienced in combination with normal physical symptoms

experienced in pregnancy. With EFV specifically, there has also been concern raised about the impact of central nervous system (CNS) side effects [52,53]. The analysis presented in Chapter 3 is a unique quantitative exploration of patterns of self-reported side effects and the associations between specific groups of reported side effects and ART adherence. Almost all women (97%) in the cohort reported at least one side effect during pregnancy on an EFV-based first-line regimen; 26% of the cohort fell into a high overall side effect group [7]. CNS side effects were the most common but alone they were not associated with an increase in missed ART doses. Notably, the results showed that it was the overall burden of self-reported side effects, rather than side effects affecting a specific system, that was associated with adherence. In pregnant women, and possibly other populations with comorbidities, the overall burden of side effects, regardless of underlying cause, may impact on adherence to ART.

Side effects from EFV may also be heightened by slow EFV metabolism. In African populations, genetic polymorphisms resulting in slower EFV metabolism and higher concentrations of EFV in the body are relatively common and have been shown to be associated with an increase in adverse effects [54–56]. Although this thesis did not examine genetic polymorphisms in this population, among the subset of women at 3-4 years postpartum (n=137 in Chapter 4), 15% of those with any detectable EFV (11% overall) had EFV concentrations above 4µg/mL, possibly indicating slow EFV metabolism [55]. This proportion may be higher among the women who had discontinued ART. Due to concerns about toxicity and potential cost reduction, the ENCORE-1 trial investigated the efficacy of 400mg EFV compared to the standard 600mg dosing and found it to be non-inferior with fewer EFV-related adverse events reported [57]. Additional studies are underway but the evidence for use in pregnant women is not yet thought to be sufficient [58] and genotype testing to inform EFV dosing is unlikely to be possible in most settings.

New, more tolerable ARVs are becoming available, but side effects are unlikely to be eliminated. Dolutegravir is widely being rolled out in first-line regimens in low- and middle-income countries [59–61]. It has far superior tolerability and efficacy to suppress viral load than other first-line ARVs [58,62], but mild side effects such as headaches and insomnia may still occur with dolutegravir and concerns remain about safety during the first trimester of pregnancy [62–64]. Currently EFV-based regimens are still recommended for women who are <8 weeks pregnant or who plan to conceive [60]. Although promoting early ANC attendance is a priority, only 25% of women presented for ANC before 12 weeks gestation in SSA in 2013 [65] and in the cohort evaluated in this thesis the average time of presentation

for ANC was 21 weeks gestation. Thus, most women initiating ART in pregnancy will be able to start on dolutegravir instead of EFV. However, very high rates of unplanned pregnancy, around 44% globally [66] and up to 70% in African cohorts [9,67–69], raise broader concerns about dolutegravir use among women of reproductive age while safety in early pregnancy is still being determined.

Regardless of ARV regimen, it is possible that normal pregnancy symptoms, or symptoms and side effects from other conditions or medication, could be perceived as ART side effects regardless of the true tolerability of the regimen. During pregnancy specifically, women may have heightened awareness of their health and the safety of their unborn child, thus the association between perceived ART side effects and ART adherence may persist. These findings call for focused counselling specific to ART- and pregnancy-related side effects at the time of ART initiation and follow-up visits. This point is discussed further in Section 8.1.6.

Mobility and transfer of care

Movement between ART clinics can occur due to relocation, personal preference, or through mandatory transfer required by the model of care. Mobility in South Africa is common with high levels of migration between rural and urban areas [70–72]. Historically under apartheid, "non-whites" were forced to migrate to economically profitable areas to work although they had to reside in rural areas. At this time, movement was difficult, highly regulated and strongly male dominated [71]. Following the transition to democracy after 1994, movement across South Africa became much easier and now women and men migrate equally across the country [71,73]. Between 2001 and 2011, 59% of in-migrants into the Western Cape province were female [72]. Today, people move around South Africa freely but often remain strongly connected to the geographic areas where they were born or grew up. There is evidence in the adult ART literature that mobility, either short-term travel or relocation, can impact on treatment adherence and retention in care [41–43,74]. Mobility has also been reported as a reason for disengagement from care in qualitative studies of pregnant and postpartum women [49,75,76] and travel from urban to rural areas to be with family and for cultural practices is common after delivery [71,76,77].

Apart from being a barrier to engagement in HIV care, mobility also presents a challenge for measuring this construct. We know from adult ART cohorts, and more recently from maternal ART cohorts specifically, that a substantial proportion of patients considered LTFU

may be actively in care at another ART clinic [78–80]. Most analyses that have traced women's outcomes to other clinics have been restricted to women considered LTFU [49,79,81]. Although the analyses presented in this thesis were not able to evaluate mobility independently of accessing HIV care, they provide novel and important insight into mobility to access HIV care among an entire cohort of women who started ART in pregnancy. The findings that the women who linked to care spread to nearly 100 different ART clinics, that 21% moved two or more times and over 40% moved outside of the health district where they started ART, highlight high levels of mobility to access HIV care in this setting [9]. This confirms findings from a cohort in Johannesburg, South Africa showing both local clinic switching and long distance mobility postpartum [79].

Transferring care, as required by different models of care for providing ART services, is another reason for moving between clinics and can be associated with disengagement. Previous work in Gugulethu, prior to the roll out of Option B+, found that up to 25% of women transferred out of the integrated ANC and ART clinic postpartum did not have evidence of accessing care at a new clinic within a year of transfer using just laboratory data [35]. The results of Chapter 7, using combined routine data sources, provide new insights into loss from care after leaving an integrated ANC and ART clinic. In this cohort, 21% of women who had started ART in pregnancy had no evidence of linking to a routine ART clinic, excluding known deaths and relocations out of the country [9]. Infant feeding guidelines in South Africa follow the World Health Organization (WHO) recommendation of breastfeeding for at least 12 months yet transfer out of integrated services in South Africa occurs routinely at 6-10 weeks postpartum, making this finding particularly important for potential postnatal HIV transmission [82]. Some countries, including Malawi, Zimbabwe and Mozambique, extend integrated antenatal and ART services to provide integrated child health and maternal ART services for one to two years after delivery [33,49,83]. This model of care still usually requires transfer of ART care postpartum, and few studies have traced outcomes beyond transfer out of integrated postpartum maternal and child health services. Moreover, the optimal approach and timing of transferring care from integrated maternal and child health services to general ART services is unclear and requires investigation.

Transfers and mobility, in the absence of interlinked data sources, make it difficult to link mother-baby pairs and therefore to monitor or intervene in both maternal and child health outcomes. As noted in Chapter 6 and discussed further in Section 8.1.5, there are a number of important considerations when deciding on the data sources and definitions to use when

measuring retention. For maternal cohorts, the use of data that can be linked across ART clinics is critical to be able to account for mandatory transfers and mobility between clinics for other reasons. Knowing which women are in care, regardless of which clinic they are attending, will ensure that resources can be focused on re-engaging women who are truly LTFU.

8.1.4 Approaches to measuring ART adherence

Poor adherence to ART is the primary reason for virologic failure and remaining adherent is critical to treatment success [84,85]. There are numerous ways to measure treatment adherence, all of which have pros and cons and none of which provide a perfect measure [86–90]. Self-reported adherence is prone to bias and often overestimates adherence [91], and this thesis confirms that self-report is not an ideal adherence measure. Compared to drug concentrations, which are the most objective measure of actual exposure to ART, self-reported adherence had worse ability to predict viral suppression. However, despite the issues with self-reported adherence, it is simple, immediate and inexpensive to measure. Until more reliable adherence measures are found that share these desirable characteristics, it is likely that self-reported adherence measures will continue to be used in routine and research contexts and ways to improve self-report measures are needed.

The three-item self-reported adherence scale used in Chapters 4 and 5 [92,93], after validation for use in South Africa (presented in Appendix 9.3) [8] , did perform better than other self-report measures, reducing the commonly observed ceiling effect and resulting in greater variability of responses than reported using other measures [89,94,95]. In cross-sectional analyses, the three-item score was associated with viral load but was only moderately able to discriminate between women with and without viral suppression.

Part of the challenge of self-reported measures is that they reflect an individual's perception of their own medication taking behaviour and their own biases. Longitudinal measures of self-reported adherence may be able to take some of this into consideration by measuring changes in reported adherence relative to the individual's baseline reporting. The results of Chapter 5 show that a decrease in self-reported adherence, using the three-item scale described in Appendix 9.3, could predict viremia and perhaps overcome some of the issues with cross-sectional measures. A decrease in reported adherence across two consecutive visits was found to be consistently associated with viral load, with the strongest association observed among women who were virally suppressed at the first visit. Unfortunately, this

thesis was unable to assess the value of change in self-reported adherence over time in comparison to drug concentrations as drug concentrations were only measured at the LACE study visit, 3-4 years postpartum. These results present an innovative proof of concept for the use of change in self-reported adherence as a flag for viremia. This novel approach requires additional investigation as an interim adherence measure within routine settings with limited access to viral load or drug concentration measures.

Chapter 4 showed, in line with previous research, that ARV drug concentrations in plasma and dried blood spots (DBS) are the best approach to measuring adherence and far outperform the cross-sectional self-reported adherence measure when predicting viral load. Tenofovir-diphosphate (TFV-DP) concentrations measured in DBS are a novel approach to measuring drug concentrations that have been used widely to measure adherence to pre-exposure prophylaxis (PrEP) among individuals without HIV. Only a few studies have reported on TFV-DP in DBS to measure ART adherence among people living with HIV, and the results presented in Chapter 4 are the first to report on the association between TFV-DP concentration in DBS and viral load among a cohort of African women. The results support the findings of a recent study reporting a strong association between TFV-DP in DBS and viral suppression among people living with HIV in the United States [96], showing a similar dose response relationship between TFV-DP DBS concentrations and viral suppression. Although the analyses presented in this thesis were unable to match TFV-DP concentrations in DBS to actual doses taken, TFV-DP in DBS has been shown to provide insight into medication taking behaviour in the past 17 days [97,98]. Just as we often attempt to gather information on adherence in the past week or 30 days using self-reported measures, the longer half-life of TFV-DP in DBS provides a more nuanced understanding of ART adherence than plasma TFV or EFV levels which are informative about ART doses taken only in the past 4-5 days [99,100]. In Chapter 4, plasma EFV and TFV did not display the same dose-response relationship with viral suppression but had similar ability to TFV-DP in DBS to discriminate between women who were and were not virologically suppressed. This is notable as plasma drug concentration assays, although complex and costly relative to self-report measures, are simpler and less expensive to run that TFV-DP assays in DBS and thus may be suitable interim adherence measures in settings with access to adequate laboratory resources. The technology for measuring drug concentrations is developing rapidly and options such as point of care urine assays may be available soon [101,102]. Advancements in cost and availability of drug concentration assays will make real-time adherence

measurement and immediate counselling or intervention a possibility, even in resource-limited settings.

While TFV-DP DBS concentrations are clearly the ideal measure of adherence for research settings, and plasma concentrations may provide a viable alternative, drug concentration assays are still unlikely to be rolled out in routine care in limited resource settings due to expense and the need for laboratory-based analyses. Thus, simple and inexpensive options of measuring ART adherence are still needed, and longitudinal self-report is one possibility for future consideration.

8.1.5 Considerations for measuring retention in HIV care

Retention in care is a key marker of the success of ART programmes. It is often measured for patient and programme monitoring as well as for research outcomes. The combined work of this thesis highlighted two important components to consider when measuring retention: the ascertainment of outcomes beyond a single facility and the choice of data sources used.

Ascertaining outcomes beyond a single facility

Facility-specific retention – the proportion of patients who start ART at the facility, or have been in care at the facility, who are still in care at the same facility – is commonly reported in the literature (Chapter 2:Table 2-1). Patients who have been transferred to other clinics may be excluded from analyses, censored or occasionally assumed to be retained in care. It is known that not all patients successfully link to a new clinic after transfer while others who do, do not always link to the intended clinic [35,103,104]. Patients are also known to sometimes "silently" transfer, or move their care to a new clinic without a documented transfer [79,80,105–107]. As noted in Chapter 2 and Section 8.1.3 above, transfers of care are often inevitable in the context of maternal ART and the timing and nature of the transfer varies across settings. The results of Chapter 7 also demonstrate that, in an urban area with a high density of ART clinics, women spread to a large number of different facilities to continue their ART care after delivery [9]. Measuring facility-specific retention, without accounting for outcomes following documented and "silent" transfers, can result in biased estimates of retention [108]. Thus, the ascertainment of outcomes beyond a single facility is particularly pertinent among women who initiate ART in pregnancy.

Interlinked data sources are recommended by the WHO to allow programmes to trace patients beyond the facility of ART initiation, to measure continuity of care and to intervene as needed [109]. The use of interlinked data sources, as described in Chapter 6, overcomes the issues of transfer, both formal and informal clinic switching, and mobility, and is going to be critical to accurately monitor long-term retention for both programme and individual intervention purposes. The use of interlinked data sources in research also enables the assessment of retention among study participants who move away from the research clinic or are lost to the study. In the research presented in this thesis, and in the primary MCH-ART trial analyses [29], the use of interlinked routine electronic data from a combination of data sources, available across all routine clinics in the Western Cape province and with laboratory data available from clinics nationally, allowed for the measurement of the retention in care without differentiation by retention in the study. This approach has clear benefits as loss from a study is often associated with LTFU from routine care, which in turn can be associated with research outcomes, often the case in HIV care retention studies [108,110].

Although the data sources exist in either paper or electronic systems in most settings in SSA, the existence of electronic data that links patients across different clinics in an area is very rare. Setting up interlinked data sources will be a resource intensive activity that relies firstly on the establishment of unique patient identifiers to facilitate linkage. However, in the long-term, these data systems would reduce the need for active tracing for individual patient interventions. They have the potential to improve retention monitoring and patient outcomes in ART programmes and for other chronic conditions. Where no interlinked data sources are available but women are known to require a transfer of care, or in settings where mobility is common, active tracing of even a sample of women can reduce the bias introduced by facility-specific retention estimates and should be prioritised to ascertain patient outcomes beyond the facility of interest [78,108].

The choice of data sources to measure retention

The results of Chapter 6 emphasized the importance of considering the most appropriate measure of retention depending on the purpose of the estimate and the available data sources. Each data source may have a different expected frequency and set of considerations. Laboratory data for example, may be the most likely to be available centrally with links across facilities. This would allow for measures of retention that account for mobility and transfers. A recent analysis of retention in South Africa used the National Health Laboratory

Services database to estimate retention in this way and found considerable improvements in retention estimates compared to methods not accounting for transfer or mobility between clinics [111]. However, laboratory data, at least in low- and middle-income countries, may be limited as routine viral load testing usually only occurs annually or in some countries every two years [112].

Pharmacy refill data and patient visit data usually align well to local visit schedules. Administrative pharmacy dispensing databases often exist but may be facility-specific and thus not allow for consideration of care accessed at other clinics. If pharmacy data can be obtained including quantity or duration of ART dispensed, it can be a valuable measure of both retention in care as well as treatment adherence. Although pharmacy refill adherence measures do not provide a direct measure of medication taking behaviour, they have been shown to correlate well with clinical and biological outcomes [113,114]. In this thesis, pharmacy data were not fully evaluated as a stand-alone data source due to inconsistent availability of data across facilities, an issue that is discussed in more detail in Section 8.2. This difficulty accessing the data highlights some of the important real-world challenges that are often experienced with the use of routine data to measure retention, even within the relatively well-resourced health system and health information platforms in the Western Cape.

Patient visit data is the most widely used data source to measure retention and, in this thesis, was found to be a robust data source. Although electronic medical records and health information systems are in place in many low- and middle-income countries, many still rely predominantly on paper patient records and clinic registers. In Chapter 6 of this thesis, clinic visit data accounted for over 80% of all women considered retained using a number of different retention definitions. This suggests that where these data are available electronically they may provide the best coverage of access to HIV care.

One emerging challenge with both pharmacy and clinic visit data is due to the scale-up and changing landscape of differentiated models of care. Differentiated models of care may result in several different ART dispensing avenues and visit schedules in a single region or even a single clinic [115]. It may be difficult to identify which model of care any one patient is receiving and expected visit frequency is key to understanding context-specific retention in HIV care. For programme monitoring, a more broadly generalisable retention measure that can cut across programmes and models of care is desirable. The measure must be consistent

enough to allow comparison within a programme over time and comparison of outcomes across different programmes as well as research studies [116,117]. A 180-day gap with no visits has proven to be a robust marker of programme retention. Chi *et al*, in a large analysis across three continents, found that this length of gap in care minimised misclassification based on whether or not people returned to care in the 12 months after they had been counted as lost [117]. This definition was also the strongest predictor of viremia in Chapter 6 of this thesis.

The appropriateness of using different data sources is likely to evolve over time as health information systems develop. Combining data sources may be useful to better understand engagement in care. For example, facility-specific clinic visit data could be used for a context-appropriate retention measure in the facility, while a central, linked laboratory or pharmacy data source could be used to ascertain whether patients not in care at the facility of interest are accessing care at another clinic. Together with investing in unique patient identifiers, where existing clinical, clerical or administrative data sources are available they should be leveraged as a starting point for developing interlinked health information systems.

8.1.6 Opportunities to support long-term engagement in HIV care

The results of this thesis show estimates of retention ranging from 41%-72% using different definitions and data sources in Chapter 6. Only 72% of women had viral loads <1000 copies/mL among those who completed a study visit at 3-4 years postpartum in Chapter 4. This is could be an overestimate as women who returned to the study may have been more likely to be retained in HIV care compared to women who did not return. Overall, these findings are in line with estimates of the second and third 90s in South Africa [6,21], but well below the UNAIDS targets [1]. Together, these results highlight several important opportunities to support engagement in HIV care following ART initiation in pregnancy. This section will discuss these opportunities in the following two areas: i) preparation and counselling, and ii) interventions beyond the facility of ART initiation. These two broad areas are covered by an overarching need for patients, providers and health systems to be flexible to the changing needs of patients and the health services as women transition through pregnancy, breastfeeding and into post-breastfeeding motherhood.

Preparation and counselling

The barriers presented by ART side effects and mobility are not unique to pregnant and postpartum women and have also been reported as barriers to engagement in care in adult and adolescent cohorts [38,42,46,118]. However, as discussed in Section 8.1.3, these barriers have some unique considerations among women starting ART in pregnancy and focused counselling on these issues may be a useful strategy to address these considerations. The novel quantitative findings on reported side-effects in pregnancy in Chapter 3 [7] and LTFU after transfer from an integrated antenatal and ART clinic in Chapter 7 [9], support findings from qualitative work conducted in Option B+ cohorts across SSA. A number of studies have found that women report ART side effects and a lack of counselling at ART initiation as reasons for poor engagement in care [18,48,49,119–121]. One study in Malawi found that women no longer in care reported receiving less counselling when they started ART compared to women who remained in care [75]. The same study highlighted that mobility resulted in challenges accessing HIV care in a new place.

The results of Chapters 3 and 7 both call for adequate counselling and preparation within our ART programmes. Patient preparation about side effects during pregnancy, both related to HIV and ART as well as related to pregnancy or any other existing conditions, is critical to ensure women know what to expect. There is also a need to prepare women for any transfers of care required by local ART programmes and to provide specific counselling on how to navigate adherence and retention through times of mobility. Counselling and support interventions have shown promise to improve adherence and retention in HIV care in adult cohorts [122,123]. The impact of counselling messages specific to side effects, mobility and transfer, embedded into routine ART counselling for pregnant and postpartum women, requires investigation.

Preparedness for ART has been a topic of much discussion in the era of test-and-treat due to concerns about the implications of rapid ART initiation on later outcomes. A recent systematic review found no association between rapid ART initiation and clinical outcomes and little evidence for increased LTFU [124]. Studies in pregnant women specifically report mixed results [125,126], but ART initiation as soon as possible in pregnancy is essential to ensure viral suppression by the time of delivery and minimise the risk of perinatal transmission. What is critical now is to ensure that the counselling on potential ART side effects, transfer of care and mobility, and long-term adherence beyond the pregnancy and

postpartum transmission risk periods is adequate, and that avenues exist for women requiring additional support.

Moving beyond the facility of ART initiation

For both the measurement and support of lifelong engagement in care it is not sufficient to focus only on the facility of ART initiation. The results of Chapter 7 show that women who started ART in the same clinic during pregnancy spread out to attend almost 100 different ART clinics in the first two years on treatment. Among women who linked to care after leaving the integrated clinic, 21% accessed two or more different clinics in the first two years on ART. Other studies have actively traced patients considered to be lost to follow-up and found a number of them to be attending other clinics [78,79,107,127]. The results presented in Chapter 7 are the first to document mobility for routine HIV care in a full cohort of postpartum women and they add important insights to an emerging literature on mobility and engagement in HIV care [42,43,76]. These novel findings draw attention to the critical need for interventions that bridge across facilities, facilitate continued engagement in care through times of geographic mobility or movement between clinics, and that can provide support for women living with HIV where they are and when they need it.

The use of routine interlinked data sources is one way to support engagement in care beyond the facility of ART initiation. Existing routine clinical, administrative or clerical data sources, such as those obtained from the Provincial Health Data Centre for use in this thesis, can be linked using a unique patient identifier [128]. These data can then be used to flag patients considered LTFU or those with raised viral loads and reports listing patients requiring additional support or intervention can be generated for follow-up. Linking these data across facilities in a region will allow facilities to easily follow up on patients who have transferred care and will prevent facilities from investing resources into tracing patients who are actively engaged in HIV care elsewhere. Although the various data sources do exist in either paper or electronic form in most health services, many settings do not have established unique patient identifiers or the infrastructure to set up linked electronic data sources. This is a substantial barrier to the potential use of routine health data for both cohort monitoring and individual patient intervention.

Community-based interventions also provide a platform to extend support beyond a specific facility and to intervene in some of the broader social barriers to engagement in care. In the Option B+ literature, lack of support from partners, family and the community is often cited

as a barrier to engagement in HIV care [11,47,129,130]. Stigma also remains a major barrier to engagement and can prevent women from seeking support when needed [47,131]. Community-level engagement has been highlighted as crucial to address issues of stigma and to improve social support for women living with HIV [132]. Peer models to support maternal ART can encompass both counselling, support and community engagement [18,133–135] and they have been successful in improving the uptake of ART in pregnancy and early infant HIV testing in SSA [136,137]. Community-based peer support models can be successfully implemented and have been found to perform similarly to facility-based models to improve engagement in HIV care in SSA and other low- and middle-income settings [138,139], including maternal ART uptake and retention under Option B+ specifically [18]. Community-based support interventions could provide an additional avenue to support long-term engagement in care beyond the facility of ART initiation.

Mobile health (mHealth) is another approach with the potential to offer support regardless of where a woman is accessing care. mHealth interventions have shown promise to improve ART adherence in adult cohorts as well as in the context of PMTCT [140,141]. Interventions using a mobile phone platform have the advantage that the mode of intervention resides with the patient or healthcare worker and is already part of their everyday life. It is therefore able to provide interventions that bridge across facilities and models of care to provide support even in the context of transfer and geographic mobility. In addition, mobile technology can be used as the platform to deliver many types of interventions to both patients (such as counselling, peer support, case management and adherence reminders) and healthcare workers (such as training and job aids). Interventions such as *MomConnect* in South Africa, a text message service to support all women during and after pregnancy, is one example of a national support intervention that is not tied to a single facility or region, however the impact of this on engagement in HIV care specifically has not yet been evaluated [142].

Most mHealth interventions to date make use of short-text messaging service (SMS) or phone calls [143]. Smartphone technology provides a mobile platform for a multitude of interactive combination interventions [144]. It is estimated that about 51% of South Africans own a smart phone (Figure 8-2) and the technology is becoming more and more accessible, even in developing countries [145]. New intervention designs are emerging to take advantage of smartphone and wireless technology to support health outcomes. *Just-in-time adaptive interventions* (JITAIs) are interventions designed to "adapt over time to an individual's time-varying status, with the goal to address the individual's changing needs for support" [146].

They make use of technology such mobile applications to deliver prompts or provide access to specific support based on feedback received by the user at a particular time. Although barriers to access still exist, these and other mHealth intervention designs present an opportunity to provide long-term support to women living with HIV on a large scale, adapting to their changing needs as they transition through the stages of maternal lifelong ART, different clinics and different geographic areas.

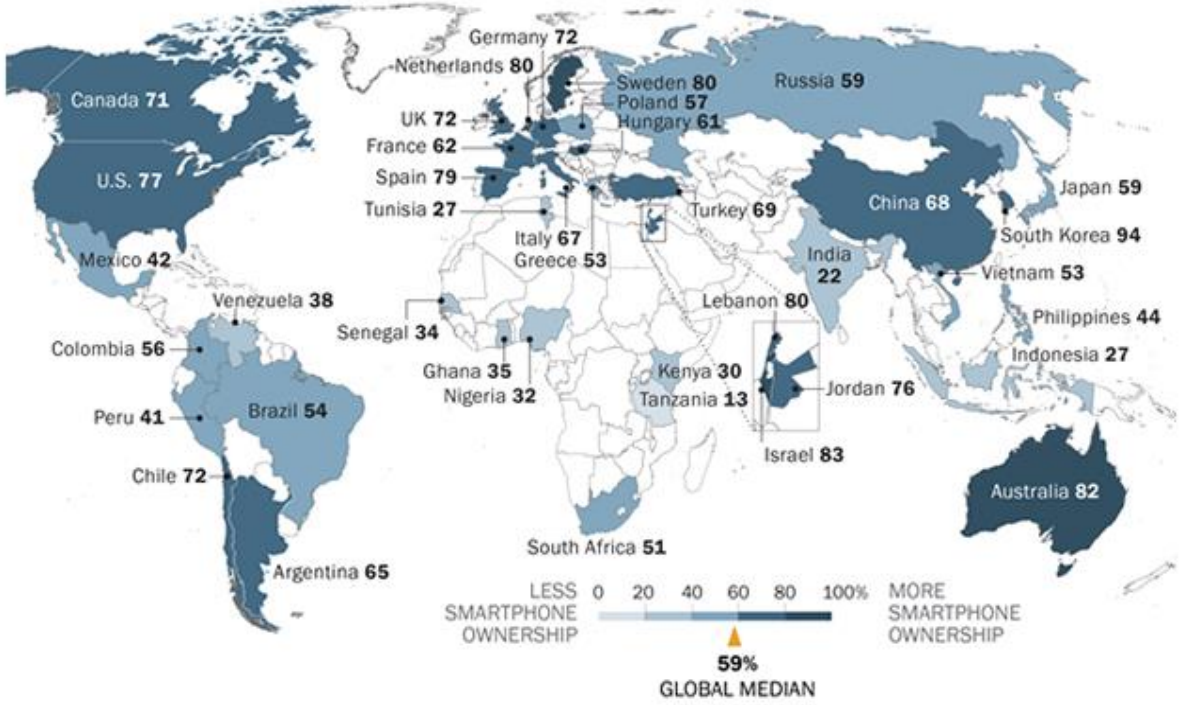

Figure 8-2 A map showing the proportion of adults who reported owning a smartphone in 2017, from the Pew Research Center [145].

Summary

Cutting across all the opportunities for supporting engagement in care is the need for flexibility. Hoddinott *et al*, in a large qualitative analysis of households in Zambia and South Africa, concluded that "responsive, flexible health service delivery systems designed to accommodate the many shifts in client circumstances" were critical to support engagement in HIV care [42]. This is pertinent in the context of maternal ART where a woman is going through many life transitions and, in parallel, transfers into and out of different ART services may be required. Over time, regimens and treatment practices will change, differentiated models of care will evolve and scale up, and patients will move between clinics and between geographical areas. Just as pregnant and postpartum women need to adapt to their changing

life circumstances, our health services, interventions and even the way we monitor engagement in HIV care must also adapt.

Not only is there a need for adaptability in supporting long-term engagement in care, but there is also perhaps a need to acknowledge that despite our best efforts, just as with other chronic conditions, people living with HIV are unlikely to remain continuously engaged in HIV services for life [147–149]. It is crucial that there is also a focus on preparing patients and providers for potential lapses in care, identifying points of re-entry into care for patients who do disengage and promoting systems and attitudes that encourage re-engagement in HIV care as soon as possible when this occurs.

8.2 Strengths and limitations

Strengths and limitations specific to each analysis are presented within the discussion section of each chapter, however the following additional overarching strengths and limitations of this thesis should be considered.

Both a strength and a limitation of this work is the cohort from which it is drawn. All the results presented in this thesis are from a single cohort of women who initiated ART during pregnancy at the time of roll out of universal ART for pregnant women in Gugulethu, South Africa. This is a strength as this cohort provides unique insights into adherence and retention during and after pregnancy from one of the first Option B+ cohorts in South Africa. Thus, this work provides lessons for universal ART in pregnant and postpartum women, but also for universal ART more broadly. A related limitation is the generalisability of the findings. While these findings are likely to be generalisable in many ways to other similar settings in South Africa and SSA, the results from this single cohort may not be directly applicable in other settings where aspects of the analyses such as the local model of care and available data sources differ. These results are situated within the context of an integrated antenatal and ART care model, with mandatory postpartum transfer to general ART clinics. The issues of transfer and mobility are relevant beyond this setting, but results should be transferred to other models of care with careful consideration of the potential differences. Similarly, the routine health data used in this thesis comes from an established health information exchange, the Provincial Health Data Centre of the Western Cape Department of Health. Although the component data sources are available in many other settings, the process of linking and deduplicating health records and the presence of a unique provincial patient identifier, both major advantages of this work, are quite unique to this setting.

Another disadvantage is that these results represent a relatively short follow-up time with retention outcomes through to 24 months on ART (Chapter 6) and adherence in a small sample of women at approximately four years on ART (Chapter 4). With universal ART for all, more focus is needed on long-term ART outcomes and patterns of engagement in HIV care over time. To date there have only been two studies reporting on routine care outcomes of women who initiated ART in pregnancy beyond three years on treatment [13,19]. Thus, despite this limitation, these findings contribute to our understanding of longer-term outcomes as well as methodological considerations as we move towards exploring long-term engagement in care after pregnancy. This cohort was also limited to women aged 18 years and older. Adolescents and young women are known to be vulnerable to poor retention and adherence[150,151] and younger age was consistently a risk factor for poor outcomes in this thesis but this work cannot speak directly to younger populations.

Both self-reported and routine data sources are subject to known limitations which have been discussed in the results chapters. However, the use of these data sources was central to this thesis with a view towards readily available adherence and retention measures. Interlinked routine electronic data to measure retention has the potential for misclassification and we cannot be sure that the quality of data was the same across all clinics. However, the use of these data allowed ascertainment of retention outcomes in all women, even those lost from face-to-face study follow-up. Repeated self-reported adherence measures in the MCH-ART study provided unique data to examine longitudinal changes in self-reported adherence. Similarly, the numerous viral load measures collected by this study allowed for inclusion of viral load outcomes in all analyses except for Chapter 3. The analyses presented in Chapter 3 were conducted early in the study when batched viral load results were not yet available. The study collected viral load measures and high study retention rates meant that viral load outcomes were available for almost all women, even those that were no longer engaged in routine HIV care.

Another limitation of this work is that it only examined engagement in HIV care among mothers and did not include any child outcomes. Children's engagement in routine health care, including adherence to infant HIV prophylaxis and visit attendance for early infant diagnosis, is crucial for optimal child health and patterns of engagement of mothers and their children are likely to be linked [152,153]. Reduced mother-to-child transmission of HIV and improved child health outcomes are key potential benefits of universal ART for pregnant and breastfeeding women. Furthermore, routine child health visits present an opportunity to

support maternal engagement in care in the postpartum period. The combined outcomes of maternal and child engagement in care, and how they are related, should be considered in future work.

In addition, this thesis has focused on women who initiated ART during pregnancy but women who conceive on ART are also vulnerable to disengagement from care. There is some evidence that they may even have a greater risk of postpartum virologic failure compared to women who initiate ART in pregnancy [154]. Once on ART, women who conceive may be required to transition into integrated antenatal and ART services and then again transfer out to general ART services postpartum. These transitions require consideration in future research to ensure continuity of care in this critical period.

8.3 Recommendations for policy, research practice and future research

The findings of this thesis have provided insight into factors contributing to high levels of disengagement from ART during pregnancy and after delivery. They also provide evidence for novel approaches to measure ART adherence and considerations for using interlinked routine electronic health data to measure retention in care. Based on this evidence, this section will outline recommendations for policy, research practice and future research priorities.

8.3.1 Policy recommendations

The combined work of this thesis has resulted in three recommendations for policy. Firstly, a call for strengthened counselling about ART side effects among women starting ART in pregnancy, as well as preparation for postpartum transfer, mobility, and long-term engagement in ART care beyond the period of risk of perinatal or breastfeeding transmission of HIV. Ensuring that women are prepared for what to expect as they initiate ART during pregnancy, what side effects to expect for their specific regimen, and to navigate the transition to general ART care is a key step towards overcoming some of the barriers to sustained engagement in HIV care. The Western Cape province already has a Standard Operating Procedure for mobile patients, showing a move towards a health system that can be prepared for and adapt to patients' changing circumstances [155]. The protocol covers both planned and unplanned travel, but work is still needed to counsel patients and train providers on the implementation of this protocol. Moreover, given the frequency of mobility outside of the province, this also needs to be extended into national protocols.

The second recommendation is around consideration of models of care for maternal ART. Integrated antenatal and ART care with continued integrated care for mother-baby pairs postpartum has shown clear benefits for sustaining engagement in care through the highest risk periods of pregnancy and breastfeeding and ensuring adherence to early infant diagnosis protocols [29,31,32]. It also offers the opportunity to integrate other critical services such as reproductive health and family planning services [156]. Programmes should consider implementing integrated maternal and child health services at least until the child's final HIV status is ascertained following cessation of breastfeeding to minimise the risk of transmission and ensure rapid ART initiation if needed. Even with this policy, systems to support movement to a new clinic through transfer or times of mobility will still be needed. In addition, both research and programmes need to explore the optimal model and timing for transferring women out of integrated services into routine adult care when required to ensure ongoing engagement in care beyond this risk period. The optimal components of integrated care also require consideration but at a minimum should cover maternal ART and reproductive health services, infant wellness and immunisations, as well as early infant HIV diagnosis and either treatment or optimal referral of HIV-infected infants to paediatric care.

Finally, the establishment of unique patient identifiers and the development of interlinked health information systems should be prioritised. In the era of universal lifelong ART, it is critical that patients be able to access HIV care wherever they move to over time. To be able to support this, it is critical for health information systems to be able to link across facilities. In maternal ART cohorts, there is also the need to link mother-baby pairs to ensure completion of the PMTCT cascade and intervene where necessary. Many countries already have existing clinical, clerical or administrative data systems that could be leveraged to start to form an interlinked health information system. There is probably no perfect system but linking data sources that already exist will provide a platform from which to develop interventions to improve patient care and strengthen programme monitoring. The Provincial Health Data Centre of the Western Cape is a useful case study of this approach. Although this thesis has focused specifically on the importance of these systems for ART programmes, the benefits will extend to all primary health services.

8.3.2 Recommendations for research practice

The recommendations for research practice speak to the measurement of ART adherence and retention in HIV care in research studies. The possible measures will be dependent on the

local setting, the scope of the research and available funding, but these recommendations aim to provide some guidance.

For research measuring adherence, our findings confirm that the use of TFV-DP in DBS is a very strong measure of ART adherence among people living with HIV [96]. TFV-DP in DBS also has the added benefit of providing insight into dosing over a longer period than other drug concentration assays and therefore providing a more nuanced measure of adherence. This measure should be used in-so-far as resources allow. Plasma EFV and TFV concentrations were also strongly associated with viral suppression in Chapter 4, however previous research has found single plasma ARV concentrations to be poor predictors of viral load [157]. Plasma ARV concentrations provide a simpler and less expensive alternative to TFV-DP in DBS, but further research is needed to better understand the value of these assays to detect viremia or ARV resistance in the context of routine viral load monitoring.

When measuring retention in HIV care, these results highlight the need for the inclusion of sensitivity analyses using different retention measurement approaches. Researchers need to carefully consider the most appropriate retention definition depending on the available data sources, the local context, the question being asked, and the intended use of the estimates. Based on this, researchers might choose a very context-specific primary retention definition to best meet their needs. However, in order to promote comparability within and between programmes and research studies, the inclusion of a more generalisable retention measure in sensitivity analyses, such as a 180-day gap in care which is widely used [116,117], should be encouraged. In addition, journals should encourage researchers to clearly describe the local model of care and the data sources used. This would allow readers to assess the rationale for the choice of measurement approach used and the potential impact of any differences in measurement approach across studies.

Finally, researchers should be strongly encouraged to select data sources and definitions of retention that allow for consideration of mobility and transfer of care. Chapters 6 and 7 of this thesis clearly highlight the need to ascertain retention outcomes beyond the facility of ART initiation, particularly in settings with required health care transfers and where mobility is common. Attempts to ascertain retention outcomes beyond a single facility should be standard practice for research on long-term retention in HIV care.

8.3.3 Future research priorities

This research points to a number of important future research priorities. Chapters 4 and 5 demonstrated that drug concentrations are superior to self-reported adherence measures but that longitudinal self-reported adherence performs better than cross-sectional self-report. This work provides a proof of concept for the use of change in self-reported adherence to detect the risk of viremia, but questions remain about the feasibility and potential uses in routine care. Future research should validate the use of change in self-reported adherence as an interim adherence measure in a routine care setting. Viral loads alone do not differentiate between poor adherence or non-retention and ARV resistance. The value of both drug concentrations and change in self-reported adherence, in combination with routine viral load monitoring, still requires investigation and the potential value for flagging potential treatment resistance requires consideration.

The results of Chapter 7 show that many women do not link to care after transferring from an integrated antenatal and ART clinic. Further research is needed to evaluate the optimal timing and approach to transfer of care. There is also a need for the development of interventions to support continued engagement in HIV care through the postpartum transfer and beyond. Future research into engagement in HIV care must consider mobility and movement between clinics in order to accurately measure engagement and to most effectively use resources to intervene in patient care.

Lastly, there is growing recognition of the dynamic nature of retention and adherence, emphasising that patients will move in and out of care over their life on ART [148,149,158]. Most research, including this thesis, uses cross-sectional measures of adherence and retention or aggregate measures over time. These approaches do not consider the dynamic nature of engagement in care and do not necessarily provide accurate insights into an ART programme or an individual's treatment status. As we shift focus to long-term engagement in HIV care, future research should include strategies to incorporate change in engagement in care into measurement approaches. It should also focus on understanding the impact of changing engagement in care over time as well as identifying opportunities to support re-engagement of patients who are lost.

In summary, this thesis highlights the importance of future research on patterns of engagement in HIV over place and time as well as appropriate measures and interventions to support engagement in care in the long-term. All the individual-, family- and population-level

benefits of universal lifelong ART among pregnant and postpartum women can only be achieved through sustained engagement in HIV care. Thus, future research must prioritise better understanding and optimal support of lifelong ART.

8.4 Conclusions

This thesis investigated barriers to engagement in HIV care with specific considerations among pregnant and postpartum women. It also explored novel adherence measurement approaches and the use of routine interlinked data sources to measure retention in HIV care after ART initiation in pregnancy in South Africa. For both adherence and retention, regardless of measurement approach, the combined findings of this thesis highlight substantial disengagement from HIV care during and after pregnancy, posing a threat to the potential benefits of lifelong ART.

Two aspects of this thesis speak to the need for improved ART counselling and preparation for potential barriers. This work provides new evidence of the high burden of self-reported ART side effects among women who start ART in pregnancy, finding that it is the overall side effect burden, rather than system-specific side effects, that are most strongly associated with ART adherence. Given the many normal physiological changes a women experiences during pregnancy, adequate preparation for potential ART side effects is needed to ensure optimal adherence in the early months on ART. In addition, this thesis presents a novel description of LTFU and mobility to different ART clinics following routine transfer out of integrated antenatal and ART services. These findings again call for the need for adequate counselling on how to navigate required transfers of care as well as how to remain engaged in care through times of mobility. ART counselling should place emphasis not only on the pregnancy and breastfeeding periods, but also on the importance of sustained long-term engagement in care for optimal maternal health.

This thesis contributes pioneering results comparing TFV-DP in DBS, plasma EFV, plasma TFV and self-reported adherence to predict viral load among an African cohort of women living with HIV. Drug concentrations in DBS and plasma provide robust measures of adherence. In routine care settings with limited resources for viral load or drug concentration testing, the value of an innovative adherence measurement approach using longitudinal change in self-reported adherence warrants further investigation.

Lastly, the finding that women spread out to almost 100 different clinics after leaving an integrated antenatal and ART clinic is significant and provides evidence of the importance of interlinked data sources to accurately measure retention in care postpartum. These novel findings are likely to hold for other settings with required transfer of HIV care or where mobility is common. Even when using interlinked data, considerable variation in retention estimates was observed using different data sources and definitions, with clinic visit data emerging as the most robust data source for retention measurement. Recommendations include prioritising the establishment of unique patient identifiers and leveraging existing administrative, clerical and clinical data systems to improve patient care and programme monitoring.

In conclusion, this thesis provides a unique picture of barriers to and considerations for the measurement of engagement in HIV care among pregnant and postpartum women. Despite substantial progress with the scale-up of ART programmes and uptake of lifelong ART, there is a critical need to focus on long-term sustained engagement in HIV care in order to realise the individual-, family- and population-level benefits of lifelong ART. Careful consideration of the appropriate measurement approach is required to accurately measure engagement in HIV care and to allow comparison within and between programmes and research. Just as women are adapting to many changes as they transition through pregnancy, breastfeeding and post-breastfeeding motherhood, the health system, providers and our measurement approaches, must be flexible to women's changing health care needs and life circumstances. Further research is needed to evaluate optimal models of care for providing maternal ART and to develop interventions to support engagement beyond the facility of ART initiation. This ongoing work will be critical to ensure sustained maternal engagement in HIV care in the long term and ultimately to end the HIV epidemic.

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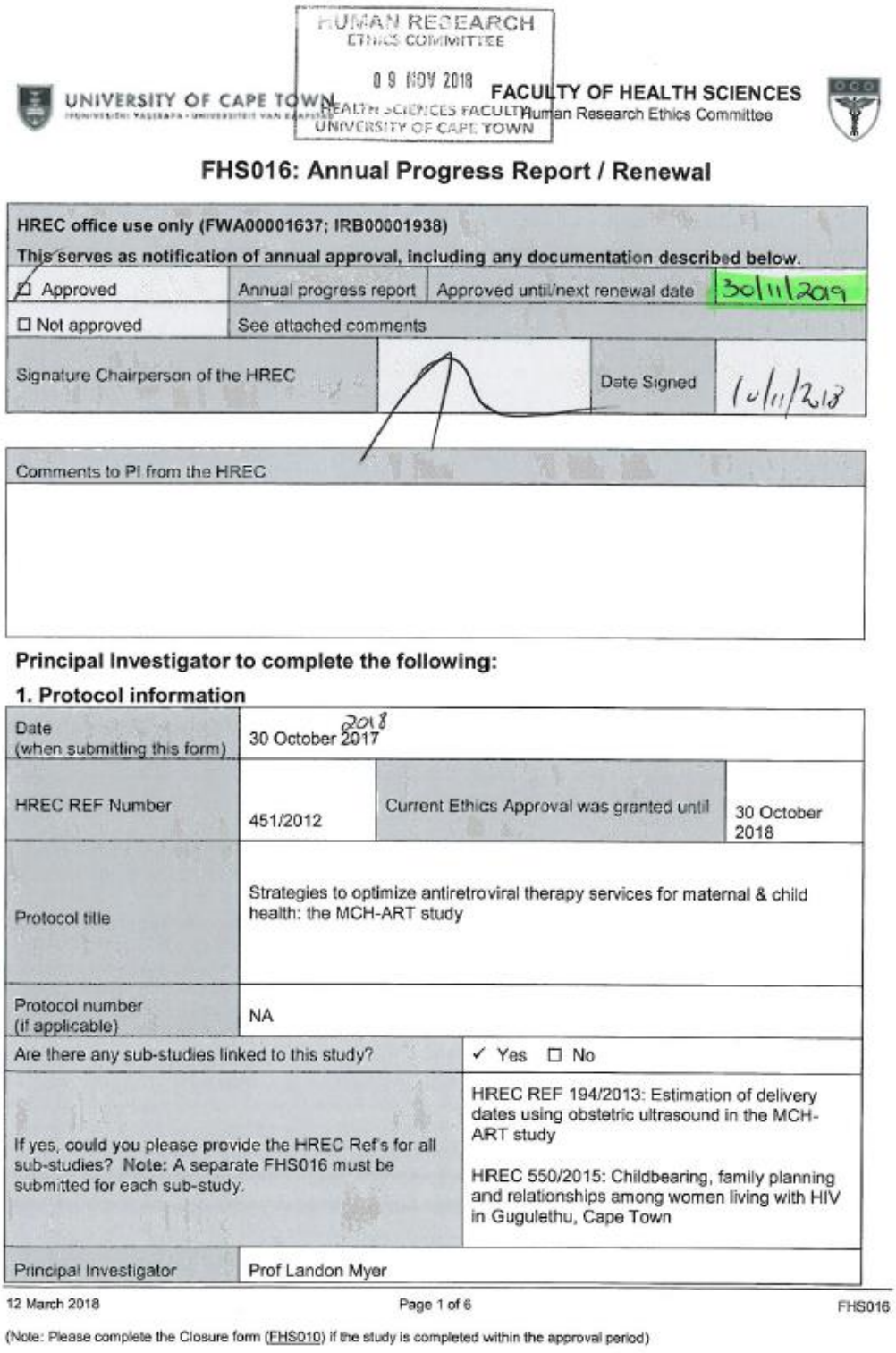
158 Camlin CS, Neilands TB, Odeny TA, Lyamuya R, Nakiwogga-Muwanga A, Diero L, *et al.* Patient-reported factors associated with reengagement among HIV-infected patients disengaged from care in East Africa. *AIDS* 2016; **30**:495–502.

Chapter 9: Appendices

9.1 Ethics approval documents

9.1.1 University of Cape Town Human Research Ethics Committee for the MCH-ART study



HUMAN RESEARCH ETHICS COMMITTEE
09 NOV 2018
HEALTH SCIENCES FACULTY UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/11/2019
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	1/11/2018

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	30 October 2017 2018		
HREC REF Number	451/2012	Current Ethics Approval was granted until	30 October 2018
Protocol title	Strategies to optimize antiretroviral therapy services for maternal & child health: the MCH-ART study		
Protocol number (if applicable)	NA		
Are there any sub-studies linked to this study?	✓ Yes ☐ No		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.	HREC REF 194/2013: Estimation of delivery dates using obstetric ultrasound in the MCH-ART study HREC 550/2015: Childbearing, family planning and relationships among women living with HIV in Gugulethu, Cape Town		
Principal Investigator	Prof Landon Myer		

12 March 2018 Page 1 of 6 FHS016

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

9.1.2 University of Cape Town Human Research Ethics Committee for the LACE study

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HUMAN RESEARCH ETHICS COMMITTEE
23 JAN 2018
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.1.2019
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	23/1/18

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	18 Jan 2018		
HREC REF Number	866/2016	Current Ethics Approval was granted until	30 Jan 2018
Protocol title	Long-term Adherence and Care Engagement (LACE): A supplement to the MCH-ART protocol		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☐ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study			
Principal Investigator	Prof Landon Myer		
Department / Office Internal Mail Address	Office 5.43 Level 5 Falmouth Building		

1.1 Does this protocol receive US Federal funding?	✓ Yes	☐ No

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

9.1.3 University of Cape Town Human Research Ethics Committee for this thesis

UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE
23 JAN 2018
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	22.2.2019
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	23/1/18

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	18 Jan 2018		
HREC REF Number	117/2017	Current Ethics Approval was granted until	28 Feb 2018
Protocol title	Antiretroviral therapy care engagement among HIV-infected women during pregnancy, breastfeeding and into ongoing care		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ✓ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study			
Principal Investigator	Prof Landon Myer		
Department / Office Internal Mail Address	Office 5.43 Level 5 Falmouth Building		

1.1 Does this protocol receive US Federal funding?	☐ Yes	✓ No

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

9.2 Supplementary material for Chapters 3-7

9.2.1 Chapter 3

Supplementary Table 9-3-1 Comparison of the fit of Latent Class Analysis (LCA) models with different number of classes according to different criteria.

N	LL	AIC	aBIC	Entropy	BLR p	min SIZE %
1	-3618.07	7258.13	7269.95	1	-	100%
2	-3323.78	6693.55	6718.25	0.75	<0.001	47%
3	-3296.47	6662.94	6700.52	0.67	0.200	20%
4	-3278.07	6650.13	6700.60	0.74	0.016	17%
5	-3266.45	6650.89	6714.25	0.71	0.730	9%

N = Number of latent classes; LL = Log-Likelihood; AIC = Akaike's Information Criterion; aBIC=sample size adjusted Bayesian Information Criterion; Entropy = Classification Entropy (as calculated by Mplus, i.e. rescaled so that values closer to 1 indicate better discrimination); BLR p = p-value for the Bootstrap Likelihood Ratio test with null hypothesis that the fit of the model with n classes is not different from the fit of the model with n-1 classes (50 bootstrap draws).

Models with one through five latent classes were compared in order to identify the number of distinct patterns of SE reported by women starting ART during pregnancy. The sample-size adjusted Bayesian Information Criterion (aBIC), which some simulation studies have shown to be superior to other indices in the LCA, reached its minimum with both the three- and four-class solutions, with no meaningful differences.[1] However, the lower value of the Akaike's Information Criterion (AIC) and the results of the Bootstrap Likelihood Ratio test (BLR) both were in agreement, suggesting a better fit for the four-class model. Moreover, the four-class model was accompanied with higher classification entropy indicating a lower level of uncertainty in the classification of the individuals. The four-class solution was therefore selected to represent the data. The values of the various indices of fit used for the models and the results of the BLR test are reported here.

Reference:

1. Yang. Evaluating latent class analysis models in qualitative phenotype identification. Computational Statistics & Data Analysis. 2006; 50(4):1090-1104.

Supplementary Table 9-3-2 Multinomial logistic regression model predicting latent class membership.

Class[§]	Predictor	A) Crude associations (n=517, except CD4, n=500)			B) Adjusted associations (n=500)		
		OR	(95% CI)	p-value	OR	(95% CI)	p-value
Class 2	**One-year increase in age**	0.99	(0.91-1.07)	0.042			
	Socioeconomic status						
	Low	(ref)			(ref)		-
	Middle	4.66	(4.66-4.66)	<0.001	4.56	(1.71-12.17)	0.002
	High	2.88	(1.04-7.94)	0.518	3.59	(1.28-10.07)	0.015
	Married/cohabiting	0.67	(0.32-1.40)	0.379	1.19	(0.51-2.79)	0.680
	Primigravid	2.68	(1.07-6.71)	0.469	1.71	(0.65-4.49)	0.277
	1 unit increase in natural logarithm of pre-ART CD4	1.77	(0.98-3.20)	0.303	2.21	(1.04-4.70)	0.040
	Diagnosed prior to pregnancy	0.52	(0.25-1.10)	0.380	0.66	(0.28-1.58)	0.351
	ARV history						
	ARV naive	(ref)		-			
	Previous PMTCT	0.86	(0.36-2.04)	0.443			
	Previous ART	0.51	(0.05-5.40)	1.209			
	Increasing weeks gestation at ART start	1.11	(1.06-1.16)	0.024	1.12	(1.03-1.22)	0.010
	Increasing weeks on ART	0.93	(0.89-0.97)	0.021	1.00	(0.93-1.07)	0.911
Class 3	**One-year increase in age**	1.01	(0.96-1.07)	0.042			
	Socioeconomic status						
	Low	(ref)		-	(ref)		-
	Middle	2.98	(1.35-6.58)	<0.001	2.9	(1.25-6.71)	0.013
	High	2.7	(1.26-5.78)	0.518	3.04	(1.28-7.22)	0.012
	Married/cohabiting	0.53	(0.28-0.99)	0.379	0.76	(0.38-1.52)	0.437
	Primigravid	1.18	(0.50-2.81)	0.469	0.71	(0.27-1.90)	0.499
	1 unit increase in natural logarithm of pre-ART CD4	1.35	(0.83-2.19)	0.303	1.65	(0.95-2.86)	0.077
	Diagnosed prior to pregnancy	0.66	(0.36-1.21)	0.380	0.68	(0.34-1.36)	0.274
	ARV history						
	ARV naive	(ref)		-			
	Previous PMTCT	0.97	(0.47-1.97)	0.443			
	Previous ART	1.51	(0.37-6.17)	0.209			
	Increasing weeks gestation at ART start	1.03	(0.98-1.08)	0.024	1.02	(0.96-1.08)	0.575
	Increasing weeks on ART	0.98	(0.94-1.01)	0.021	0.98	(0.93-1.02)	0.327
Class 4	**One-year increase in age**	1.02	(0.97-1.07)	0.042			
	Socioeconomic status						
	Low	(ref)		-	(ref)		-
	Middle	1.92	(0.96-3.83)	<0.001	2.27	(1.06-4.86)	0.035
	High	1.43	(0.72-2.82)	0.518	2.25	(0.99-5.10)	0.052
	Married/cohabiting	0.7	(0.40-1.24)	0.379	0.93	(0.48-1.81)	0.829
	Primigravid	1.12	(0.49-2.53)	0.469	0.99	(0.42-2.32)	0.974
	1 unit increase in natural logarithm of pre-ART CD4	1.86	(1.13-3.07)	0.303	2.11	(1.23-3.63)	0.007
	Diagnosed prior to pregnancy	0.67	(0.38-1.18)	0.380	0.79	(0.41-1.52)	0.489
	ARV history						
	ARV naive	(ref)		-			
	Previous PMTCT	1.11	(0.59-2.12)	0.443			
	Previous ART	0.22	(0.01-4.67)	0.209			
	Increasing weeks gestation at ART start	1.11	(1.06-1.16)	0.024	1.07	(0.99-1.16)	0.097
	Increasing weeks on ART	0.91	(0.88-0.95)	0.021	0.95	(0.88-1.02)	0.169

§ Compared to reference class 1

Supplementary Table 9-3-3 Description of demographic and clinical characteristics according to the frequency of side effects (SE), systems-based SE categories, and latent SE classes.

	Median frequency of reported SE (IQR)	Any GIT SE	Any CNS SE	Any skin SE	Any systemic SE	Class 1 (high SE)	Class 2 (moderate SE, high systemic)	Class 3 (moderate SE, low systemic)	Class 4 (low SE)
All women	5 (3-7)	417 (81)	437 (85)	161 (31)	406 (79)	133 (26)	89 (17)	156 (30)	139 (27)
Median age (IQR)	-	27 (24-31)	28 (25-32)	28 (24-31)	27 (24-31)	28 (24-31)	27 (23-31)	28 (25-32)	28 (25-33)
Socioeconomic status									
lowest	6 (3-8)	161 (39)	168 (38)	66 (41)	149 (37)	63 (47)	27 (30)	51 (33)	56 (40)
medium	5 (3-7)	120 (29)	127 (29)	43 (27)	121 (30)	32 (24)	34 (38)	47 (30)	39 (28)
highest	5 (3-7)	136 (33)	142 (32)	52 (32)	136 (34)	38 (29)	28 (31)	58 (37)	44 (32)
Education level									
Finished high school	5 (3-7)	108 (26)	114 (26)	39 (24)	106 (26)	26 (20)	25 (28)	49 (31)	34 (24)
Did not finish high school	5 (3-8)	309 (74)	323 (74)	122 (76)	300 (74)	107 (80)	64 (72)	107 (69)	105 (76)
Employment status									
Employed	5 (3-7)	151 (36)	159 (36)	58 (36)	152 (37)	46 (35)	38 (43)	55 (35)	54 (39)
Not employed	5 (3-7)	266 (64)	278 (64)	103 (64)	254 (63)	87 (65)	51 (57)	101 (65)	85 (61)
Relationship status									
Married/cohabiting	6 (3-8)	160 (38)	178 (41)	62 (39)	152 (37)	60 (45)	34 (38)	52 (33)	52 (37)
Not married/cohabiting	5 (3-7)	257 (62)	259 (59)	99 (61)	254 (63)	73 (55)	55 (62)	104 (67)	87 (63)
Median gravidity (IQR)	-	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)	2 (1-3)	2 (2-3)	2 (2-3)
Primigravida	6 (3-7)	82 (20)	75 (17)	23 (14)	77 (19)	21 (16)	25 (28)	25 (16)	22 (16)
Multigravida	5 (3-7)	335 (80)	362 (83)	138 (86)	329 (81)	112 (84)	64 (72)	131 (84)	117 (84)
Timing of HIV diagnosis									
In the current pregnancy	6 (3-7)	230 (55)	236 (54)	90 (56)	179 (44)	65 (49)	54 (61)	88 (56)	79 (57)
Prior to this pregnancy	5 (3-8)	187 (45)	201 (46)	71 (44)	227 (56)	68 (51)	35 (39)	68 (44)	60 (43)
ARV history									
ARV naïve	5 (3-7)	303 (73)	316 (72)	112 (70)	299 (74)	96 (72)	67 (75)	111 (71)	100 (72)
Previous PMTCT	5 (3-7)	100 (24)	104 (24)	40 (25)	92 (23)	32 (24)	20 (22)	37 (24)	37 (27)
Previous ART	6 (4-8)	14 (3)	17 (4)	9 (6)	15 (4)	5 (4)	2 (2)	8 (5)	2 (1)
Median CD4 cell count at ART initiation (IQR) [§]	-	351 (235-528)	355 (239-528)	345 (213-528)	354 (236-531)	318 (220-466)	403 (246-548)	367 (239-539)	400 (276-589)*
CD4≤200	6 (4-8)*	78 (19)	75 (18)	33 (22)	75 (19)	29 (23)	13 (15)	28 (19)	15 (11)
CD4 201 - 350	6 (3-8)	122 (30)	130 (31)	45 (29)	116 (29)	43 (34)	24 (28)	42 (28)	41 (30)
CD4>350	5 (3-7)	202 (50)	217 (51)	75 (49)	203 (52)	56 (44)	50 (57)	80 (53)	79 (59)
Median gestation(weeks) at ART initiation (IQR)	-	21 (16-26)	20 (16-26)	21 (16-26)	20 (16-26)	19 (15-23)	24 (19-30)	20 (15-26)	23 (18-29)**
Median weeks on ART (IQR)	-	19 (13-24)	19 (13-24)	19 (14-24)	19 (14-24)	21 (16-25)	16 (11-22)	19 (12-25)	16 (10-21)**

[§]17missing CD4 counts

**denotes p<0.05, **denotes p<0.001 using Kruskal Wallis for continuous and chi-squared for categorical variables*

Supplementary Table 9-3-4 Logistic regression models predicting any missed dose.

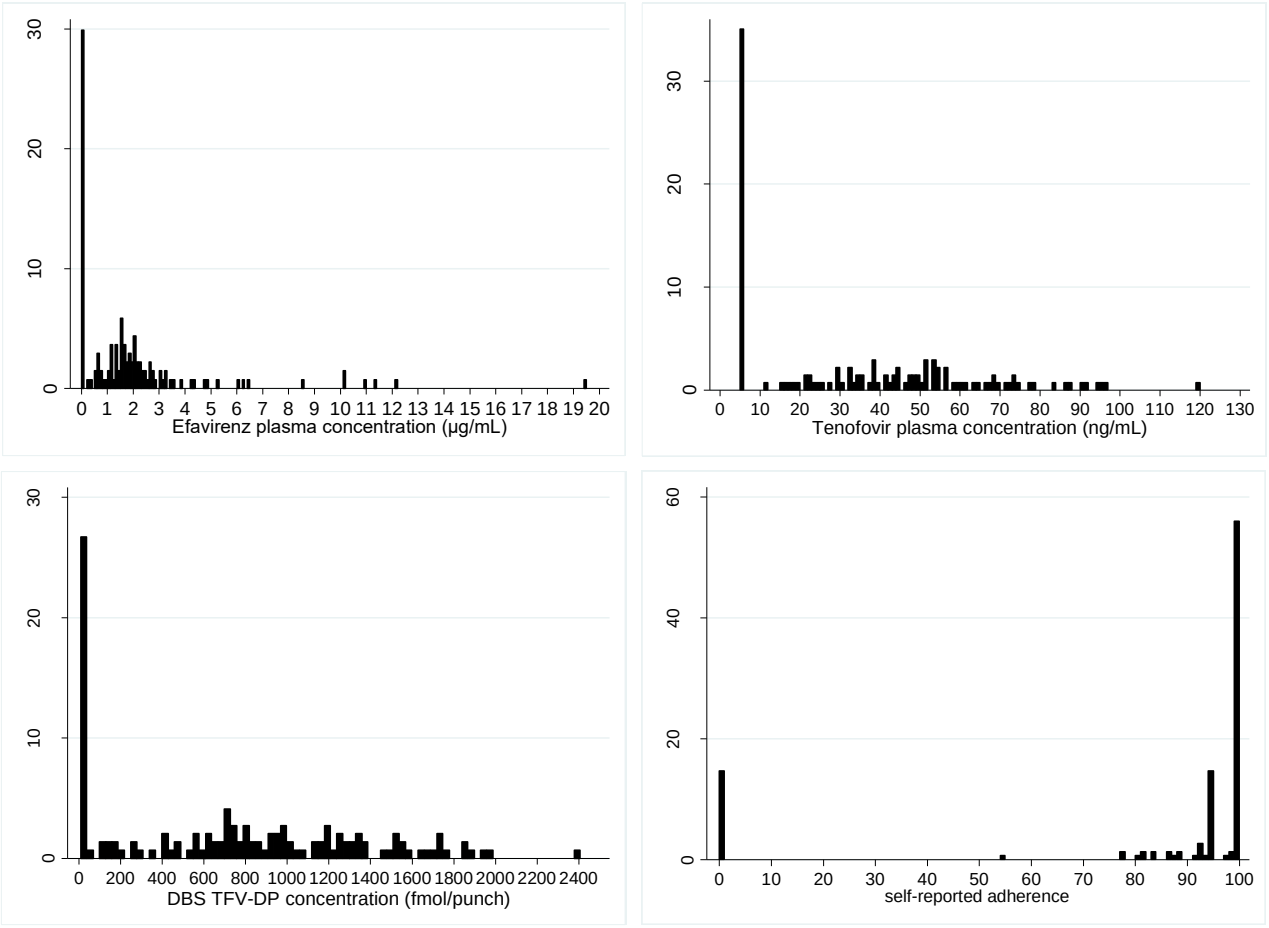
	A) Crude associations (n=517, except CD4, n=500)			B) Adjusted associations using number of side effects (n=517)			C) Adjusted associations using system categories (n=517)			D) Adjusted associations using latent classes* (n=517)		
	OR	**(95% CI)**	**p-value**	**OR**	**(95% CI)**	**p-value**	**OR**	**(95% CI)**	**p-value**	**OR**	**(95% CI)**	**p-value**
One-year increase in age	0.95	(0.92-0.99)	0.005	0.97	(0.93-1.01)	0.105	0.97	(0.93-1.01)	0.125	0.97	(0.93-1.01)	0.094
Socioeconomic status												
Low	(ref)											
Middle	1.15	(0.73-1.81)	0.538									
High	1.11	(0.71-1.73)	0.640									
Married/cohabiting	0.72	(0.49-1.06)	0.097	0.72	(0.47-1.09)	0.116	0.77	(0.51-1.16)	0.213	0.73	(0.48-1.11)	0.137
Primigravid	1.60	(1.01-2.54)	0.047	1.21	(0.71-2.09)	0.482	1.17	(0.68-2.01)	0.575	1.16	(0.67-2.01)	0.593
1 unit increase in natural logarithm of pre-ART CD4	1.00	(0.49-2.03)	0.991									
Diagnosed prior to pregnancy	0.96	(0.66-1.39)	0.825									
ARV history												
ARV naive	(ref)											
Previous PMTCT	0.69	(0.44-1.08)	0.107									
Previous ART	1.06	(0.38-2.93)	0.909									
Increasing weeks gestation at ART start	0.98	(0.95-1.01)	0.113									
Increasing weeks on ART	1.03	(1.01-1.05)	0.011	1.02	(0.99-1.04)	0.128	1.02	(1.00-1.04)	0.111	1.02	(1.00-1.04)	0.113
Any GIT SE	2.51	(1.45-4.34)	0.001				1.78	(1.00-3.17)	0.051			
Any CNS SE	1.76	(1.01-3.09)	0.047				1.25	(0.68-2.30)	0.479			
Any Skin SE	1.34	(0.91-1.99)	0.138				1.18	(0.79-1.79)	0.419			
Any Systemic SE	3.48	(1.97-6.13)	<0.001				2.65	(1.46-4.81)	0.001			
Increasing no. of reported SE	1.21	(1.12-1.30)	<0.001	1.20	(1.12-1.29)	<0.001						
Class 1 (high SE)	1	(ref)								1	(ref)	
Class 2 (moderate SE, high systemic)	0.72	(0.19-1.26)	0.389							0.79	(0.45-1.39)	0.409
Class 3 (moderate SE, low systemic)	0.62	(0.24-1.00)	0.124							0.61	(0.37-0.99)	0.046
Class 4 (low SE)	0.17	(0.04-0.31)	<0.001							0.25	(0.14-0.45)	<0.001

**Panel D is adjusted for the probability of class membership*

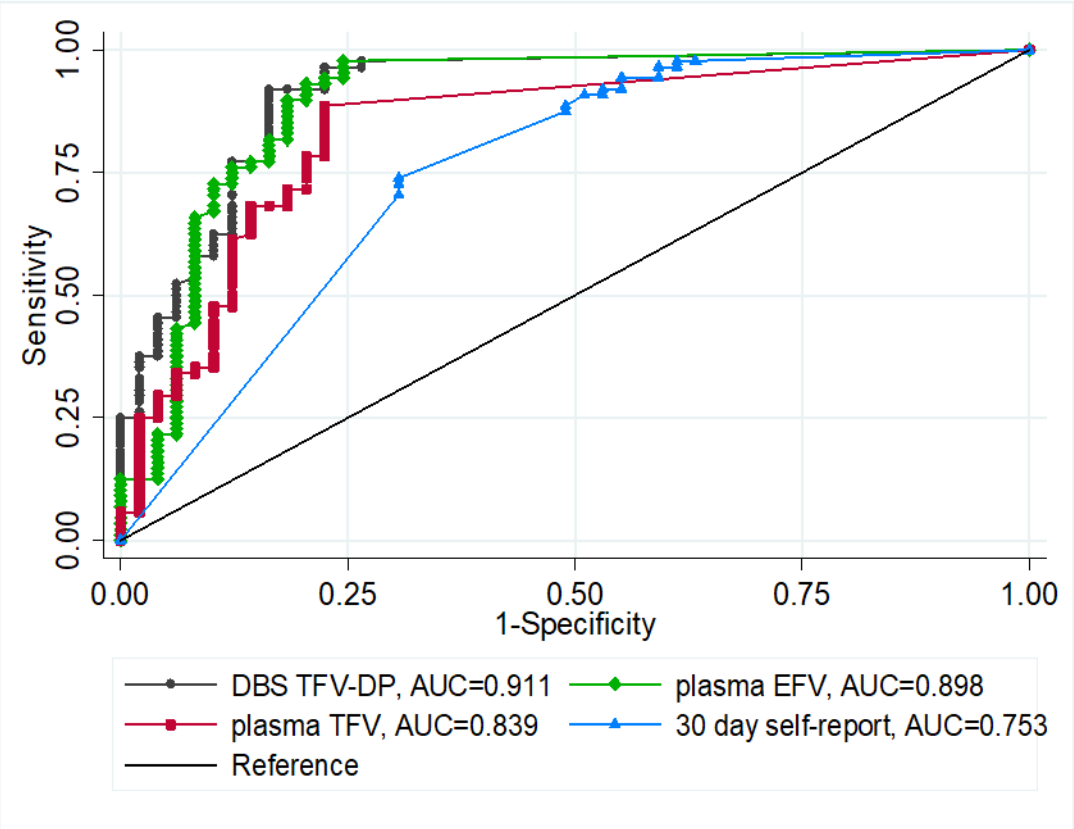
Supplementary Table 9-3-5 Reported reasons provided for missing 30 or more ART doses.

	Reason for missing 30 or more ART doses
1.	"I ran out of treatment and did not go back to get more from clinic, I did not have transport money"
2.	"I feel stressed, that is why I'm not taking my treatment. **I vomit after taking the pill**"
3.	"I ran out of treatment…I wanted to **avoid side effects**"
4.	"Because of **side effects**. I **vomited and lost appetite**"
5.	"I stopped taking treatment due to exams, because they **made me sleepy and weak**. After that I became lazy to collect, avoiding explaining why I defaulted"
6.	"After being discharged at hospital [after delivery], I did not come back to fetch my treatment. I was very late for my scheduled appointment to collect treatment and was afraid thereafter to come again. There is no reason for not taking treatment and it is not hard to take."

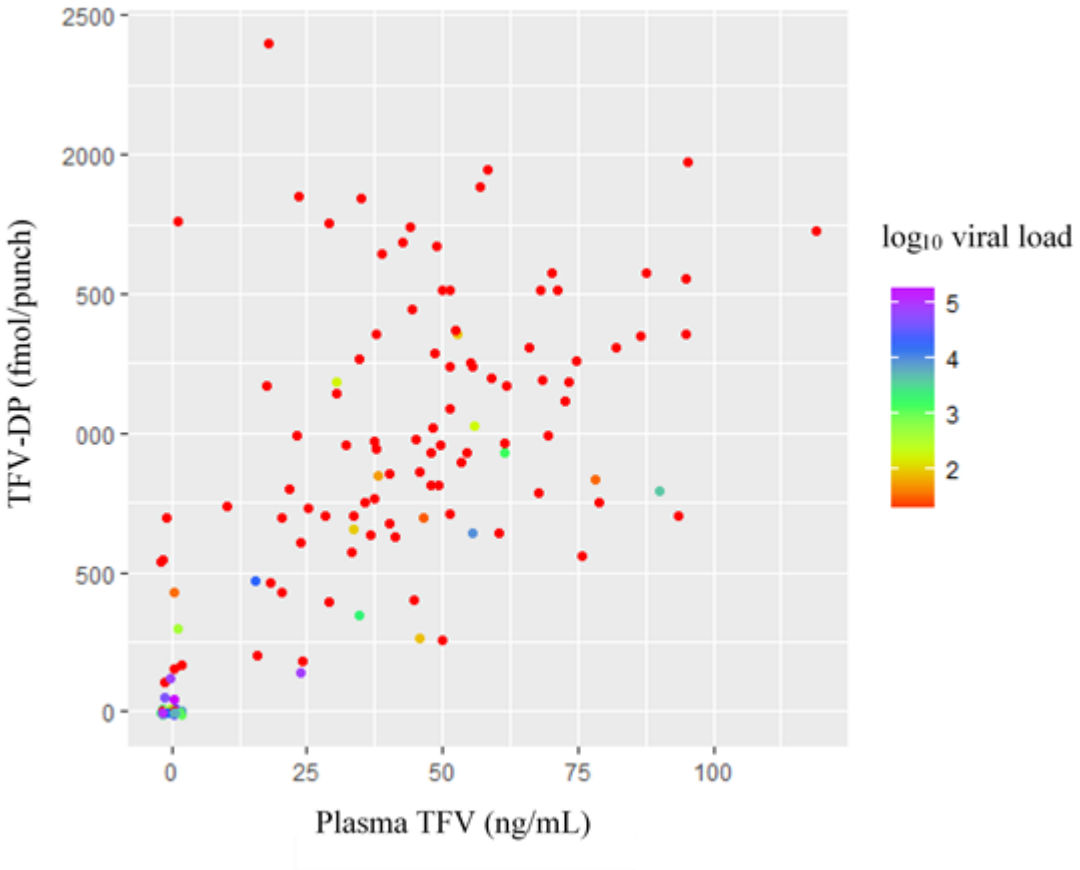
9.2.2 Chapter 4



Supplementary Figure 9-4-1 Histograms of a) plasma efavirenz, b) plasma tenofovir, c) tenofovir-diphosphate (TFV-DP) concentrations in dried blood spots (DBS), d) self-reported adherence in the past 30 days (three-item scale score).



Supplementary Figure 9-4-2 Unadjusted area under the receiver operating characteristics (ROC) curves of DBS TFV-DP (grey), plasma EFV (green), plasma TFV (maroon), and self-reported adherence (blue) to predict viral suppression; n=137.



Supplementary Figure 9-4-3 Scatter plot of tenofovir-diphosphate (TFV-DP) in DBS and plasma tenofovir (TFV) concentrations.

Supplementary Table 9-4-1 Characteristics of DBS TFV-DP thresholds restricted to women who report taking ART in the last 30 days (n=87). Odds ratios (OR) predicting viral load <50, <400 and <1000 copies/mL are presented.

TFV-DP threshold (approximate doses per week[1])	**<350 (<2)**	**350-699 (2-3)**	**700-1249 (4-6)**	**≥1250 (7)**
Total number of women	27	19	41	30
Median viral load log_{10} copies/mL (IQR)	3.7 (2.5-4.6)	1.3 (1.3-1.3)	1.3 (1.3-1.3)	1.3 (1.3-1.3)
Median viral load copies/mL (IQR)	4884 (282-38325)	20 (20-20)	20 (20-20)	20 (20-20)
Viral load <50 copies/mL				
Viral load <50 copies/mL, n (%)	5 (19)	16 (84)	36 (88)	29 (97)
OR (95% CI)	Ref	23 (5-113)	32 (8-122)	128 (14-1172)
aOR2 (95% CI)	Ref	28 (5-142)	34 (8-139)	135 (14-1268)
Viral load <400 copies/mL				
Viral load <400 copies/mL, n (%)	7 (26)	17 (89)	39 (95)	30 (100)
OR (95% CI)	Ref	24 (4-133)	56 (11-293)	Omitted
aOR[2] (95% CI)	Ref	35 (5-230)	74 (12-462)	Omitted
Viral load <1000 copies/mL				
Viral load <1000 copies/mL, n (%)	8 (30)	17 (89)	39 (95)	30 (100)
OR (95% CI)	Ref	20 (4-109)	46 (9-240)	Omitted
aOR[2] (95% CI)	Ref	29 (5-178)	59 (10-360)	Omitted

[1]As previously described by Castillo-Mancilla *et al* (CID, 2018)

[2]Adjusted for age and duration on ART

Supplementary Table 9-4-2 Univariable logistic regression models predicting viral load <50, <400 and <1000 copies/mL among 137 women.

	Viral load <50 copies/mL OR 95% CI	**Viral load <400 copies/mL OR 95% CI**	**Viral load <1000 copies/mL OR 95% CI**
Increasing years of age	1.10 (1.02-1.18)	1.11 (1.03-1.20)	1.08 (1.00-1.17)
Increasing years on ART	1.38 (0.28-6.75)	1.76 (0.33-9.26)	2.30 (0.43-12.40)
Increasing BMI (kg/m^2)	1.05 (1.00-1.11)	1.04 (0.99-1.09)	1.04 (0.99-1.10)
Serum Creatinine (n=74)	1.01 (0.95-1.07)	1.03 (0.96-1.10)	1.03 (0.96-1.10)

Supplementary Table 9-4-3 Women with detectable plasma tenofovir (TFV) and efavirenz (EFV) concentrations but very low tenofovir-diphosphate concentration in dried blood spots (DBS TFV-DP).

Patient	**Viral load (copies/mL)**	**DBS TFV-DP (fmol/punch)**	**Plasma TFV (ng/mL)**	**Plasma EFV (µg/mL)**
1	20	178	25.2	1.16
2	20	209	15.1	2.04
3	87	270	47.5	1.12
4	88741	136	22.6	0.54

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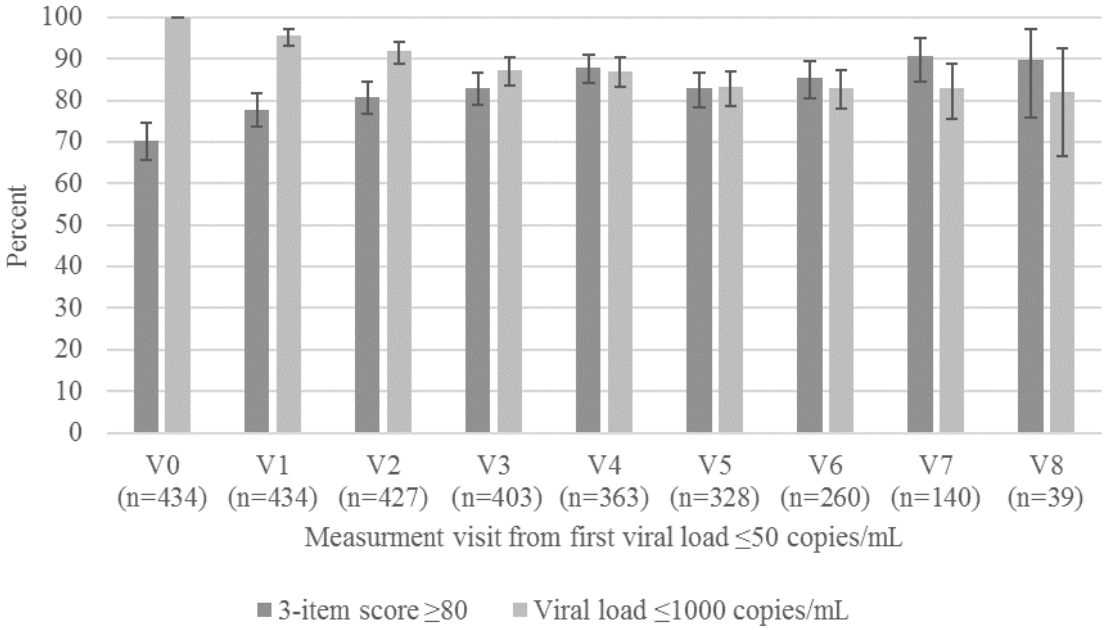
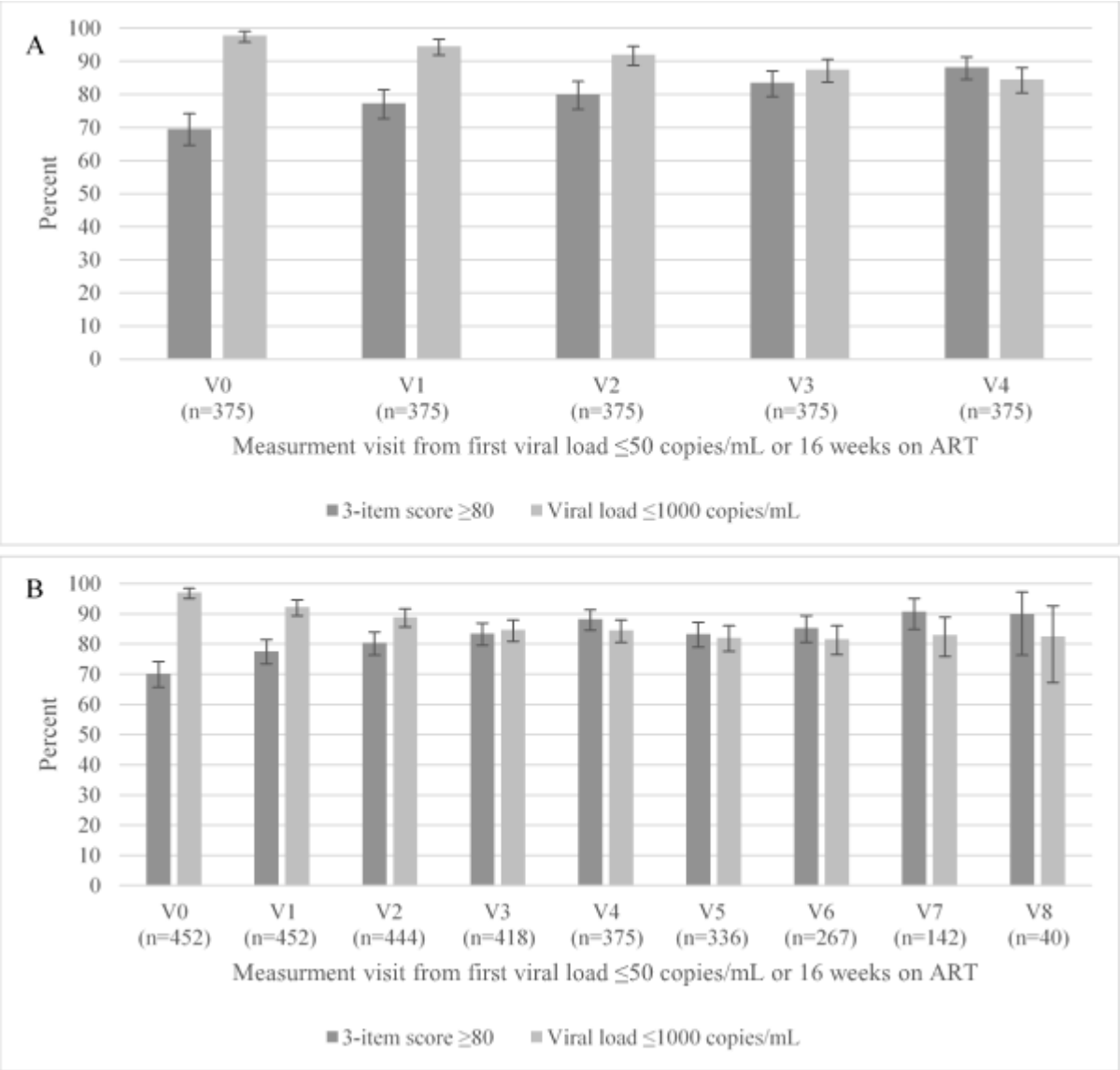
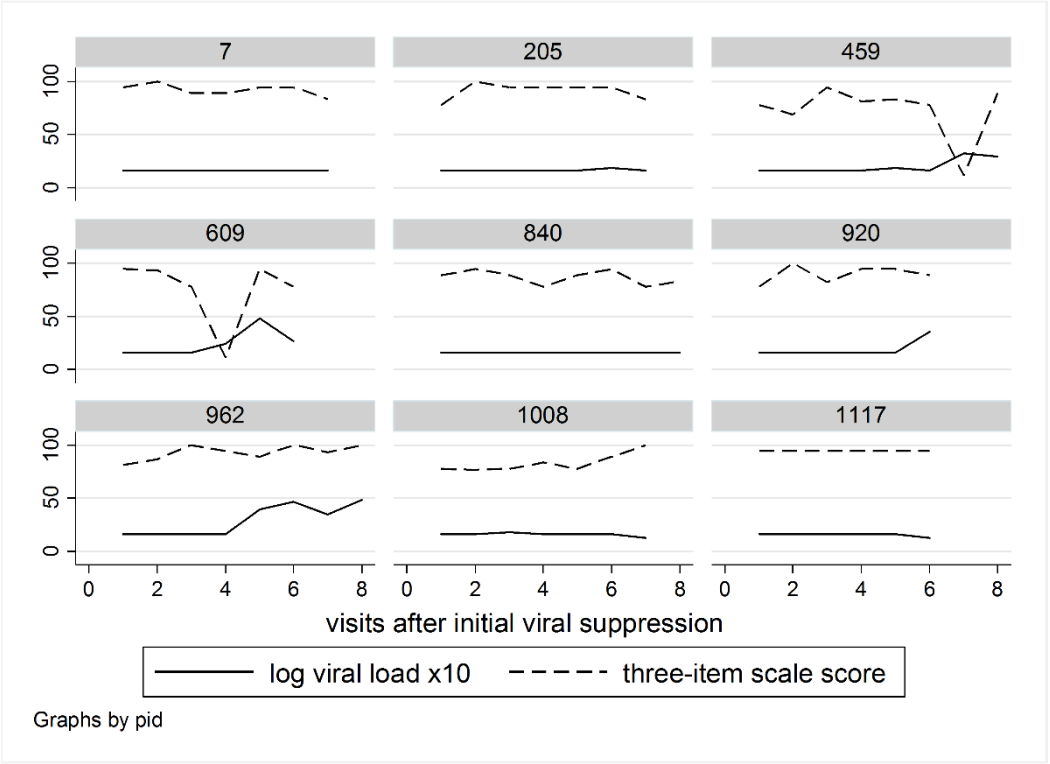


Supplementary Figure 9-5-1 Proportion of women with adherence scores ≥80 and HIV viral loads ≤1000 copies/mL among 434 with at least one study visit after V_0 (first visit with a viral load ≤50 copies/mL after ART initiation during pregnancy). Data are shown from V_0 through up to 8 additional visits (V_1-V_8).



Supplementary Figure 9-5-2 Sensitivity analyses showing the proportion of women with adherence scores ≥80 and HIV viral loads ≤1000 copies/mL among from V_0 (first visit with a viral load ≤50 copies/mL or, if never suppressed, first visit at least 16 weeks after ART initiation during pregnancy). Data are shown for A) women with at least 4 consecutive visits after V_0, and B) for all included women from V_0 through up to 8 additional visits (V_1-V_8).



Supplementary Figure 9-5-3 Random selection of individual three-item self-reported adherence scale scores and 10 times the $\log_{10}$ viral load over time.

Supplementary Table 9-5-1 Distribution of self-reported adherence and HIV viral load among 434 women at consecutive measurement times from V_0 (the first visit with viral load ≤50 copies/mL after ART initiation in pregnancy) through up to 8 additional visits. Results presented as n (%) unless otherwise specified.

	V_0	**V_1**	**V_2**	**V_3**	**V_4**	**V_5**	**V_6**	**V_7**	**V_8**
Number of women	434	434	427	403	363	328	260	140	39
Postpartum	123 (28)	332 (77)	427 (100)	403 (100)	363 (100)	328 (100)	260 (100)	140 (100)	39 (100)
Median months postpartum (IQR)	1 (0.2-2)	0.2 (0.1-1)	1 (1-3)	3 (3-6)	6 (6-9)	9 (8-12)	12 (9-14)	18 (12-18)	18 (18-19)
Median months on ART (IQR)	3 (1-4)	5 (3-6)	6 (5-7)	8 (6-10)	11 (9-13)	14 (12-15)	17 (14-19)	21 (16-23)	23 (21-23)
Individual adherence items Mean (SD)									
1. Proportion of days with no missed doses in past 30 days	98 (6)	99 (6)	98 (10)	98 (12)	98 (6)	98 (9)	96 (16)	99 (9)	99 (5)
2. How good a job did you do taking your medication in the past 30 days?	78 (15)	81 (14)	81 (15)	82 (16)	83 (14)	81 (16)	81 (17)	83 (14)	85 (12)
3. How often did you take your medicines as directed in the past 30 days?	84 (15)	84 (15)	84 (16)	85 (16)	86 (15)	86 (14)	84 (17)	88 (14)	89 (12)
Mean 3-item score (SD)	87 (10)	88 (9)	88 (11)	88 (12)	89 (9)	88 (10)	87 (14)	90 (10)	91 (7)
Median 3-item score (IQR)	89 (78-94)	89 (83-94)	89 (83-94)	89 (83-94)	89 (83-94)	89 (83-94)	89 (83-94)	93 (83-94)	89 (88-94)
3-item score ≥80	305 (70)	338 (78)	345 (81)	335 (83)	319 (88)	272 (83)	222 (85)	127 (91)	35 (90)
3-item score ≥90	154 (35)	176 (41)	176 (41)	179 (44)	180 (50)	136 (41)	118 (45)	74 (53)	19 (49)
3-item score =100	59 (14)	61 (14)	55 (13)	62 (15)	45 (12)	53 (16)	31 (12)	23 (16)	8 (21)
Viral load ≤50 copies/mL	434 (100)	394 (91)	374 (88)	338 (84)	298 (82)	255 (78)	196 (75)	105 (75)	26 (67)
Viral load ≤1000 copies/mL	434 (100)	415 (96)	392 (92)	352 (87)	316 (87)	273 (83)	216 (83)	116 (83)	32 (82)
Mean log_{10} viral load (SD)	1.6 (0.02)	1.7 (0.6)	1.8 (0.8)	1.9 (0.9)	2.0 (0.9)	2.1 (1.0)	2.1 (1.0)	2.1 (1.0)	2.1 (0.9)
Median log_{10} viral load (IQR)	1.6 (1.6-1.6)	1.6 (1.6-1.6)	1.6 (1.6-1.6)	1.6 (1.6-1.6)	1.6 (1.6-1.6)	1.6 (1.6-1.6)	1.6 (1.6-1.7)	1.6 (1.6-1.7)	1.6 (1.6-2.6)

Supplementary Table 9-5-2 Change in self-reported adherence and change in viral load from V_i to V_{i+1} among 2085 visit pairs from 433 women who ever suppressed, presented as n (%).

	Viral load stayed ≤50 copies/mL	**Viral load stayed >50 copies/mL**	**Viral load decreased from >50 to ≤50 copies/mL**	**Viral load increased from ≤50 to >50 copies/mL**	**All visit pairs**
Number of visit pairs	1828 (88)	127 (6)	26 (1)	104 (5)	2085
Changed in self-reported adherence					
Change ≤4 missed doses, both Likert items stayed the same	1082 (59)	61 (58)	12 (46)	54 (52)	1209 (58)
Increased by ≥1 level or ≥5 missed doses on any item	389 (21)	30 (24)	7 (27)	21 (20)	447 (21)
Decreased by ≥1 level or ≥5 missed doses on any item	357 (20)	36 (28)	7 (27)	29 (28)	429 (21)

Supplementary Table 9-5-3 Sensitivity analyses showing univariable GEE models for change in each reported adherence from Vi to Vi+1 to predict viremia >50 and >1000 copies/mL at Vi+1 including all visits from first suppression or from 16 weeks on ART among women who never suppressed. Results presented as odds ratios with 95% confidence intervals; statistically significant associations are in bold.

	All women from first suppression or 16 weeks on ART		
Number of women	451		
Number of visit pairs	2151		
	Number of visit pairs, N (%)	To predict viral load >50 copies/mL	To predict viral load >1000 copies/mL
Change in item 1 (missed dose)			
No change in missed doses	1670 (78)	Ref	Ref
Increased ≥1 missed dose	230 (11)	0.94 (0.66-1.32)	0.93 (0.64-1.35)
Decreased ≥1 missed dose	251 (12)	**1.40 (1.07-1.83)**	1.25 (0.95-1.64)
Change in item 2 (good job)			
No change	1883 (88)	Ref	Ref
Increased ≥1 level	145 (7)	1.08 (0.76-1.55)	0.93 (0.60-1.44)
Decreased ≥1 level	123 (6)	**1.90 (1.39-2.60)**	**1.70 (1.24-2.33)**
Change in item 3 (how often)			
No change	1655 (77)	Ref	Ref
Increased ≥1 level	247 (11)	0.95 (0.73-1.24)	0.79 (0.57-1.08)
Decreased ≥1 level	249 (12)	1.25 (0.94-1.65)	1.03 (0.77-1.38)
Change in combined score			
No change in missed doses	586 (27)	Ref	Ref
Increased ≥1 missed dose	811 (38)	0.97 (0.79-1.20)	0.94 (0.75-1.16)
Decreased ≥1 missed dose	754 (35)	1.16 (0.96-1.41)	1.12 (0.92-1.37)
Change ≤4 missed doses	1251 (58)	Ref	Ref
Increased ≥1 level or ≥5 missed doses	460 (21)	0.99 (0.78-1.24)	0.92 (0.71-1.19)
Decreased ≥1 level or ≥5 missed doses	440 (20)	**1.26 (1.03-1.54)**	1.19 (0.97-1.46)
Change ≤9 missed doses or 1 level	1369 (64)	Ref	Ref
Increased ≥2 levels or ≥10 missed doses	398 (19)	0.91 (0.72-1.16)	0.88 (0.67-1.15)
Decreased ≥2 levels or ≥10 missed doses	384 (18)	1.20 (0.98-1.47)	1.19 (0.95-1.47)

Supplementary Table 9-5-4 Multivariable GEE models to predict viral load >50 and >1000 copies/mL at V_{i+1} among 2085 visit pairs from women who ever suppressed. The primary predictors were A) one level change in item 2 of the adherence scale, and B) ≥5 dose change in item 1 or a one level change in item 2 or 3 of the adherence scale. Statistically significant associations are in bold.

	A. One level change in item 2		**B.** ≥5 dose change in item 1 or a one level change in item 2 or 3	
	>50 copies/mL aOR (95% CI)	>1000 copies/mL aOR (95% CI)	>50 copies/mL aOR (95% CI)	>1000 copies/mL aOR (95% CI)
Increasing years of maternal age	0.95 (0.92-0.98)	0.96 (0.92-1.00)	0.95 (0.92-0.98)	0.96 (0.92-1.00)
Increasing months on ART	**1.04 (1.00-1.08)**	**1.08 (1.03-1.13)**	**1.04 (1.00-1.08)**	**1.08 (1.04-1.13)**
Married/cohabiting	**0.65 (0.46-0.91)**	**0.57 (0.37-0.88)**	**0.65 (0.47-0.91)**	**0.57 (0.37-0.88)**
Employed	0.77 (0.56-1.07)	**0.61 (0.40-0.94)**	0.79 (0.57-1.09)	**0.62 (0.40-0.95)**
Increasing weeks gestation at presentation for antenatal care	**1.04 (1.01-1.06)**	**1.05 (1.02-1.08)**	**1.04 (1.01-1.06)**	**1.05 (1.02-1.08)**
Increasing baseline reported adherence score	0.95 (0.89-1.01)	0.93 (0.86-1.00)	0.95 (0.89-1.01)	0.93 (0.86-1.00)
Viral load >50 copies/mL at V_i	**34.45 (23.58-50.35)**	**10.23 (7.21-14.51)**	**35.94 (24.36-53.01)**	**10.12 (7.14-14.33)**
Increasing months between Vi and Vi+1	**1.33 (1.16-1.53)**	**1.21 (1.06-1.38)**	**1.33 (1.16-1.53)**	**1.21 (1.06-1.38)**
Change in adherence score from V_i to V_{i+1}				
score remained the same	Ref	Ref	Ref	Ref
score increased	1.31 (0.73-2.35)	1.21 (0.69-2.14)	1.23 (0.82-1.83)	1.09 (0.74-1.61)
score decreased	**2.60 (1.57-4.30)**	**1.91 (1.15-3.17)**	**1.62 (1.11-2.38)**	**1.42 (1.00-2.03)**

Supplementary Table 9-5-5 Sensitivity analyses showing multivariable GEE models to predict viral load >50 and >1000 copies/mL at V_{i+1} including 2151 visit pairs from first suppression or from 16 weeks on ART among women who never suppressed. The primary predictors were A) one level change in item 2 of the adherence scale, and B) ≥5 dose change in item 1 or a one level change in item 2 or 3 of the adherence scale. Statistically significant associations are in bold.

	All women from suppression or 16 weeks on ART			
	A. One level change in item 2		**B.** ≥5 dose change in item 1 or a one level change in item 2 or 3	
	>50 copies/mL aOR (95% CI)	>1000 copies/mL aOR (95% CI)	>50 copies/mL aOR (95% CI)	>1000 copies/mL aOR (95% CI)
Increasing years of maternal age	0.95 (0.92-0.98)	0.94 (0.91-0.98)	0.95 (0.92-0.98)	0.94 (0.91-0.98)
Increasing months on ART	1.02 (0.98-1.07)	**1.07 (1.03-1.11)**	1.03 (0.98-1.07)	**1.07 (1.03-1.12)**
Married	**0.68 (0.49-0.95)**	**0.59 (0.39-0.88)**	**0.69 (0.50-0.97)**	**0.59 (0.39-0.89)**
Employed	0.78 (0.57-1.07)	**0.65 (0.44-0.97)**	0.81 (0.59-1.11)	**0.66 (0.44-0.98)**
Increasing weeks gestation at presentation for antenatal care	**1.03 (1.01-1.05)**	**1.05 (1.02-1.08)**	**1.03 (1.01-1.05)**	**1.05 (1.02-1.08)**
Increasing baseline reported adherence score	0.96 (0.90-1.03)	0.94 (0.97-1.01)	0.96 (0.90-1.03)	0.94 (0.87-1.02)
Viral load >50 copies/mL at V_i	**72.49 (46.12-113.93)**	**15.79 (11.00-22.66)**	**79.32 (49.79-126.34)**	**15.72 (1.96-22.54)**
Increasing months between V_i and V_{i+1}	**1.35 (1.16-1.57)**	**1.19 (1.04-1.36)**	**1.35 (1.16-1.57)**	**1.19 (1.04-1.36)**
Change in adherence score from V_i to V_{i+1}				
score remained the same	Ref	Ref	Ref	Ref
score increased	1.30 (0.70-2.41)	1.20 (0.71-2.04)	1.20 (0.77-1.88)	1.01 (0.70-1.47)
score decreased	**2.58 (1.49-4.48)**	**1.78 (1.05-3.04)**	**1.62 (1.06-2.47)**	1.25 (0.88-1.77)

Supplementary Table 9-5-6 Univariable GEE models to predict viral load >50 and >1000 copies/mL at V_{i+1} among 2085 visit pairs from women who ever suppressed. Results presented as odds ratios with 95% confidence intervals; statistically significant associations are in bold.

	viral load >50 copies/mL	viral load >1000 copies/mL
Increasing years of maternal age	**0.95 (0.92-0.99)**	0.95 (0.91-0.99)
Increasing months on ART	**1.13 (1.10-1.16)**	**1.15 (1.12-1.78)**
Married	**0.53 (0.35-0.80)**	**0.51 (0.31-0.83)**
Employed	**0.64 (0.43-0.94)**	**0.54 (0.34-0.86)**
Completed high school	0.77 (0.50-1.20)	0.76 (0.45-1.26)
Increasing weeks gestation at presentation for antenatal care	**1.03 (1.01-1.06)**	**1.04 (1.01-1.07)**
Primigravida	1.23 (0.77-1.98)	1.14 (0.65-1.98)
Diagnosed in this pregnancy	0.86 (0.59-1.25)	0.82 (0.53-1.28)
Increasing baseline adherence score	0.94 (0.86-1.01)	0.92 (0.85-1.00)
Increasing months between V_i and V_{i+1}	**1.39 (1.29-1.49)**	**1.41 (1.31-1.51)**
Viral load >50 copies/mL at the previous visit	**33.93 (23.99-48.01)**	**17.22 (12.46-23.79)**

9.2.4 Chapter 6

Supplementary Table 9-6-1 Data source descriptions.

Data source name	Description	Included in HIV-specific contacts
Clinic visits	Information on clinic visits attended and medication received that is captured from the patient folder into the provincial clerical information system by a data clerk	Visits marked as ART visits and records of antiretroviral drugs dispensed
Laboratory tests	Laboratory test results covering all public health facilities in South Africa	CD4 and HIV viral load tests
Pharmacy dispensing	Pharmacy dispensing records from the central administrative pharmacy databases used in most public health facilities in the province	Dispensing of any antiretroviral drugs used to treat HIV

Supplementary Table 9-6-2 Characteristics of 617 women who initiated ART during pregnancy enrolled in the MCH-ART study, and the subset of 475 women who had a viral load available between 12 and 24 months on ART. Displayed as n (%) unless specified.

	Whole cohort	**Women with a 12-24 month viral load available**	**Women with no 12-24 month viral load available**
Number of women	617	475	142
Characteristics at presentation for ANC			
Mean age (SD)	29 (5)	29 (5)	28 (5)
Age <25 years	170 (28)	124 (26)	46 (32)
Currently employed	234 (38)	181 (38)	53 (37)
Finished high school	163 (26)	124 (26)	39 (27)
Married/cohabiting	253 (41)	193 (41)	60 (42)
Newly diagnosed HIV+ in this pregnancy	336 (54)	252 (53)	84 (59)
Mean gestation at presentation for ANC (SD)[1]	21 (8)	21 (7)	22 (8)
Presented for ANC prior to 20 weeks gestation	293 (48)	226 (48)	67 (48)
Median CD4 cell count at ART start[2]	345 (237-515)	348 (241-417)	340 (234-503)
CD4 <350 cells/μL	305 (51)	231 (50)	74 (52)
Enrolment in MCH-ART study			
Observational cohort only	152 (25)	60 (13)	92 (65)
SOC trial arm	236 (38)	212 (43)	24 (17)
Intervention trial arm	229 (37)	203 (45)	26 (18)
Retention estimates			
All data sources			
Cross-sectional (0-12 m)	614 (100)	474 (100)	140 (99)
Cross-sectional (12-24 m)	445 (72)	395 (83)	50 (35)
6m visit constancy (0-24 m)	294 (48)	277 (58)	17 (12)
12m visit constancy ((0-24 m)	445 (72)	395 (83)	50 (35)
HRSA-HAB (0-24 m)	378 (61)	343 (72)	35 (25)
No 180-day gap	256 (41)	243 (51)	13 (9)
Clinic visit data only			
Cross-sectional (0-12 m)	610 (98)	470 (100)	140 (94)
Cross-sectional (12-24 m)	388 (63)	349 (74)	39 (26)
6m visit constancy (0-24 m)	251 (40)	232 (49)	19 (13)
12m visit constancy ((0-24 m)	387 (62)	349 (74)	38 (26)
HRSA-HAB (0-24 m)	324 (52)	297 (63)	27 (18)
No 180-day gap	211 (34)	198 (42)	13 (9)
Viral load 12-24 m on ART			
Viral load <1000 copies/mL		354 (75)	
Viral load <50 copies/mL		319 (67)	

[1] Gestation at presentation for antenatal care (ANC) was available for 613 women; [2] CD4 counts available for 601 women; SD – standard deviation; m – months

Supplementary Table 9-6-3 Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of different definitions of non-retention up to 24 months on ART, to predict viral load (VL) ≥1000 copies/mL among women with a viral load available 12-24 months on ART (n=475).

	Data source	VL≥1000 (n=121)	VL<1000 (n=354)	Sensitivity	Specificity	PPV	NPV	AUC	LR+	LR-	Crude OR
<100% 6-month visit constancy	Clinic visits, laboratory tests & pharmacy	99	97	82 (74-88)	72 (67-77)	50 (43-58)	92 (88-95)	0.77 (0.73-0.81)	3.0 (2.5-3.6)	0.3 (0.2-0.4)	11.9 (7.1-19.9)
	Clinic visits & laboratory tests	102	111	84 (77-90)	69 (64-73)	48 (41-55)	93 (89-96)	0.77 (0.72-0.81)	2.7 (2.2-3.2)	0.2 (0.2-0.3)	11.8 (6.9-20.0)
	Laboratory tests	116	340	96 (91-99)	4 (2-7)	25 (22-30)	74 (49-91)	0.50 (0.48-0.52)	1.0 (1.0-1.0)	1.0 (0.4-2.8)	0.9 (0.4-2.6)
	Clinic visits	108	132	89 (82-94)	63 (57-68)	45 (39-52)	95 (91-97)	0.76 (0.72-0.80)	2.4 (2.1-2.8)	0.2 (0.1-0.3)	13.7 (7.4-25.1)
<100% 12-month visit constancy	Clinic visits, laboratory tests & pharmacy	51	29	42 (33-52)	92 (88-94)	64 (52-74)	82 (78-86)	0.67 (0.62-0.72)	5.2 (3.4-7.7)	0.6 (0.5-0.7)	8.2 (4.8-13.8)
	Clinic visits & laboratory tests	53	30	44 (35-53)	92 (88-94)	64 (53-74)	83 (79-86)	0.61 (0.52-0.72)	5.2 (3.5-7.7)	0.6 (0.5-0.7)	8.4 (5.0-14.1)
	Laboratory tests	67	90	55 (46-64)	75 (70-79)	43 (35-51)	83 (78-87)	0.65 (0.60-0.70)	2.2 (1.7-2.8)	0.6 (0.5-0.7)	3.5 (2.3-5.5)
	Clinic visits	69	54	57 (48-66)	85 (81-88)	56 (47-65)	85 (81-89)	0.71 (0.66-0.76)	3.7 (2.8-5.0)	0.5 (0.4-0.6)	7.2 (4.5-11.4)
<100% HRSA-HAB	Clinic visits, laboratory tests & pharmacy	77	55	64 (54-72)	85 (80-88)	58 (49-67)	87 (83-91)	0.74 (0.69-0.79)	4.1 (3.1-5.4)	0.4 (0.3-0.5)	9.5 (6.0-15.2)
	Clinic visits & laboratory tests	83	60	69 (60-77)	83 (79-87)	58 (50-66)	89 (85-92)	0.76 (0.71-0.80)	4.1 (3.1-5.3)	0.4 (0.3-0.5)	10.7 (6.7-17.2)
	Laboratory tests	107	290	88 (81-94)	18 (14-23)	27 (23-32)	82 (72-90)	0.53 (0.50-0.58)	1.1 (1.0-1.2)	0.6 (0.4-1.1)	1.7 (0.9-3.1)
	Clinic visits	91	84	75 (67-83)	76 (72-81)	52 (44-60)	90 (86-93)	0.76 (0.71-0.80)	3.2 (2.6-3.9)	0.3 (0.2-0.4)	9.8 (6.1-15.7)
Any 180-day gap	Clinic visits, laboratory tests & pharmacy	112	120	93 (86-97)	66 (61-71)	48 (42-55)	96 (93-98)	0.79 (0.76-0.83)	2.7 (2.3-3.2)	0.1 (0.1-0.2)	24.3 (12.0-48.9)
	Clinic visits & laboratory tests	112	147	93 (86-97)	59 (53-64)	43 (37-50)	96 (92-98)	0.76 (0.72-0.79)	2.2 (2.0-2.6)	0.1 (0.1-0.2)	17.5 (8.7-35.2)
	Laboratory tests	120	350	99 (96-100)	1 (0.3-3)	26 (22-30)	80 (28-100)	0.50 (0.49-0.51)	1.0 (1.0-1.0)	0.7 (0.1-6.5)	1.4 (0.2-12.4)
	Clinic visits	112	162	93 (86-97)	54 (49-60)	41 (35-47)	96 (92-98)	0.73 (0.70-0.77)	2.0 (1.8-2.3)	0.1 (0.1-0.3)	14.7 (7.3-29.6)

Supplementary Table 9-6-4 Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of different definitions of non-retention 0-24 months on ART, to predict viral load (VL) ≥1000 copies/mL, assuming missing viral loads were ≥1000 copies/mL (n=617).

	Data source	VL≥1000 (n=263)	VL<1000 (n=354)	Sensitivity	Specificity	PPV	NPV	AUC	LR+	LR-	Crude OR
<100% 6-month visit constancy	Clinic visits, laboratory tests & pharmacy	222	97	84 (80-89)	73 (68-77)	70 (64-75)	86 (82-90)	0.79 (0.75-0.82)	3.1 (2.6-3.7)	0.2 (0.2-0.3)	14.3 (9.6-21.5)
	Clinic visits & laboratory tests	225	111	86 (81-90)	69 (64-73)	67 (62-72)	987 (82-90)	0.77 (0.74-0.80)	2.7 (2.3-3.2)	0.2 (0.2-0.3)	13.0 (8.6-19.5)
	Laboratory tests only	258	340	98 (96-99)	4 (2-7)	43 (39-47)	74 (49-91)	0.51 (0.50-0.52)	1.0 (1.0-1.1)	0.5 (0.2-1.3)	2.1 (0.8-5.7)
	Clinic visits only	234	132	89 (85-93)	63 (57-68)	64 (59-69)	88 (84-92)	0.76 (0.73-0.79)	2.4 (2.1-2.8)	0.2 (0.1-0.3)	13.6 (8.7-21.1)
<100% 12-month visit constancy	Clinic visits, laboratory tests & pharmacy	143	29	54 (48-61)	92 (88-94)	83 (77-88)	73 (69-77)	0.73 (0.70-0.76)	6.6 (4.6-9.6)	0.5 (0.4-0.6)	13.4 (8.5-20.1)
	Clinic visits & laboratory tests	146	30	56 (49-62)	92 (88-94)	83 (77-88)	74 (69-78)	0.74 (0.70-0.77)	6.6 (4.6-9.4)	0.5 (0.4-0.6)	13.5 (8.6-21.0)
	Laboratory tests	185	90	70 (64-76)	75 (70-79)	67 (61-73)	77 (72-82)	0.73 (0.69-0.76)	2.8 (2.3-3.4)	0.4 (0.3-0.5)	7.0 (4.9-9.9)
	Clinic visits	177	54	67 (61-73)	85 (81-88)	77 (71-82)	78 (73-82)	0.76 (0.73-0.79)	4.4 (3.4-5.7)	0.4 (0.3-0.5)	11.4 (7.8-16.8)
<100% HRSA-HAB	Clinic visits, laboratory tests & pharmacy	184	55	70 (64-75)	85 (80-88)	77 (71-82)	79 (75-83)	0.77 (0.74-0.81)	4.5 (3.5-5.8)	0.4 (0.3-0.4)	12.7 (8.6-18.7)
	Clinic visits & laboratory tests	196	60	75 (69-80)	83 (79-87)	77 (71-82)	81 (77-85)	0.79 (0.76-0.82)	4.4 (3.5-5.6)	0.3 (0.2-0.4)	14.3 (9.7-21.2)
	Laboratory tests	245	290	93 (89-96)	18 (14-23)	46 (42-50)	78 (68-86)	0.56 (0.53-0.58)	1.1 (1.1-1.2)	0.4 (0.2-0.6)	3.0 (1.7-5.2)
	Clinic visits	209	84	80 (74-84)	76 (72-81)	71 (66-76)	83 (79-87)	0.78 (0.75-0.81)	3.4 (2.8-4.1)	0.3 (0.2-0.3)	12.4 (8.5-18.3)
Any 180-day gap	Clinic visits, laboratory tests & pharmacy	241	120	92 (88-95)	66 (61-71)	67 (62-72)	91 (87-95)	0.79 (0.76-0.82)	2.7 (2.3-3.1)	0.1 (0.1-0.2)	21.4 (13.1-34.7)
	Clinic visits & laboratory tests	241	147	92 (88-95)	59 (53-64)	62 (57-67)	90 (86-94)	0.75 (0.72-0.78)	2.2 (1.9-2.5)	0.1 (0.1-0.2)	15.4 (9.5-25.0)
	Laboratory tests	262	350	99 (98-100)	1 (0.3-3)	43 (39-47)	80 (28-100)	0.50 (0.50-0.51)	1.0 (1.0-1.0)	0.3 (0.1-3.0)	3.0 (0.3-26.9)
	Clinic visits	244	162	93 (89-96)	54 (49-60)	60 (55-65)	91 (86-95)	0.74 (0.71-0.77)	2.0 (1.8-2.3)	0.1 (0.1-0.2)	15.2 (9.2-25.3)

9.2.5 Chapter 7

Supplementary Table 9-7-1 Description of 485 HIV-positive women, who had evidence of linking to care after leaving the integrated clinic, by the number of different clinics attended up to 30 months after ART initiation. Presented as n (%) unless specified.

	Attended 1 clinic	**Attended ≥2 clinics**	**All women**	**p-value**
Number of women	384 (79)	101 (21)	485 (100)	
Characteristics at enrolment				
Mean age (SD)	29 (5.3)	28 (5.3)	28 (25-32)	0.034
Age ≤25	86 (22)	36 (36)	122 (25)	0.006
Married/cohabiting	169 (44)	47 (47)	216 (45)	0.650
Completed secondary school	104 (27)	20 (20)	124 (26)	0.136
Employed	152 (40)	30 (30)	182 (38)	0.068
First pregnancy	61 (16)	22 (22)	83 (17)	0.161
Intended pregnancy	114 (30)	32 (32)	146 (30)	0.697
Diagnosed with HIV in this pregnancy	199 (52)	56 (55)	255 (53)	0.516
Mean weeks gestation (SD)	21 (7.4)	21 (7.4)	21 (7.4)	0.373
Presented for ANC ≤20 weeks	183 (48)	48 (48)	231 (48)	0.981
Median (IQR) CD4 cell count at presentation for ANC (n=481)	341 (236-522)	343 (211-496)	341 (235-509)	0.344
Characteristics at delivery				
Place of delivery (n=467)				
Delivered in primary care	150 (40)	40 (42)	190 (41)	0.826
Delivered at tertiary hospital	221 (60)	56 (58)	277 (59)	
Delivery outcome				
Live birth	369 (96)	95 (94)	464 (96)	0.486
Stillbirth	8 (2)	3 (3)	11 (2)	
Miscarriage	5 (1)	1 (1)	6 (1)	
Unknown	2 (1)	2 (2)	4 (1)	
Characteristics postpartum				
Median (IQR) months from ART initiation until last evidence of accessing care	28 (21-29)	28 (22-29)	28 (21-29)	0.787
Median furthest distance (km) moved between clinics (SD)	1.06 (0.01-2.55)	4.14 (1.73-863.78)	1.07 (0.69-3.23)	<0.001
Area moved after integrated clinic				
Same health district	231 (60)	39 (39)	270 (56)	<0.001
Cape Town Metropole	133 (35)	24 (24)	157 (32)	
Western Cape Province	5 (1)	7 (7)	12 (2)	
Out of the Western Cape Province	15 (4)	31 (31)	46 (9)	
Retention in HIV care after ART initiation				
Retained at 12 months	340 (89)	98 (97)	438 (90)	0.010
Retained at 24 months	310 (81)	88 (87)	398 (82)	0.136
Retained at 12 and 24 months	278 (72)	85 (84)	363 (75)	0.015
Retained at 18 months after delivery	315 (82)	90 (89)	405 (84)	0.088

Supplementary Table 9-7-2 Poisson regression model among 485 women who linked to care after the integrated clinic, predicting whether women moved to more than one additional clinic. Presented as unadjusted (RR) and adjusted (aRR) risk ratios with 95% confidence intervals (CI).

	Crude		**Adjusted**	
	RR	**95% CI**	**aRR**	**95% CI**
Age ≤25	1.09	1.02-1.18	1.10	1.02-1.18
Not employed	1.06	1.00-1.13	1.06	0.99-1.12

Supplementary Table 9-7-3 Poisson regression model among 485 women who linked to care after the integrated clinic, predicting A) retention in care at 12 and 24 months after ART initiation, B) retention in care at 24 months after ART initiation, and C) retention in care at 18 months postpartum. Presented as unadjusted (RR) and adjusted (aRR) risk ratios with 95% confidence intervals (CI).

	Crude		**Adjusted**	
A: retention in care at 12 and 24 months after ART initiation				
	RR	**95% CI**	**aRR**	**95% CI**
Age >25	1.17	1.02-1.34	1.17	1.02-1.33
Married/cohabiting	1.13	1.02-1.26	-	
Primigravida	0.88	0.75-1.04	-	
Planned pregnancy	1.20	1.09-1.33	1.20	1.09-1.33
Presented for ANC <20 weeks gestation	1.13	1.02-1.25	1.10	0.99-1.21
Employed	1.09	0.98-1.21	-	
B: retention in care at 24 months after ART initiation				
	RR	**95% CI**	**aRR**	**95% CI**
Age >25	1.06	0.95-1.17	-	
Married/cohabiting	1.07	0.99-1.16	-	
Primigravida	0.89	0.78-1.02	0.87	0.76-0.99
Planned pregnancy	1.15	1.07-1.24	1.17	1.08-1.27
Presented for ANC <20 weeks gestation	1.08	0.99-1.17	-	
Employed	0.92	0.85-1.00	1.07	0.99-1.16
C: retention in care at 18 months postpartum				
	RR	**95% CI**	**aRR**	**95% CI**
Age >25	1.07	0.97-1.18	-	
Married/cohabiting	1.07	0.99-1.16	-	
Primigravid	0.89	0.78-1.01	0.87	0.77-0.99
Planned pregnancy	1.14	1.06-1.22	1.16	1.07-1.25
Presented for ANC <20 weeks gestation	1.06	0.98-1.15	-	
Employed	1.04	0.93-1.13	-	

Supplementary Table 9-7-4 Description of 338 women with viral load (VL) ≤50 and >50 copies/mL who were retained at both 12 and 24 months after ART initiation and had a VL available at least 12 months after ART initiation. Presented as n (%) unless specified.

	VL ≤50 copies/mL	**VL >50 copies/mL**	**All women**	**p-value**
Number of women	273 (81)	65 (19)	338 (100)	
VL source				
NHLS	174 (64)	32 (49)	206 (61)	0.031
MCH-ART study	99 (36)	33 (51)	132 (39)	
Median (IQR) months postpartum at time of VL test	18 (18-20)	18 (17-21)	18 (18-20)	0.933
Median months since ART start at time of VL test	23 (22-24)	23 (21-24)	23 (21-24)	0.449
Characteristics at enrolment				
Mean age (SD)	30 (5.4)	27 (4.8)	29 (5.4)	0.003
Age ≤25	53 (19)	22 (34)	75 (22)	0.012
Married/cohabiting	133 (49)	24 (37)	157 (46)	0.087
Completed secondary school	74 (27)	11 (17)	85 (25)	0.089
Employed	117 (43)	18 (28)	135 (40)	0.025
First pregnancy	39 (14)	13 (20)	52 (15)	0.251
Intended pregnancy	101 (37)	17 (26)	118 (35)	0.099
Diagnosed with HIV in this pregnancy	149 (55)	24 (37)	173 (51)	0.010
Mean weeks gestation (SD)	21 (8.9)	20 (7.1)	20 (7.2)	0.118
Presented for ANC ≤20 weeks gestation	143 (52)	29 (45)	172 (51)	0.260
Median (IQR) CD4 cell count at presentation for ANC (n=330)	341 (235-520)	350 (232-440)	337 (235-504)	0.525
Characteristics at delivery				
Place of delivery (n=327)				
Delivered in primary care	109 (41)	25 (41)	134 (41)	0.999
Delivered at tertiary hospital	157 (59)	36 (59)	193 (59)	
Delivery outcome				
Live birth	263 (96)	63 (97)	326 (96)	0.131
Stillbirth	4 (1)	1 (2)	5 (1)	
Miscarriage	6 (2)	0(0)	6 (2)	
Unknown	0 (0)	1 (2)	1 (<1)	
Characteristics postpartum				
Number of clinics after the integrated clinic				
Attended 1 clinic	221 (81)	40 (62)	261 (77)	0.001
Attended ≥ 2 clinics	52 (19)	25 (38)	77 (23)	
Median furthest distance (km) moved between clinics	1.06 (0.69-3.04)	1.99 (0.71-3.23)	1.06 (0.69-3.23)	0.110
Area moved after integrated clinic				
Same health district	160 (58)	35 (54)	195 (57)	0.508
Cape Town Metropole	89 (33)	21 (32)	110 (33)	
Western Cape Province	6 (2)	3 (5)	9 (3)	
Out of the Western Cape Province	118 (7)	6 (9)	24 (7)	

Supplementary Table 9-7-5 Description of 338 HIV-positive women with viral load (VL) ≤1000 and >1000 copies/mL who were retained at both 12 and 24 months after ART initiation and had a VL available at least 12 months after ART initiation. Presented as n (%) unless specified.

	VL ≤1000 copies/mL	**VL >1000 copies/mL**	**All women**	**p-value**
Number of women	294 (87)	44 (13)	338 (100)	
Characteristics at enrolment				
Mean age (SD)	29 (5.4)	27 (5.0)	29 (5.4)	0.010
Age ≤25	59 (20)	16 (36)	75 (22)	0.015
Married/cohabiting	146 (50)	11 (25)	157 (46)	0.002
Completed secondary school	78 (27)	7 (16)	85 (25)	0.130
Employed	126 (43)	9 (20)	135 (40)	0.005
First pregnancy	42 (14)	10 (23)	52 (15)	0.148
Intended pregnancy	109 (37)	9 (20)	118 (35)	0.031
Diagnosed with HIV in this pregnancy	156 (53)	17 (39)	173 (51)	0.074
Mean weeks gestation (SD)	21 (8.9)	23 (7.0)	20 (7.2)	0.012
Presented for ANC <20 weeks gestation	155 (53)	17 (39)	172 (51)	0.081
Median (IQR) CD4 cell count at presentation for ANC (n=328)	345 (237-512)	320 (200-436)	337 (235-504)	0.253
Characteristics at delivery				
Place of delivery (n=327)				
Delivered in primary care	118 (42)	16 (37)	134 (41)	0.590
Delivered at tertiary hospital	166 (58)	27 (63)	193 (59)	
Delivery outcome				
Live birth	283 (96)	43 (98)	326 (96)	0.736
Stillbirth	4 (1)	1 (1)	5 (1)	
Miscarriage	6 (2)	0 (0)	6 (2)	
Unknown	1 (<1)	0 (0)	1 (<1)	
Characteristics postpartum				
Number of clinics after the integrated clinic				
Attended 1 clinic	232 (79)	29 (66)	261 (77)	0.055
Attended ≥ 2 clinics	62 (21)	15 (34)	77 (23)	
Area moved after integrated clinic				
Same health district	170 (58)	25 (57)	195 (57)	0.398
Cape Town Metropole	94 (32)	16 (36)	110 (33)	
Western Cape Province	7 (3)	2 (5)	19 (3)	
Out of the Western Cape Province	23 (8)	1 (2)	24 (7)	

Supplementary Table 9-7-6 Description of study outcomes by the design of follow up received in the parent MCH-ART study.

	Not enrolled in the MCH-ART trial (no prospective follow-up after delivery)	**Enrolled in the MCH-ART trial and received standard transfer out of the integrated clinic**	**Enrolled in the MCH-ART trial and received delayed transfer out of the integrated clinic**
Number of women	152	236	229
Median months of follow-up after leaving the integrated clinic	26 (24-27)	25 (24-26)	18 (14-23)
Linked to care	122 (80)	193 (82)	170 (74)
If linked (n=485), attended ≥2 clinics	28 (23)	32 (17)	41 (24)
Retained in care at 12 months on ART	106 (70)	176 (75)	193 (84)
Retained in care at 24 months on ART	95 (63)	149 (63)	158 (69)
Retained at both 12 and 24 months on ART	80 (53)	136 (58)	150 (66)
Number of women retained in care at both 12 and 24 months on ART and with viral load after 12 months on ART available (n=341)	62 (41)	132 (56)	147 (64)
Viral load ≤50 copies/mL	52 (84)	104 (79)	119 (81)
Viral load ≤1000 copies/mL	57 (92)	113 (86)	126 (86)

9.3 Validation of the self-reported adherence measure used in Chapters 4 and 5

Phillips TK, Brittain K, Mellins CA, Zerbe A, Remien RH, Abrams EJ, Myer L, Wilson IB. A self-reported adherence measure to screen for elevated HIV viral load in pregnant and postpartum women on antiretroviral therapy. *AIDS Behav* 2017; **21**:450–461.

Relevance of this paper to the thesis:

This manuscript is included in this thesis as an appendix as it presents a preliminary cross-sectional validation of the self-reported adherence scale used in Chapters 4 and 5. The paper shows that a simple three-item self-reported adherence scale that was developed in the United States, was successfully translated into isiXhosa with good psychometric characteristics and moderate ability to detect viremia. This initial work laid the foundation for the longitudinal analyses in Chapter 5.

Contribution of the student and co-authors:

TP conceived the design with support from IW and LM. IW originaly developed the self-report scale in the United States and provided technical and conceptual feedback. TP conducted the analysis and drafted the manuscript. All co-authors reviewed the manuscript and provided conceptual and intellectual comment. All authors were involved in the final draft of the manuscipt.

Abstract

Maternal adherence to antiretroviral therapy (ART) is a concern and monitoring adherence presents a significant challenge in low resource settings. We investigated the association between self-reported adherence, measured using a simple three-item scale, and elevated viral load (VL) among HIV-infected pregnant and postpartum women on ART in Cape Town, South Africa. This is the first reported use of this scale in a non-English speaking setting and it achieved good psychometric characteristics (Cronbach α=0.79). Among 452 women included in the analysis, only 12% reported perfect adherence on the self-report scale, while 92% had a VL<1000 copies/mL. Having a raised VL was consistently associated with lower median adherence scores and the area under the curve for the scale was 0.599, 0.656 and 0.642 using a VL cut off ≥50, ≥1000 and ≥10000 copies/mL, respectively. This simple self-report adherence scale shows potential as a first stage adherence screener in this setting. Maternal adherence monitoring in low resource settings requires attention in the era of universal ART, and the value of this simple adherence scale in routine ART care settings warrants further investigation.

Introduction

Expanding access to antiretroviral therapy (ART) for HIV-infected pregnant and postpartum women living in low- and middle-income countries (LMIC) has improved maternal health and reduced the risk of mother-to-child transmission (PMTCT) [1–3]. These improvements rely on optimal adherence to ART both during pregnancy and following delivery. Following successful initiation of treatment, the next challenge is successful implementation of the ART regimen for as long as a woman remains on lifelong ART [4]. Treatment implementation and persistence among pregnant and postpartum women is often suboptimal [5–7], and measurement of ART adherence in LMICs presents a significant challenge.

Long a standard tool for monitoring HIV treatment in high-income countries, viral load (VL) testing is being promulgated by the World Health Organization (WHO) as an important tool for HIV patient management in LMIC [2]. Although VL may be influenced by numerous factors, including drug resistance, poor ART adherence is the main cause of non-suppressed VL globally [8–11] and identification of patients with adherence difficulties is a major goal of VL testing. Viral load is indispensable for determining treatment failure and is potentially a valuable tool to reinforce adherence, however it is expensive, measurement is often infrequent, and it also does not directly capture medication taking behaviour. Because of this, both clinicians and researchers are interested in the development of measures which can be conducted frequently with limited resources, which adequately capture patient behaviour, and which can potentially identify adherence problems prior to the development of high viremia [2,12–14].

There are trade-offs for virtually every approach to measuring medication adherence [15,16]. Objective adherence measures, such as electronic drug monitoring (EDM), are often significantly associated with VL, but are generally not feasible in low resource settings [17–20]. EDM is also prone to measurement bias. Although objective, EDM does not directly measure medication taking and may overestimate adherence if pills are pocketed. Pill counts are inexpensive but require time from trained staff and are prone to pill dumping. Pharmacy refill has shown potential but is retrospective and still relies on the assumption that patients ingest the medication they have collected. Self-report is also prone to social desirability, recall bias and question misinterpretation, as well as ceiling effects, where large fractions of a population score at the top of a scale [9,16]. However, self-reported adherence measures are simple and inexpensive to administer and are often the only practical method available for routine adherence monitoring in low resource settings [9,21]. Self-reported adherence has at

times been shown to correlate with VL and objective adherence measures, with the added advantage of allowing for the immediate discussion between patient and provider of reasons for adherence problems and potential solutions [21].

There are a multitude of self-reported measures available both in research and in routine care, and there has been ongoing work to improve the validity, reliability and practicality of these measures [9,16,17,21–25]. One concern with self-report is that the adherence questions asked may be understood differently by different people and that varying recall periods and types of questions illicit responses of varying accuracy [22,23]. Through a rigorous process of cognitive interviewing, Wilson *et al* found that many of the phrases commonly used in self-reported adherence tools were not consistently understood across a diverse cohort in the United States (US) [26]. Following interviews and a larger field test, they selected the three best performing and consistently understood items to form a simple three-item adherence screening tool [26]. The tool has potential to be a first stage adherence screener to prompt discussion of adherence problems and to flag individuals requiring more resource-intensive second stage screening, adherence counselling and intervention as appropriate. These items have not yet been tested outside the US [26,27].

There is an urgent need for low cost, sensitive and easy to administer adherence screening tools that have been tested in diverse contexts, including among pregnant and postpartum women for whom non-adherence has consequences for both individual health and transmission risk [14,22,23,28,29]. To fill this gap, we assessed the above mentioned, short self-report adherence measure in a cohort of pregnant and post-partum women in South Africa who had persisted on treatment up to the time of assessment. We translated the adherence items into the predominant local language, isiXhosa, and aimed to investigate the performance of the scale as a screening tool to identify sub-optimal adherence, using VL as the reference standard. A secondary aim was to assess differences in reported adherence across sociodemographic subgroups, including psychosocial risk groups.

Methods

We conducted a cross-sectional analysis of self-reported adherence and VL using data from a larger multi-phase implementation science study which aims to optimize ART services for maternal and child health (MCH-ART study, ClinicalTrial.gov NCT01933477). The study took place at a large public sector primary care facility in Cape Town, South Africa. The surrounding community is characterised by high levels of poverty and unemployment, and

high HIV prevalence (33% of antenatal clinic attenders were HIV-infected in 2013). ART services have been provided at this facility since 2004 and all care is provided free of charge.

Participants

Between April 2013 and June 2014, consecutive HIV-infected women, 18 years and older, booking for antenatal care (ANC) and eligible to start ART were approached to enrol. ART eligibility was based on CD4≤350 cells/μL and clinical staging until July 2013, when universal ART for all pregnant women was introduced [30]. ART initiation and follow-up is routinely provided by nurse-midwives working within the antenatal clinic. As per local PMTCT guidelines, all ART-eligible women initiate a once daily fixed-dose combination of efavirenz (EFV), emtricitabine (FTC) or lamivudine (3TC), and tenofovir (TDF). Dispensing is monthly for the first 4 months on treatment and every 1-2 monthly thereafter. Adherence is assessed at routine ART consultations by either self-report of missed doses or pill counts, with adherence support and counselling provided by trained lay counsellors to those who need it.

Of 658 eligible women, 628 were enrolled in the MCH-ART study (3 women refused participation and 27 were not successfully enrolled prior to delivery due to advanced gestation at ANC booking). All women provided written informed consent prior to participation and completed up to four study measurement visits between ART initiation and six weeks post-delivery, with study visits occurring separately from routine ART and ANC services. This study was reviewed and approved by the Human Research Ethics Committee of the University of Cape Town, Faculty of Health Sciences as well as the Institutional Review Board of the Columbia University Medical Centre.

Procedures

Study visits including adherence assessments were scheduled a) at 2-4 weeks after ART initiation, b) at 34 weeks gestation, c) within 7 days of delivery, and d) at 6 weeks postpartum. They included interviewer-administered questionnaires and venepuncture for VL testing. We translated all interview measures into isiXhosa, the predominant local language, with back translation to confirm accuracy [31]. Questionnaires were administered by trained isiXhosa-speaking interviewers working in private rooms.

Measures

Demographic characteristics, including age, education level, gravidity, timing of HIV diagnosis and prior antiretroviral (ARV) use were collected at enrolment. A composite poverty score, including employment and a standardised asset index score, was compiled and used to categorise participants into tertiles based on their relative level of disadvantage.

Self-reported adherence was measured using a three-item adherence scale, developed through rigorous cognitive interviewing, as previously reported [26,27]. The three items included (1) an assessment of the number of days with missed ART doses in the preceding 30 days; (2) a scale rating of how good a job you did taking your medicines in the preceding 30 days and (3) a scale rating of how often you took your medicines the way you were supposed to in the preceding 30 days (Table 9-1). The items making up the tool were previously found to be consistently understood by a diverse cohort in the US where the tool had excellent internal consistency (α=0.86) [26].

Depression was measured using the Edinburgh Postnatal Depression Scale (EPDS), a 10-item measure of recent depressive symptoms validated for use both in antenatal and postnatal women. We used a threshold value of $\geq$13 for possible major depression as described in the original scale development [32].

Alcohol use in the 12 months prior to booking for ANC was measured using the Alcohol Use Disorders Identification Test (AUDIT), one of the most widely used measures of risky alcohol use. The full 10-item tool was developed by the WHO to identify people with hazardous or harmful patterns of alcohol consumption. In this analysis, we have used the AUDIT-C tool, comprised of the first three items in the AUDIT, to serve as a rapid screening tool for problem drinking. We used the recommended threshold of three or above to identify hazardous drinking [33].

HIV RNA VL was measured at all study visits. We conducted venepuncture for HIV RNA VL at each study measurement visit. Five mL venous blood was drawn for testing conducted by the National Health Laboratory Services using the Abbott RealTime HIV-1 assay (Abbott Laboratories, Illinois, USA). Viral load and self-reported adherence measures always took place on the same day. All items in the adherence tool refer to the 30 days prior to the measurement visit, meaning reported adherence problems were likely to reflect in the VL measure. We included women in this analysis who had at least one study visit including VL and adherence measurement after at least 16 weeks on treatment, and who had persisted on

ART from initiation up to the time of assessment. These restrictions were used to ensure that, assuming good treatment implementation, all women could be reasonably expected to have reached viral suppression at the time of assessment [30,34].

Table 9-1 Three-item self-reported adherence scale items.

Item	**Response**
1. In the last 30 days, on how many days did you miss at least one dose of any of your HIV medicines?	# of days (0-30)
2. In the last 30 days, how good a job did you do at taking your HIV medicines in the way that you were supposed to?	Very poor = 1 Poor = 2 Fair = 3 Good = 4 Very good = 5 Excellent = 6
3. In the last 30 days how often did you take your HIV medicines in the way that you were supposed to?	Never = 1 Rarely = 2 Sometimes = 3 Usually = 4 Almost always = 5 Always = 6

Analyses

Data were analysed in STATA V12.0 (Stata Corporation, College Station, Texas, USA). The distribution of the three individual adherence items was described using medians with interquartile range (IQR). In addition, an aggregate scale was developed, based on a re-coding of each item with equal weighting, to create a score ranging from 0-100, with the latter representing the best possible self-reported adherence. We assessed internal consistency using Cronbach's alpha, and determined the association between VL and the adherence scale using logistic regression and Receiver Operating Characteristic (ROC) curve analysis. In the primary analyses, we used a VL cut point of 1000copies/mL to indicate elevated VL based on local and international threshold for treatment failure and regimen change [2,30]. This measure was based on a single VL, taken at the same time as the self-reported adherence assessment. Additional cut points of 50 and 10000 cps/mL were used in sensitivity analyses. We compared the area under the curve (AUC) for the three-item scale across sociodemographic and psychosocial categories in order to compare the performance of the scale across different subgroups.

Results

Patients

A total of 628 women were enrolled in the parent study. We included 452 women who had at least one study visit that included adherence and VL measures after a minimum of 16 weeks on ART. The majority of exclusions (n=169) were as a result of having insufficient time on ART at all available study assessments. An additional 7 women were missing the required measures and were also excluded. When we compared women excluded and included, we found no differences at baseline other than a later gestation at ART initiation among women excluded, as expected with the cut off of 16 weeks on treatment. All included women had persisted on treatment up to the time of the assessment and they are described in Table 9-2. The median age was 28 years, 74% of women had not completed secondary school and 41% were married or cohabiting. The median pre-ART VL was 10,587copies/mL (IQR, 2,603-43,099copies/mL). Twenty-six percent of women reported hazardous drinking prior to ANC booking, and 10% of women had an EPDS score suggesting possible depression. At the time of the adherence assessment, 33% (n=147) of women were pregnant (median gestation 34 weeks) and the remaining 305 women had recently delivered (median time postpartum 1.4 weeks). The median duration of ART use at the time of adherence assessment was 19 weeks (IQR, 18-21 weeks), and 92% of women had VL below 1000copies/mL.

Table 9-2 Description of 452 women who started ART during pregnancy and had an adherence assessment and viral load (VL) after at least 16 weeks on ART.

	Median (IQR) or N (%)
At the time of booking for ANC	
Median age (IQR)	28 (25-32)
18-24	111 (24)
25-30	193 (43)
30+	148 (33)
Education	
Completed secondary school	117 (26)
Did not complete secondary school	335 (74)
Poverty level (assets + employment)	
Least poverty	144 (32)
Moderate poverty	147 (32)
Most poverty	161 (36)
Hazardous drinking (Median AUDIT-C score)	0 (0-3)
Below threshold (<3)	334 (74)
Above threshold (≥3)	118 (26)
Depression Symptoms (Median EPDS score)	4 (1-8)
Below threshold (<13)	405 (90)
Above threshold (≥13)	47 (10)
Relationship	
Single	265 (59)
Married/ Cohabiting	187 (41)
HIV diagnosis/previous ARV exposure	
Diagnosed in this pregnancy	241 (53)
Diagnosed before; no past ARV use	88 (20)
Diagnosed before with past ARV use	123 (27)
Previous antiretroviral exposure	
ARV naive	329 (73)
Past ART use	18 (4)
Past PMTCT	105 (23)
Median gravidity (IQR)	2 (2-3)
Primigravida	80 (18)
Pre-ART HIV VL	
<50 copies/mL	16 (3)
50-1000 copies/mL	54 (12)
1001-10,000 copies/mL	148 (33)
10,001-100,000 copies/mL	186 (41)
>100,000 copies/mL	48 (11)
At the time of adherence assessment	
Pregnant at time of sampling	147 (33)
Median gestation (weeks)	34.1 (34.0-34.4)
Postpartum at time of sampling	305 (67)
Median weeks postpartum (IQR)	1.4 (1-6)
Median weeks of ART use at time of sampling	19.4 (17.7-21.1)
Median VL at the time of assessment (IQR)	10587 (2603-43099)
<50 copies/mL	374 (83)
50-1000 copies/mL	30 (9)
1001-10,000 copies/mL	20 (4)
10,001-100,000 copies/mL	13 (3)
>100,000 copies/mL	5 (1)

Item and scale characteristics

Table 9-3 shows descriptive statistics for the three individual adherence items and the combined scale. The item scores were higher (better adherence) for the item assessing days on which doses were missed (mean 97.1, median 100) compared with the rating and frequency items (means (medians) 78.5 (83.3) and 82.6 (83.3), for item 2 and 3 respectively). The distributions of the individual adherence items and the scale score are displayed in Figure 9-1. All histograms were right-skewed with high levels of reported adherence on all three individual items, however in the combined three-item scale, only 12% of women (n=55) reported the highest score in all three items and achieved a perfect score in the combined scale. The overall Cronbach's alpha was good, at 0.79.

Table 9-3 Summary of item and scale characteristics. All item scores converted to a standardised score out of 100.

	Item summary			Cronbach's Alpha			
	Mean (SD)	Median (IQR)	Max score obtained	item-test correlation	item-rest correlation	average inter-item correlation	alpha
Days missed item (Item 1)	97 (13)	100 (100-100)	100	0.823	0.600	0.596	0.747
Rating item (Item 2)	79 (16)	83 (67-83)	100	0.834	0.621	0.569	0.725
Frequency item (Item 3)	83 (17)	83 (67-100)	100	0.860	0.672	0.504	0.670
three-item scale	86 (13)	89 (78-94)	100	-	-	0.556	0.790

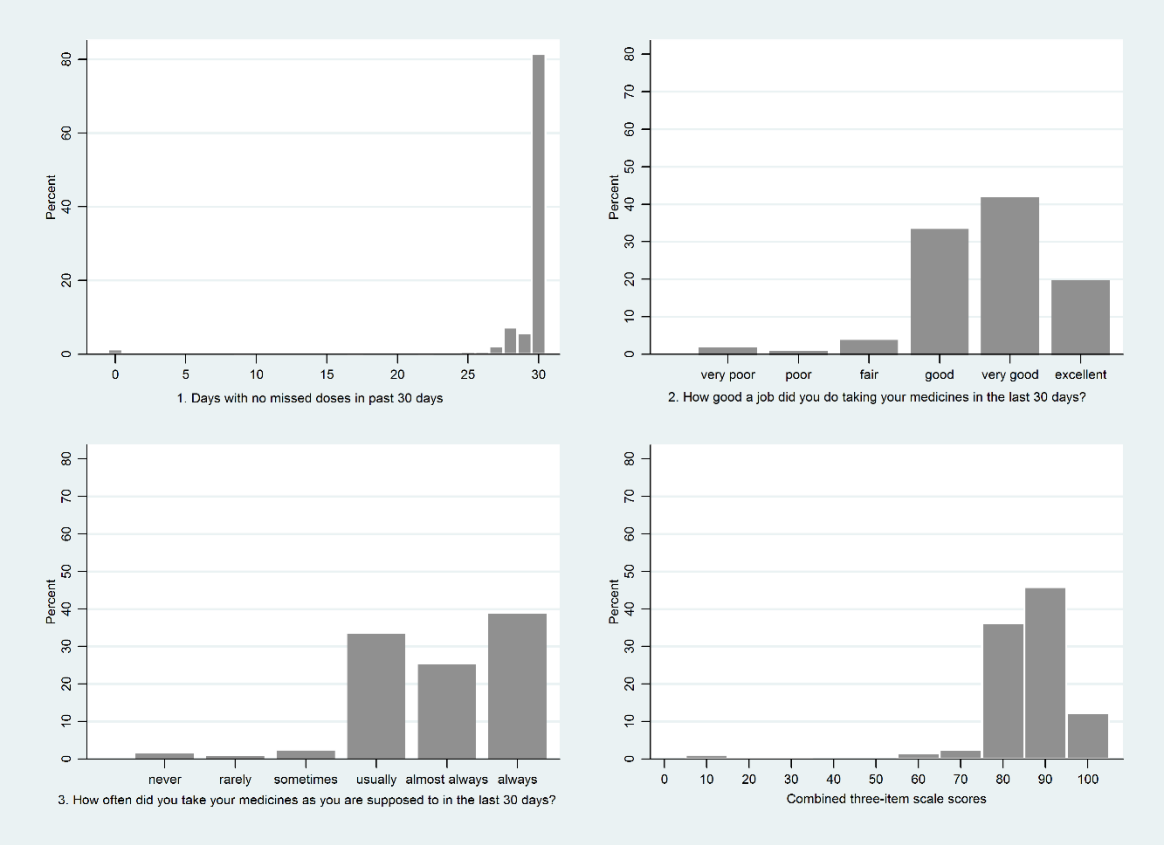


Figure 9-1 Histogram showing distribution of individual items and the combined three-item scale score.

Table 9-4 describes the distribution of item responses across sociodemographic and psychosocial strata and by VL above or below 1000 copies/mL. Overall, variations in scale scores within subgroups were of small magnitude, and varied significantly only by education, with higher scores among women who had completed secondary school compared to those who had not ($p<0.001$). Duration of ART use did not alter the scale score; however, women with longer time on treatment were more likely to have a raised VL using a cut off of both 50 and 1000copies/mL ($p<0.001$) (Table 9-5).

Table 9-4 Distribution of scale responses across participant subgroups and stratified by viral load (VL) ≥1000 copies/mL. Presented as median (IQR) of standardised score and area under the curve (AUC) for predicting VL ≥1000 copies/mL.

	Median three-item scale score (IQR)			ROC analysis	
	All women N=452	VL<1000 N=414	VL≥1000 N=38	AUC	p-value (AUC across categories)
All women	88.9 (77.8-94.4)	88.9 (77.8-94.4)	81.1 (75.6-88.9)	0.656	
Age					
18-24	88.9 (77.8-94.4)	88.9 (77.8-94.4)	81.1 (77.8-83.3)	0.676	0.952
25-30	88.9 (77.8-94.4)	88.9 (80-94.4)	83.9 (48.9-94.4)	0.643	
30+	88.9 (77.8-94.4)	88.9 (77.8-94.4)	82.2 (77.8-88.9)	0.639	
Education					
Completed secondary school	88.9 (83.3-94.4)*	92.2 (83.3-94.4)*	88.9 (81.1-88.9)	0.735	0.295
Did not complete secondary school	87.8 (77.8-94.4)	88.9 (77.8-94.4)	78.9 (75.6-94.4)	0.643	
Poverty level (assets + employment)					
Least poverty	88.9 (77.8-94.4)	88.9 (77.8-94.4)	83.3 (77.8-88.9)	0.631	0.281
Moderate poverty	88.9 (77.8-94.4)	88.9 (77.8-94.4)	77.8 (77.8-83.3)	0.762	
Most poverty	88.9 (77.8-94.4)	88.9 (81.1-94.4)	81.1 (62.2-94.4)	0.617	
Relationship					
Single	88.9 (77.8-94.4)	88.9 (77.8-94.4)	81.1 (77.8-88.9)	0.668	0.770
Married/ Cohabiting	88.9 (77.8-94.4)	88.9 (77.8-94.4)	81.1 (71.1-94.4)	0.635	
HIV diagnosis/previous ARV exposure					
Diagnosed in this pregnancy	88.9 (77.8-94.4)	88.9 (77.8-94.4)	81.1 (71.1-94.4)	0.629	0.441
Diagnosed before; no past ARV use	88.9 (77.8-94.4)	88.9 (77.8-94.4)	81.1 (63.3-83.3)	0.758	
Diagnosed before with past ARV use	88.9 (77.8-94.4)	88.9 (77.8-94.4)	80.6 (76.7-91.7)	0.641	
Hazardous alcohol use (AUDIT-C)					
Below threshold (<3)	88.9 (77.8-94.4)	88.9 (81.1-94.4)	81.1 (77.8-94.4)	0.635	0.327
Above threshold (≥3)	88.9 (77.8-94.4)	88.9 (77.8-94.4)	81.1 (71.1-83.3)	0.729	
Depressive symptoms (EPDS)					
Below threshold (<13)	88.9 (77.8-94.4)	88.9 (77.8-94.4)	81.1 (76.7-91.7)	0.639	0.394
Above threshold (≥13)	87.8 (77.8-94.4)	88.9 (77.8-94.4)	77.8 (11.1-83.3)	0.752	
Pregnant or postpartum at time of assessment					
Pregnant	88.9 (77.8-94.4)	88.9 (77.8-94.4)	81.1 (77.8-88.9)	0.677	0.867
Postpartum	88.9 (77.8-94.4)	88.9 (81.1-94.4)	77.8 (71.1-88.9)	0.655	
Median weeks on treatment					
16-20	88.9 (77.8-94.4)	88.9 (77.8-94.4)	81.1 (75.6-94.4)	0.639	0.777
20.1-24	88.9 (77.8-94.4)	88.9 (78.9-94.4)	82.2 (78.9-88.9)	0.646	
>24	88.9 (77.8-94.4)	93.3 (81.1-94.4)	77.8 (11.1-88.9)	0.719	

*p<0.05, **p<0.001 using Kruskal Wallis or Wilcoxon Rank Sum tests for scores within participant subgroups

Table 9-5 Proportion of women virally suppressed (<50 & <1000 copies/mL) by weeks on ART at the time of sampling (n=452).

	VL<50 N=374	VL≥50 N=78	VL<1000 N=414	VL≥1000 N=38
Median weeks on ART at time on sampling (IQR)	19.4 (17.6-21)	19.5(18-22.9)	19.4(17.6-21)	20.4(18-27.4)
16-20 weeks	221(59)	45(58)**	247(60)	19(50)**
20.1-24 weeks	134(36)	17(22)	145(35)	6(16)
>24 weeks	19(5)	16(21)	22(5)	13(34)

*p<0.05, **p<0.001 using Chi-squared Test for differences by viral load (VL) category

Relationships of three-item scale to viral loads

Crude and adjusted associations between the three-item adherence scale and VL ≥50, and ≥1000copies/mL are presented in Table 9-6. In bivariate analyses, having a raised VL was consistently associated with lower median scores on the adherence scale using a VL cut off of both ≥50 (median adherence scores 88.9 and 83.3, p=0.005), and ≥1000 copies/mL (median adherence scores 88.9 and 81.1, p=0.001). These associations persisted in multivariable analyses which adjusted for age and education. The AUC for the three-item scale was 0.599, 0.656 and 0.642 using a VL cut off of ≥50, ≥1000 and ≥10000 copies/mL, respectively (Figure 9-2). The AUC using a VL cut off of 1000copies/mL remained above 0.6 and did not vary significantly across subgroups of sociodemographic and psychosocial characteristics (Table 9-4).

Table 9-6 Distribution of three-item adherence scale scores stratified by VL≥50, and VL≥1000 copies/mL respectively (N=452). Scores presented as median (IQR) of a standardised score out of 100.

	Number of women	Median three-item score(IQR)	Crude regression coefficient (95% CI)	Age & education adjusted regression coefficient (95% CI)
VL<50	374	88.9 (77.8-94.4) *	-0.03 (-0.05, -0.02) **	-0.03 (-0.05, -0.01) *
VL≥50	78	83.3 (77.8-92.2)		
VL<1000	414	88.9 (77.8-94.4) *	-0.05 (-0.07, -0.03) **	-0.04 (-0.06, -0.02) **
VL≥1000	38	81.1(75.6-88.9)		

*p<0.05, **p<0.001 using the Wilcoxon Rank Sum test & logistic regression for differences by viral load (VL) category

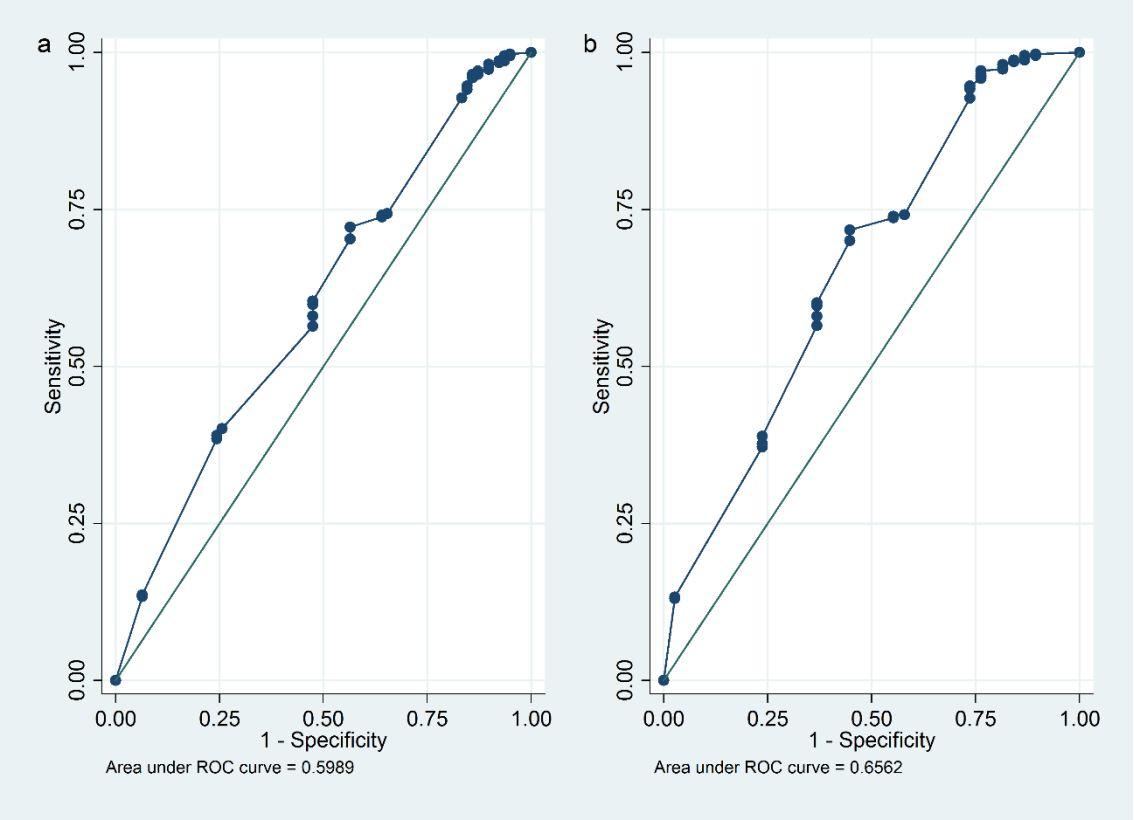


Figure 9-2 Receiver operating characteristic curves for three-item scale detecting VL≥50 (a) and VL≥1000 (b).

The sensitivity and specificity of the adherence scale for predicting VL ≥50, and ≥1000copies/mL, is presented in Table 9-7. Using a scale score cut off of <80, the scale had a low sensitivity for detecting those who truly had a VL above 50 or 1000 copies/mL (36 and 45%, respectively). Using a scale score cut off of <90, 74% and 76% of women with VLs ≥50 and ≥1000copies/mL were correctly identified using the three-item adherence scale, and a cut off of <100 identified more than 90% of women with VLs ≥50 and ≥1000copies/mL. All cut off scores resulted in very high negative predictive values with women with summary scale scores above or equal to 80, 90 and 100, having a 94, 95 or 98% chance of having a VL<1000copies/mL, respectively.

Table 9-7 Sensitivity, specificity and positive and negative predictive values of three-item adherence scale predicting viral load ≥50 and ≥1000 copies/mL, using a scale cut off score of <80, <90 and <100.

	Viral load		Sensitivity	Specificity	PPV	NPV
Adherence (three-item scale score)	Detectable (≥50)	Non-detectable (<50)				
Non-adherent (<80)	28	97	36%	74%	22%	85%
Adherent (≥80)	50	277				
	Detectable (≥50)	Non-detectable (<50)				
Non-adherent (<90)	58	224	74%	40%	21%	88%
Adherent (≥90)	20	150				
	Detectable (≥50)	Non-detectable (<50)				
Non-adherent (<100)	73	324	94%	13%	18%	91%
Adherent (100)	5	50				
	Detectable (≥1000)	Non-detectable (<1000)				
Non-adherent (<80)	17	108	45%	74%	14%	94%
Adherent (≥80)	21	306				
	Detectable (≥1000)	Non-detectable (<1000)				
Non-adherent (<90)	29	253	76%	39%	10%	95%
Adherent (≥90)	9	161				
	Detectable (≥1000)	Non-detectable (<1000)				
Non-adherent (<100)	37	360	97%	13%	9%	98%
Adherent (100)	1	54				

(PPV – positive predictive value, NPV – negative predictive value)

Discussion

This analysis had three main findings. First, the three-item self-reported adherence scale that we tested in pregnant and post-partum women on ART in South Africa had good psychometric characteristics and did not demonstrate the ceiling effects that self-report items often show. Second, self-reports had significant associations with elevated VL in both bivariate and multivariable models, and third, using ROC curves, the scale had only moderate ability to discriminate between patients elevated and non-elevated VL.

The scale used in our analysis consisted of three simple and easily understood adherence questions developed in English through a process of cognitive interviewing. Reviews have shown that self-reported measures range from single items asking for the number of prescribed doses missed in a specified time period to numerous complex items requiring detailed recall; very few studies report using the same self-reported adherence measure, making it difficult to compare results across studies [9,21,23]. An analysis in South Africa evaluating the performance of five commonly used self-reported adherence questions found

that all questions were poor predictors of virologic and/or immunologic failure [35]. Similarly, another study in Cape Town using a short adherence scale in HIV-infected adults found no correlation between the scale score and having a detectable VL [36]. Both of these studies used recall periods of seven days, much shorter than the 30-days used in our analysis. In the current analysis we found that although the effect sizes were relatively small, all individual adherence items, as well as the three-item scale, were significantly correlated with VL. The cognitive interviewing approach used in developing this scale, which resulted in a word choice aimed at minimizing social desirability as well as misinterpretation, may have resulted in improved responses to the adherence questions even in this new setting.

The distribution of each item and the three-item scale (Figure 9-1) found in this study was very similar to that reported in the US population of predominantly male adults on ART, though in our cohort a lower proportion obtained maximum scores on all three items and reached a score of 100 on the combined scale [26]. Our data did not show a large ceiling effect, a common problem for self-report adherence measures [9,16]. While ceiling effects can occur if the population is in fact highly adherent, in many cases it is rather a result of patients overestimating their adherence, typically due to social desirability effects [36–38]. While we did observe a ceiling effect for the missed doses item alone (80% reporting no missed doses), only 12% of women reported perfect adherence in the three-item scale. This three-item scale was developed paying particular attention to a word choice that optimizes accurate reporting. This scale may therefore be more sensitive to reported non-adherence than other scales that have shown more prominent ceiling effects, although this cannot be known definitively unless scales are compared head to head in the same populations. Previous studies in pregnant and postpartum women in Latin America and in Kenya using combination adherence scores based on pill counts and self-report have reported optimal adherence in more than 80% of women [10,39]. This aligns with our results using missed doses alone, and also with the finding of 92% of women with VL below 1000copies/mL at the time of assessment, however this is much higher than the 12% that we found using the combined scale score. Although there are few data assessing the performance of self-reported adherence measures in pregnant and postpartum women in low resource settings or in this particular context, the lack of a ceiling effect may be indicative of a more at risk population than other cohorts previously studied, and perhaps the three-item scale, which has been developed to be sensitive to reported non-adherence, is detecting more subtle difficulties with treatment implementation that have not yet impacted on VL.

Our results found that the three-item adherence scale scores were consistently significantly associated with elevated VL, however the effect sizes were relatively small. This is mirrored in the ROC analyses and suggests that although the three-item scale score is associated with VL, it may not be a very strong predictor of having an elevated VL. For the purposes of a first stage screening tool, we are looking for a measure with high sensitivity rather than perfect predictive ability, as would be required for a diagnostic tool. The scale achieved an AUC of 0.656 to detect a VL≥1000copies/mL, similar to what has been previously reported for different self-report measures as well as for pharmacy refill and VL, though lower than other combined self-report questions and lower than EDM and VL [19,40–42], and with further evaluation shows potential to fill this gap.

Global recommendations are moving towards making VL monitoring the standard of care for ART programmes, however in reality there are still likely to be problems with access in low resource settings due to feasibility and cost constraints. With infrequent VL testing and potential delays in feedback of results in many low resource settings, there is still a need for interim adherence assessments, particularly in the time sensitive context of PMTCT [2]. In many settings, adherence self-reports will remain the most feasible option that allows for rapid assessment of adherence risk and immediate feedback and counselling. Our findings suggest that this simple, low cost adherence screening tool may provide an early warning of poor adherence and prompt second stage adherence screening or VL testing. With a cut point of <90 or <100, the combined scale was able to detect 76 and 97% of women with VL above 1000copies/mL, respectively. This is an important advance for first stage self-reported adherence screening, with reported sensitivities of other tools ranging from 24-57% [23]. This scale had very high negative predictive values (94-98% depending on the scale cut-off) meaning that women with above threshold adherence scores had a very small probability of having a raised VL and could be potentially screened out of more resource intensive second stage adherence screening.

Although this scale shows promising performance in this setting, further research is needed to determine how appropriate it will be in a routine care setting and how it could fit into local routine ART management plans. In this analysis, considering anyone scoring below the maximum score on any item as non-adherent (a combined scale score of <100), 88% of women reported some adherence difficulty. However, at the time of assessment 92% of women had a VL<1000copies/mL and 360 women who had a VL below 1000copies/mL reported some adherence difficulty. An unexplored benefit of this scale is the opportunity of

the health care provider to discuss adherence challenges and solutions immediately after any reported difficulty with implementing treatment is admitted. This finding of suboptimal reported adherence in the absence of raised VL, points perhaps to more subtle early adherence difficulties being detected by this scale in a cohort of women recently initiated on ART. These women may be at increased risk of non-adherence and poor treatment outcomes over time and their early reports of adherence difficulty may provide an opportunity for additional adherence counselling, before their adherence behaviour can impact their VL. Further investigation into the longitudinal prognostic value of this scale should be considered and use of this simple tool in routine care as a flag to prompt further assessment and decide on an appropriate adherence support intervention may warrant consideration [14,26]. The successful use of this translated scale suggests that it can withstand cross-cultural adaptation and may also be useful in other settings.

Although, these data suggest that this three-item scale could successfully be used as a first stage adherence screening tool, the following limitations must be noted. The scale was administered by trained research interviewers outside of the routine ART care service, reducing the risk of social desirability bias and in the absence of the time constraints normal in a busy routine ART clinic. For these reasons, generalizability to routine clinical settings in high volume ART clinics is not known. In this analysis we were not able to compare the three-item scale to other objective adherence measures. We were also unable to compare this tool with adherence measures taken at routine ART follow up visits as these data were not available. We were able to compare the three-item scale to single missed doses item alone, a common measure of adherence in routine care, however an important next step will be to evaluate how this tool could be used in routine care and comparing it to measures currently in use in low resource settings. Pharmacy dispensing records and pill count have also been recommended as potential adherence measurement tools in low resource routine programme settings and comparison and combination with these measures will be an area of future research focus [19,42–44]. Optimal cut off values and an appropriate diagnosis and intervention strategy based on the scale result need to be established for routine clinical care. Although this tool appears to be valid and well understood across diverse populations, the optimal cut-offs and possible second stage screening and interventions are likely to differ across population groups so further research in other contexts is recommended. It must also be noted that the women in this study were all newly initiated on ART but had persisted on treatment to the time of assessment. How the scale will perform if used repeatedly over time, and generalizability of our findings to treatment experienced cohorts is not known.

Conclusion

In summary, these findings show that a simple three-item self-reported adherence scale could be used to screen for poor adherence and potentially flag current or pending elevated VL in this HIV-infected pregnant and postpartum population on ART. This is the first reported use of this scale outside of the US and it has performed well after translation in this setting. Adherence monitoring during pregnancy and after delivery in low resources settings requires more attention in the era of universal ART for all pregnant and breastfeeding women, and with further validation within routine care, this simple scale may add value to maternal adherence monitoring in low resource settings.

Compliance with ethical standards

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Conflict of interest: Ms. Phillips declares that she has no conflict of interest. Ms. Brittain declares that she has no conflict of interest. Dr Mellins declares that she has no conflict of interest. Ms. Zerbe declares that she has no conflict of interest. Dr Remien declares that he has no conflict of interest. Dr Abrams declares that she has no conflict of interest. Dr Myer declares that he has no conflict of interest. Dr Wilson declares that he has no conflict of interest.

Ethical approval: This study was conducted in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments and was approved and conducted in accordance with the standards of the Human Research Ethics Committee of the University of Cape Town, Faculty of Health Sciences as well as the Institutional Review Board of the Columbia University Medical Centre. Written informed consent was obtained from all individual participants included in the study.

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