UNIVERSITY OF CAPE TOWN

Retention in care among HIV-infected women initiating ART during pregnancy: a cohort study

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PHLTAM004

Dissertation submitted in partial fulfilment of the requirements for the degree

MASTER OF PUBLIC HEALTH in Epidemiology

in the

School of Public Health & Family Medicine

University of Cape Town

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April 2014

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PREAMBLE

Declaration

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Acknowledgments

My heartfelt thanks go to my supervisor Prof. Landon Myer who has guided me through every step if this dissertation process. Your insight and patience through countless discussions and drafts has really been appreciated.

Thank you to Prof. James McIntyre, my co-supervisor, for his feedback as this research and document developed. Thank you to Prof. Elaine Abrams and Prof. Linda-Gail Bekker for their valuable comments on the manuscript.

Thank you to the staff at Gugulethu MOU and Hannan Crusaid Treatment Centre and to the fieldworkers; Nomfezeko, Thoko, Dimakatso and Nondikho, who tirelessly searched for folders and completed the record review.

Thank you to Laryn and Lindsay for your editorial inputs; and lastly, thank you to Brendan and to my friends and family who have encouraged and supported me every step of the way.

I would like to acknowledge the following individuals as co-authors on this paper:

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Abstract

Background: Recent international guidelines call for universal use of triple-drug antiretroviral therapy (ART) in HIV-infected women during pregnancy and postpartum. There are however concerns regarding potentially high levels of non-adherence and/or loss to follow-up (LTF) that may attenuate the benefits of ART for HIV transmission and maternal health. We investigated missed visits and LTF among women initiating ART during pregnancy in Cape Town, South Africa.

Methodology: A retrospective cohort study was conducted of women starting ART between January 2011 and September 2012, at a large primary care antenatal clinic. Eligible women were identified in prevention of mother-to-child transmission (PMTCT) services based on CD4 ≤350 cells/μl, and women initiated a regimen of tenofovir, lamivudine and efavirenz. Women eligible for ART were either referred to general adult ART services nearby (January-December 2011) or received ART integrated into ANC services (January-September 2012). Outcomes were measured up to six months postpartum: (i) LTF (no attendance within 56 days of a scheduled visit) and (ii) missed visit (returning to care 14-56 days late for a scheduled visit).

Results: A total of 358 women (median age, 28 years; median gestational age at initiation, 26 weeks) initiated ART during pregnancy. By six months postpartum 24% of women (n=86) had missed at least one visit and 32% (n=115) were LTF. Overall, 49% of women had either missed a visit or were LTF by six months postpartum. LTF was more than twice as frequent postpartum compared to in the antenatal period (6.2 vs 2.4 per 100 woman-months, respectively; p=0.0004). In a proportional hazards model, later gestational age at initiation (HR: 1.04; 95% CI: 1.00-1.07; p=0.030) and being newly diagnosed with HIV (HR: 1.57; 95% CI: 1.07-2.33; p=0.022) were significant predictors of LTF after adjusting for patient age, starting CD4 cell count and site of ART initiation. Site of ART initiation was not a significant predictor of LTF in this analysis.

Conclusions: These results demonstrate that missed visits and LTF occur frequently among HIV-infected women initiating ART during pregnancy, particularly post-delivery. Further research is required to understand reasons for non-adherence and LTF and the implications thereof in the context of pregnancy. Women newly diagnosed with HIV and those presenting at later gestational ages may be particularly vulnerable and there is an urgent need for interventions to promote retention among all HIV-infected women during pregnancy and after delivery.

List of Abbreviations

3TC	Lamivudine
ANC	Antenatal Care
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT	Azidothymidine
CI	Confidence interval
FTC	Emtricitabine
HCTC	Hannan Crusaid Treatment Centre
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
IQR	Interquartile range
LTF	Loss to follow-up
MOU	Midwife Obstetric Unit
MTCT	Mother-to-child transmission
NIMART	Nurse initiated and managed antiretroviral therapy
NHLS	National Health Laboratory Services
PMTCT	Prevention of mother-to-child transmission
sdNVP	Single dose nevirapine
SSA	Sub- Saharan Africa
TDF	Tenofovir
TFO	Transfer out
UCT-HREC	University of Cape Town Human Research Ethics Committee
WHO	World Health Organization

Contents

List of Tables

A. Protocol

B. Literature Review

C. Manuscript

D. Appendices

List of Figures

A. Protocol

C. Manuscript

D. Appendices

A.PROTOCOL

1 Protocol Synopsis

In South Africa, 30% of all women presenting for antenatal care (ANC) are HIV-infected. Antiretroviral therapy (ART) is known to be a highly effective method of preventing mother-to-child transmission (PMTCT) of HIV and promoting maternal health, however adequate adherence to ART throughout the antenatal and breastfeeding period is needed to ensure women maintain viral suppression, and to maximise the success of the PMTCT programme. Poor retention is a major barrier to ART adherence and loss to follow-up (LTF) is common among pregnant women on ART [1–3].

For pregnant HIV-infected women, the shift from formula feeding to exclusive breastfeeding has heightened the importance of continued ART adherence after delivery. In 2011 the South African National Department of Health began promoting exclusive breastfeeding, regardless of a woman's HIV status. More recently, the Western Cape Department of Health adopted a policy of universal initiation of lifelong ART for all HIV-infected pregnant women. Both of these policies rely on retaining HIV-infected women in care during pregnancy and postpartum.

The overall aim of the proposed research is to describe retention in maternal ART services during pregnancy and after delivery, and to investigate possible predictors of retention in this population. The analysis is part of a study in Gugulethu, Cape Town that investigated the linkage of HIV-infected ART eligible pregnant women to ART services at either a nearby general ART clinic, or an integrated ART service within the antenatal clinic. The key finding of the parent study was that the proportion of women initiating ART before delivery was greatest, and the delays to ART initiation minimized, in a model of care that integrated ART into ANC [4]. Retention of women on ART following initiation during pregnancy was not addressed in the parent study.

The proposed study will investigate retention in ART services from ART initiation up to six months postpartum among women who initiated ART during pregnancy. The primary objective is to describe the timing of LTF in ART care during pregnancy and after delivery. The secondary objective is to investigate possible predictors of retention in maternal ART services. The primary outcome of the proposed study will be maternal retention in ART services up to six months post-delivery. The study population will be assembled retrospectively using routine medical service records, and will include all women attending ANC at Gugulethu Midwife Obstetric Unit (MOU) who initiated ART during pregnancy between January 2011 and September 2012. Women who initiated ART after delivery and those who presented for ANC already on ART will be excluded.

With the movement towards initiation of ART in all HIV-infected pregnant women, the numbers of women initiating ART during pregnancy are rapidly increasing. The proposed research will contribute to the growing knowledge base on retention in ART services during pregnancy and after delivery, and inform future research to promote ART retention in the context of pregnancy.

2 Introduction

2.1 Background

Mother-to-child transmission (MTCT) of HIV is an important contributor to new childhood HIV infections. It is estimated that globally, 1.4 million HIV-infected women give birth each year and that 91% of pregnant women living with HIV are in sub-Saharan Africa (SSA) [5]. In 2010, 30% of pregnant women attending antenatal care (ANC) services in South Africa were HIV-infected [6]. In 2011 it was estimated that 70% of maternal deaths and 50% of under-5 mortality in South Africa was associated with HIV [6,7].

Antiretroviral therapy (ART) has become widely accepted as a safe and efficacious method of prevention of mother-to-child transmission (PMTCT) of HIV. In 2010, the South African

National Department of Health revised their clinical guidelines for PMTCT to align with recent World Health Organisation (WHO) recommendations [5]. Lifelong ART was recommended for pregnant HIV-infected women with a CD4 cell count of 350 cells/µl or less, or with WHO clinical stage III / IV disease. Women who were not ART eligible were started on azidothymidine (AZT) at 14 weeks gestation, received single-dose nevirapine (sdNVP) and three hourly AZT intrapartum, and postpartum received a single dose of tenofovir (TDF) and emtracitabine (FTC) [8].

The use of ART in PMTCT programmes has been rapidly scaled-up around the world resulting in large reductions in MTCT rates [7]. Rates of MTCT in Europe and North America are now below 1% [9]. In SSA the number of new paediatric HIV infections dropped by 24% from 2009 to 2011 [7]. In South Africa the decrease for the same period was between 40 and 59% [7]. In 2010, a national survey of infant HIV status in South Africa found MTCT rates to be between 3 and 5% [10]. In 2011, South Africa's PMTCT coverage reached 75%, well above the overall figure for SSA of 59% [6,7]. Coverage of maternal ART is influenced by the strength of linkage to ART care from the antenatal services. Among women who do link to care and initiate ART, adherence is often suboptimal. A recent meta-analysis investigating adherence to antiretroviral therapy during and after pregnancy in different income settings, reported a pooled estimate of 74% of pregnant women having above 80% ART adherence [11].

In order for ART to be successful in preventing MTCT, maternal viral suppression must be maintained from as early as possible in pregnancy, during delivery and throughout the period of breastfeeding [11,12]. HIV-infected mothers need to firstly, link successfully to PMTCT services and secondly, be retained in care and maintain adequate adherence levels throughout the pregnancy and postpartum breastfeeding period [12]. Poor adherence leads not only to increased risk of maternal disease progression and MTCT, but may also result in drug resistance [13]. There is growing recognition that loss to follow-up (LTF) from ART services is a major barrier

to adherence [14] and several studies have suggested that LTF is a particular concern among pregnant women on ART, both during pregnancy and after delivery [2,3,15,16].

Breastfeeding and HIV transmission

New paediatric HIV infections are usually the result of MTCT that takes place either *in utero*, intra-partum or postpartum during breastfeeding. In SSA, breastfeeding is thought to account for 40% of new paediatric HIV infections [17]. Reducing breastfeeding may remove the risk of MTCT but it has other significant negative impacts on child survival [18,19]. In response to growing evidence South Africa started promoting exclusive breastfeeding for HIV-positive mothers in 2011, replacing previous recommendations of formula feeding. With adequate adherence, maternal ART through pregnancy and breastfeeding is able to provide protection from MTCT and allow HIV exposed infants the widely known benefits of breastfeeding [11,17]. Women who are not retained and/or adherent to treatment will not be virally suppressed and consequently the risk of MTCT is increased. In order to achieve optimal health outcomes in HIV-exposed infants, a focus on maternal ART adherence and retention is needed in parallel with the promotion of exclusive breastfeeding.

Timing of attrition

There are multiple points in the PMTCT cascade where women are lost to care. Attrition between determination of ART eligibility and initiation of ART has been widely studied [20]. Services offering ART are often separated from ANC services. This has resulted in large losses between women being identified as HIV-positive during ANC, and presentation at an ART service. Stinson et al. [21] analysed data from four antenatal clinics in Cape Town in 2005. They found that 51% of ART eligible women had initiated ART before delivery. A further 27% received another form of PMTCT [21]. In 2010, at a single facility in Cape Town, it was found

that only 21% of ART eligible pregnant women were screened and initiated ART after referral to ART services from ANC during a pre-intervention study phase [4].

Following ART initiation, LTF appears to increase with increasing time on treatment. Studies have shown in general adult ART services that the proportion of patients remaining in care decreases over time while rates of LTF increase [20]. Some literature suggests that pregnant women may be at a higher risk of LTF than non-pregnant women and men [1,3,15]. There is also evidence to suggest that maternal ART adherence is higher during pregnancy than after delivery [11]. In contrast, an analysis of data from general ART services in seven countries in SSA from 2003-2006, found overall retention to be 85% and found no difference in ART retention rates between pregnant women, non-pregnant women and men [23].

Barriers identified to adherence and retention

Barriers to adherence and retention in ART services for PMTCT have been explored in many studies. A systematic review of adherence to ART during and after pregnancy identified physical, economic and emotional stresses, depression (particularly postpartum), substance use as well as medication frequency of the ART regimen as barriers to adequate ART adherence [11]. Economic concerns, stigma and partner related challenges have been highlighted as reasons for poor retention and adherence in SSA [24–27]. Wang et al. found that pregnant women with lower baseline CD4 cell counts were at high risk of LTF in the six months following ART initiation [3]. Younger age was also associated with higher rates of LTF in this study [3]. Toro et al. found poor retention to be associated with higher baseline WHO clinical stage, but not with CD4 cell count [23]. Service-related factors such as accessibility and quality of care have also been recognized as barriers to adherence and retention during pregnancy and postpartum [26,28–30].

2.2 Background to the proposed dissertation

In January 2012, an integrated ANC/ART service was introduced to a large primary care antenatal clinic in Gugulethu, Cape Town. Prior to this, all women found eligible for ART during ANC were referred to nearby general ART services to start ART. The uptake of ART during pregnancy in this clinic has been presented by the parent study [4], in which women were followed retrospectively through routine medical records from the time of referral from the ANC clinic until ART initiation. Retention in care following successful ART initiation during pregnancy was not evaluated.

The proposed research aims to explore retention in this population of women who have initiated ART during pregnancy in both the antenatal period and up to six months postpartum. We will investigate socio-demographic, obstetric, clinical and service characteristics, in particular the site of ART initiation, as possible predictors of retention.

2.3 Study rationale

We know that ART is highly effective at protecting against MTCT and promoting maternal health, however vertical transmission remains the main contributor to new childhood HIV-infections worldwide, even in settings with reasonable ART coverage. Poor adherence and/or LTF heighten the risk of MTCT and there is growing evidence that poor adherence and/or LTF from ART services is common during pregnancy and postpartum [2,11,31].

There are limited data investigating retention in ART services among pregnant and, in particular postpartum women. Studies assessing overall retention in ART services have suggested that pregnant women are particularly vulnerable to LTF [3,15,16]. The existing literature points to a higher risk of LTF and non-adherence in the postpartum period [2,11]. In order to ensure that governments, health care providers and patients are well equipped for these changes, it is

increasingly important that we understand the challenges of retention in ART services during pregnancy and postpartum.

There are on-going investigations into interventions to reduce delays in ART initiation during pregnancy and improve maternal ART uptake. It is important to understand the impact of more rapid initiation and increased uptake of ART on retention in ART services. We know that the uptake of ART during pregnancy is significantly lower when women are referred to general ART services compared to integrated ART services [28,29]. This may indicate that many women do not successfully navigate the many barriers to ART initiation in the absence of optimal provider support. Little is known about retention in ART services beyond treatment initiation during pregnancy.

3 Study aims and objectives

3.1 Study aim

The overall aim of this dissertation is to investigate retention in ART care during pregnancy and postpartum among women initiating ART during pregnancy.

3.2 Objectives

1. To describe the timing of LTF from ART services, pre- and post-delivery, from the time of ART initiation during pregnancy, through to six months postpartum.
2. To investigate socio-demographic, obstetric, clinical and service characteristics, in particular the site of ART initiation, as possible predictors of retention in the ART service overall, as well as during pregnancy and postpartum.

3.3 Hypothesis

The study hypothesis is that retention will be higher during the antenatal period than postpartum. Within that, women initiating ART under an integrated model of care are expected to have higher rates of retention during the antenatal period compared to women referred out for ART.

4 Methods

4.1 Study Design

The proposed research will take the form of a retrospective cohort study of HIV-infected pregnant women attending ANC at the Gugulethu Midwife Obstetric Unit (MOU) and initiating ART during pregnancy.

4.2 Study population and sampling

All HIV-infected women who initiated ART at Hannan Crusaid Treatment Centre (HCTC) or the Gugulethu MOU ART service during their antenatal care at Gugulethu MOU between January 2011 and September 2012 will be included. The cohort will be assembled by review of patient folders of all women booking for ANC between November 2010 and September 2012 (allowing for a delay between booking for ANC and initiating ART). There will be no direct contact with any patients for this research. The study schema is shown in Figure A-1. The grey shaded areas represent the proposed dissertation within the parent study [4].

Exclusion Criteria

Participants for whom there is no record of ART initiation at Gugulethu MOU or HCTC will be excluded from the analysis. Women who only initiated ART after delivery and women already on ART at presentation at the MOU will also be excluded.

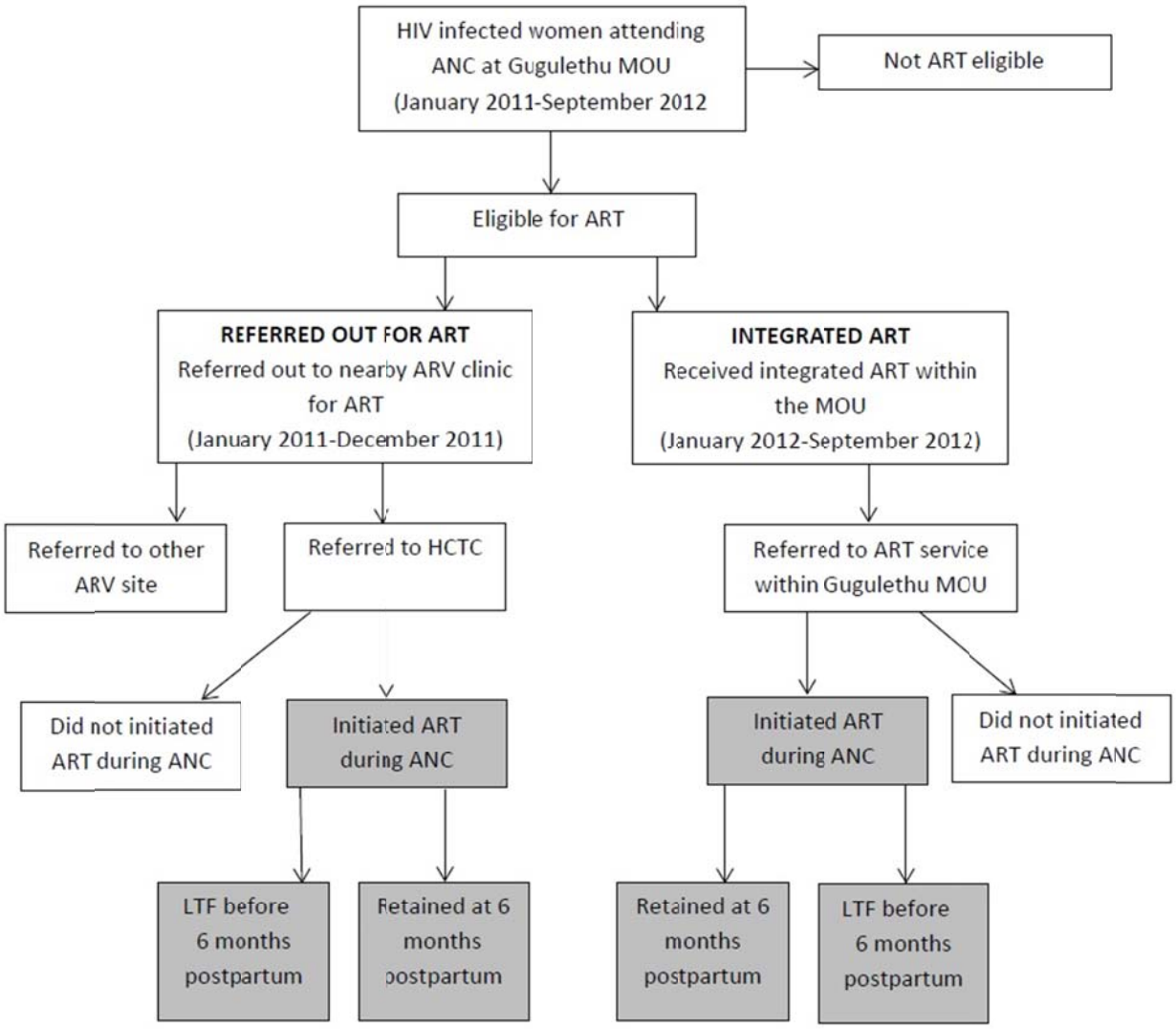

Figure A-1: *Study schema showing situation of the proposed research within the parent study.*

Site of ART initiation between January 2011 and September 2012

- Referral out to nearby ART service: From January 2011 to December 2011, women identified as ART eligible during ANC at Gugulethu MOU were referred to the nearby HCTC to initiate ART.
- ART integrated into ANC: In January 2012, integrated nurse-initiated and managed ART (NIMART) was introduced at the Gugulethu MOU. From January 2012, ART eligible women were referred directly to the ART nurse based in the Gugulethu MOU.

4.3 Study location

The study will take place at the Gugulethu MOU and HCTC in Cape Town, South Africa. The Gugulethu MOU provides basic ANC and delivery services for a wide catchment area including Philippi, Nyanga, Lower Crossroads, Heideveld and Gugulethu. Women from surrounding areas and from the Eastern Cape are also known to receive care at this facility [32]. General ART services have been provided at HCTC since 2003.

The two facilities are situated on the same premises but function independently. The integrated ART services introduced to the MOU in January 2012 fall under HCTC's administration. Approximately 5000 women book for ANC at Gugulethu MOU each year. In 2011, approximately 28% of women booking for ANC were HIV-infected [4].

In both ART services, pregnant HIV-infected women who were eligible for ART were started on a combination of one non-nucleoside reverse transcriptase inhibitor and two nucleoside reverse transcriptase inhibitors [8] and ART eligibility was based on having a CD4 cell count of ≤350 cells/μl or WHO clinical stage III or IV. Women usually received a 30 day supply of ART for the first four months on treatment and thereafter received a 30-60 day supply at the clinician's discretion. Follow up visits were scheduled on a 28 or 56 day cycle depending on the quantity of ART supplied.

4.4 Data collection

Data will be collected retrospectively from routine medical records. Existing data from ongoing operations research at HCTC will also be used. Data will be abstracted by a trained research assistant using two structured data abstraction forms. The first form (Appendix A) will collect baseline data on the period from referral to initiation of ART. The second form (Appendix B1 & B2) will collect data from ART initiation through to six months postpartum.

Where outcome data from the record review are missing, the National Health Laboratory Service (NHLS) database will be searched in attempt to complete the missing data. Delivery dates will be crucial to obtaining estimates of retention in the antenatal and postpartum periods. If no delivery date is found in the medical records or on the NHLS database, the gestational age, routinely recorded in the Gugulethu MOU, will be used. It will be assumed that delivery occurred at 40 weeks gestation.

Table A-1 displays a list of all variables to be collected for this analysis. Dates of all attended visits as well as the quantity of ART dispensed will be collected in the ART follow up form (Appendix B2). The expected visit date will be determined using the quantity of ART dispensed at the last attended visit.

Table A-1: *Variable list*

Variables	**Type**
Age at ART initiation (years)	Continuous - numerical
Parity	Continuous - numerical
Level of education	Categorical - binary (primary/secondary)
Employment status	Categorical - binary (employed/unemployed)
Time of HIV diagnosis	Categorical - binary (new/known positive)
Disclosure status	Categorical - binary (disclosed/not disclosed)
Relationship status	Categorical - binary (in a relationship/not in a relationship)
WHO stage at screening	Categorical - binary (I or II/ II or IV)
CD4 at screening (cells/µl)	Continuous - numerical
Gestational age at ART initiation (weeks)	Continuous - numerical
Site of ART initiation	Categorical - binary (integrated ANC/ART/general ART)
Pregnancy status	Categorical - binary (antenatal/postpartum)

Definition of outcome variables

In the literature there are varying definitions of LTF. Studies focusing on retention in general ART services define LTF as three to six months with no visit attendance. In the proposed study population most women have ART visits scheduled every 28 or 56 days. In previous studies of

LTF on ART in the context of PMTCT, a one or two month window for attendance from the last scheduled visit has been used to define LTF [2,31,33].

In the proposed study the outcomes will be defined as follows:

1. **Loss to follow-up (LTF)**

   Missed a scheduled ART visit and there is no evidence of clinic attendance for at least 56 days after the scheduled visit date.

2. **Missed visit**

   Missed a scheduled ART visit and returned to the clinic between 14 and 56 days of the scheduled visit date.

The study time for each woman will end 56 days following six months after delivery, allowing time for outcome definitions to be established for ART visits scheduled up to six months postpartum [34]. A woman will be considered *retained* if she is alive, has not been transferred out (TFO) and has not been LTF by the end of the study period.

Study time will commence on the date of ART initiation and censoring will occur in the following instances:

1. The end of the study period for women retained
2. Documented transfer out
3. Documented maternal death

4.5 Potential limitations

The data for this dissertation will be gathered retrospectively from routine service medical records. There may be variation in the quality and content of information recorded in these records.

Only records from Gugulethu MOU and HCTC will be reviewed and ART service attendance at other facilities will not be reviewed. Outcome definitions will be based only on attendance at the two ART initiation sites. Movement to other facilities, or transfer without relevant documentation, will result in an overestimation of LTF in this cohort of women. Routinely collected programme data which records deaths, TFO and LTF will be used to supplement the data collected during the record review.

Women who were referred out and successfully initiated ART during pregnancy may differ systematically from those who ultimately initiated ART in the integrated ANC/ART site. Differences in baseline variables collected will be adjusted for however there may be other unmeasured differences that could introduce bias or confounding into this analysis.

4.6 Logistics and time schedule

Table A- shows the expected time frame for completion of the proposed study. The schedule for this dissertation is to submit in February 2014.

Table A-2: Time schedule for completion of dissertation

Month	Sep'13	Oct'13	Nov'13	Dec'13	Jan'14	Feb'14
Literature Review						
Data collection and capturing						
Data Management						
Data Analysis						
Results						
Discussion/Write up						

4.7 Data management and analysis

The data for this dissertation are quantitative and will come from review of routine medical service records. Completed data abstraction forms will be checked for completeness and quality and will be captured into a password-protected Microsoft Access (2010) database. This data will

be cleaned where necessary and attempts will be made to complete any missing data by returning to the source medical records, routine programme database and NHLS database.

Data will be exported into STATA 12 (STATA for Windows, version 12, Stata Corp; College Station, TX) for analysis. Data will be explored using univariate and bivariate descriptive statistics. Median and inter-quartile range (IQR), or means and confidence intervals (CI) will be used to describe the continuous covariates depending on their distribution. Binary and categorical covariates will be described using frequency distributions. Frequency tables will be used to examine proportions of LTF and missed visits overall and in the antenatal and postpartum period. The frequency of LTF and missed visits will be compared in the antenatal and postpartum periods and between the integrated and referred out groups.

Kaplan Meier analyses will be used to assess time to LTF overall, during pregnancy and postpartum. Analyses will be presented for all participants overall as well as stratified by ART initiation site. The log rank test will be used to compare survival curves. Cox proportional hazards models will be used to investigate potential predictors of retention overall and in the antenatal and postpartum periods. The primary outcome of interest is LTF up to six months postpartum and secondary analyses will examine missed visits, and/or other definitions of LTF. Covariates will be examined as potential confounders or mediators prior to model building. Multivariate models will include all covariates for which there is a significant effect on the outcome as well as covariates which, when removed, influence associations of other covariates and the outcome. Model diagnostics will be done using standard methods and outputs will be expressed as hazard ratios (HR) with 95% CI [35].

5 Ethical considerations

Ethical review

Ongoing data collection from routine medical records at HCTC has been approved by the University of Cape Town human research ethics committee (UCT-HREC) (REC REF 359/2002, updated annually). The optimised linkage study described above was also approved by the UCT-REC (REC REF 391/2010). The proposed study requires additional data abstraction using routine service records at HCTC and the Gugulethu MOU, including the NHLS database.

Informed consent

The data for this study will come from retrospective review of routinely collected service data. There will be no direct contact with any study participants and informed consent will not be obtained. As part of the routine services in this setting, all women screened for ART complete a simple informed consent document allowing their anonymous health care information to be used in research (per REC REF 359/2002).

Risks

This study represents minimal risk research. Because of its retrospective nature, the major risk in this research is loss of confidentiality during data collection and management. All data collected will be kept strictly confidential but will not be anonymous until all the data has been captured. ART service folder numbers will be collected and used as unique participant identifiers. Completed data abstraction forms will be stored in a locked filing cabinet. Once captured, all identifiers will be deleted to ensure the final data set is anonymous.

There is a small risk that confidentiality could be breached during review of routine medical records. The person conducting the data abstraction will receive specific training on issues of confidentiality. Every effort will be made to ensure confidentiality is maintained.

Benefits

The proposed study holds no direct benefit for any individual patient, however knowledge gained in this study may assist in identifying where efforts should be focused to improve ART retention both during and after pregnancy. The study will contribute directly to the knowledge base on retention in maternal ART services both during pregnancy and after delivery. It will provide further understanding of the impact of integrated ART services on retention in ART care. Given the high rates of attrition from ART services over time, particularly among pregnant and postpartum women, advancing our knowledge of these issues represents a benefit to both health services and the populations served by these services.

Confidentiality

Data collected will be non-anonymous and confidential until all data has been captured, at which point identifiers will be removed. The ART service folder number will be used as a unique participant identifier. Additional identifying information such as name, date of birth and provincial folder number, may be collected for those women considered LTF. These identifiers will be collected for the purpose of searching routine service databases and the NHLS database to determine the retention status of the participant. On completion of these searches the additional identifiers will be destroyed. All data collected will be stored in locked cabinet at the University of Cape Town.

Use of Information and Publications

Publication or presentation of the results of this study will be agreed upon in collaboration with the study investigators of the parent study.

6 References

[1] Kaplan R, Orrell C, Zwane E, Bekker L-G, Wood R. Loss to follow-up and mortality among pregnant women referred to a community clinic for antiretroviral treatment. AIDS 2008;22:1679–81.

[2] Clouse K, Pettifor A, Shearer K, Maskew M, Bassett J, Larson B, et al. Loss to follow-up before and after delivery among women testing HIV-positive during pregnancy in Johannesburg, South Africa. Trop Med Int Health 2013;18:451–60.

[3] Wang B, Losina E, Stark R, Munro A, Walensky RP, Wilke M, et al. Loss to follow-up in a community clinic in South Africa--roles of gender, pregnancy and CD4 count. South African Med J 2011;101:253–7.

[4] Myer L, Manuelli V, Abrams E, McIntyre J, Bekker L-G. Optimization of ART initiation in pregnancy through linkage of services vs. integration of ART into antenatal care. 20th Conference on Retroviruses and Opportunistic Infections. March 3-6. Atlanta, GA: 2013. Paper 83.

[5] World Health Organisation. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector, progress report 2010. Geneva, Switzerland: World Health Organization; 2010 [cited 2014 February 2]. Available from: http://www.who.int/hiv/pub/2010progressreport/en/

[6] Barron P, Pillay Y, Doherty T, Sherman G, Jackson D, Bhardwaj S. Eliminating mother-to-child HIV transmission in South Africa. Bull World Health Organ 2013;91:70–4.

[7] Joint United Nations Program on HIV/AIDS. Global report: UNAIDS report on the global AIDS epidemic 2012. Geneva, Switzerland: Joint United Nations Program on HIV/AIDS; 2012 [cited 2014 February 2]. Available from: http://www.unaids.org/en/resources/publications/2012/name,76121,en.asp

[8] National Department of Health; South African National AIDS Council. Clinical guidelines: PMTCT (Prevention of Mother-to- Child Transmission). Pretoria, South Africa: National Department of Health; 2010.

[9] Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey P. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. AIDS 2008;22:973–81.

[10] Goga A, Dinh T, Jackson D, for the SAPMTCTE study group. Evaluation of the effectiveness of the National Prevention of Mother-to-Child Transmission (PMTCT) programme measured at six weeks postpartum in South Africa, 2010. South African Medical Research Council, National Department of Health of South Africa and PEPFAR/US Centers for Disease Control and Prevention; 2012 [cited 2014 February 2]. Available from: http://www.mrc.ac.za/healthsystems/SAPMTCTE2010.pdf

[11] Nachega JB, Uthman O, Anderson J, Peltzer K, Wampold S, Cotton MF, et al. Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis. AIDS 2012;26:2039–52.

[12] Ferguson L, Grant AD, Watson-Jones D, Kahawita T, Ong'ech JO, Ross DA. Linking women who test HIV-positive in pregnancy-related services to long-term HIV care and treatment services: a systematic review. Trop Med Int Health 2012;17:564–80.

[13] Paredes R, Marconi VC, Lockman S, Abrams EJ, Kuhn L. Impact of antiretroviral drugs in pregnant women and their children in Africa: HIV resistance and treatment outcomes. J Infect Dis 2013;207 Suppl :S93–100.

[14] Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review. Trop Med Int Health 2010;15 Suppl 1:S1–15.

[15] Boyles TH, Wilkinson LS, Leisegang R, Maartens G. Factors influencing retention in care after starting antiretroviral therapy in a rural South African programme. PLoS One 2011;6:e19201.

[16] Clouse K, Pettifor A, Maskew M, Bassett J, Van Rie A, Gay C, et al. Initiating antiretroviral therapy when presenting with higher CD4 cell counts results in reduced loss to follow-up in a resource-limited setting. AIDS 2013;27:645–50.

[17] Mofenson LM. Antiretroviral drugs to prevent breastfeeding HIV transmission. Antivir Ther 2010;15:537–53.

[18] Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS & the Bellagio Child Survival Study Group. How many child deaths can we prevent this year? Lancet 2003;362:65–71.

[19] Lamberti LM, Fischer Walker CL, Noiman A, Victora C, Black RE. Breastfeeding and the risk for diarrhea morbidity and mortality. BMC Public Health 2011;11 Suppl 3:S15.

[20] Gourlay A, Birdthistle I, Mburu G, Iorpenda K, Wringe A. Barriers and facilitating factors to the uptake of antiretroviral drugs for prevention of mother-to-child transmission of HIV in sub-Saharan Africa: a systematic review. J Int AIDS Soc 2013;16:18588.

[21] Stinson K, Boulle A, Coetzee D, Abrams EJ, Myer L. Initiation of highly active antiretroviral therapy among pregnant women in Cape Town, South Africa. Trop Med Int Health 2010;15:825–32.

[22] Cornell M, Grimsrud A, Fairall L, Fox M, van Cutsem G, Giddy J, et al. Temporal changes in programme outcomes among adult patients initiating antiretroviral therapy across South Africa, 2002–2007. AIDS 2011;24:2263–70.

[23] Toro PL, Katyal M, Carter RJ, Myer L, El-Sadr WM, Nash D, et al. Initiation of antiretroviral therapy among pregnant women in resource-limited countries: CD4+ cell count response and program retention. AIDS 2010;24:515–24.

[24] Duff P, Kipp W, Wild TC, Rubaale T, Okech-Ojony J. Barriers to accessing highly active antiretroviral therapy by HIV-positive women attending an antenatal clinic in a regional hospital in western Uganda. J Int AIDS Soc 2010;13:37.

[25] Awiti Ujiji O, Ekström AM, Ilako F, Indalo D, Wamalwa D, Rubenson B. Reasoning and deciding PMTCT-adherence during pregnancy among women living with HIV in Kenya. Cult Health Sex 2011;13:829–40.

[26] Lubega M, Musenze IA, Joshua G, Dhafa G, Badaza R, Bakwesegha CJ, et al. Sex inequality, high transport costs, and exposed clinic location: reasons for loss to follow-up of clients under prevention of mother-to-child HIV transmission in eastern Uganda - a qualitative study. Patient Prefer Adherence 2013;7:447–54.

[27] Stinson K, Myer L. Barriers to initiating antiretroviral therapy during pregnancy : a qualitative study of women attending services in Cape Town , South Africa. African J AIDS Res 2012;11:65–73.

[28] Killam WP, Tambatamba BC, Chintu N, Rouse D, Stringer E, Bweupe M, et al. Antiretroviral therapy in antenatal care to increase treatment initiation in HIV-infected pregnant women: a stepped-wedge evaluation. AIDS 2010;24:85–91.

[29] Stinson K, Jennings K, Myer L. Integration of antiretroviral therapy services into antenatal care increases treatment initiation during pregnancy : a cohort study. PLoS One 2013;8:e63328.

[30] Chinkonde JR, Sundby J, Martinson F. The prevention of mother-to-child HIV transmission programme in Lilongwe, Malawi: why do so many women drop out. Reprod Health Matters 2009;17:143–51.

[31] Tenthani L, Haas AD, Tweya H, Jahn A, van Oosterhout JJ, Chimbwandira F, et al. Retention in care under universal antiretroviral therapy for HIV-infected pregnant and breastfeeding women (’Option B+') in Malawi. AIDS 2014;28:589–98.

[32] Stinson K, Myer L, Boulle A. An evaluation of approaches to the initiation of antiretroviral therapy during pregnancy among HIV-infected women in Cape Town. Cape Town: University of Cape Town; 2008 [cited 2014 February 2]. Available from: http://webdav.uct.ac.za/depts/epi/publications/documents/Stinson_antenatal_HAART.pdf

[33] Myer L, Zulliger R, Bekker L, Abrams E. Systemic delays in the initiation of antiretroviral therapy during pregnancy do not improve outcomes of HIV-positive mothers : a cohort study. BMC Pregnancy Childbirth 2012;12:94.

[34] Grimsrud AT, Cornell M, Egger M, Boulle A, Myer L. Impact of definitions of loss to follow-up (LTFU) in antiretroviral therapy program evaluation: variation in the definition can have an appreciable impact on estimated proportions of LTFU. J Clin Epidemiol 2013;66:1006–13.

[35] Hosmer D, Lemeshow S, May S. Applied Survival Analysis: Regression modeling of time-to-event data. 2nd ed. Hoboken, New Jersey, USA: John Wiley & Sons, Inc; 2008.

B. LITERATURE REVIEW

1 Introduction and objectives of this literature review

In July 2011, a global plan was launched for the elimination of new human immunodeficiency virus (HIV) infections among children by 2015 [1]. According to the latest Global Progress Report there were 260 000 children newly infected with HIV globally in 2012, most of these as a result of mother-to-child transmission (MTCT). Sub-Saharan Africa (SSA), where 90% of new infections occurred, is home to 92% of pregnant women living with HIV [2]. South Africa, where 30% of women attending antenatal care (ANC) are HIV-infected, has achieved a 63% decline in new HIV-infections in children since 2009, two thirds of the way to the target of 90% reduction by 2015 [2].

Triple-drug antiretroviral therapy (ART) has repeatedly been shown to be a highly effective prevention of mother-to-child transmission (PMTCT) intervention and has been incorporated into PMTCT policy around the world [3]. South Africa has been providing ART for PMTCT since 2004 when National PMTCT guidelines recommended lifelong ART for all pregnant HIV-positive women with CD4 cell count ≤200 cells/µl; in 2010, this threshold was raised to ≤350 cells/µl. As of 2013, the South African National PMTCT guidelines now recommend ART, as treatment or prophylaxis, for all HIV-infected pregnant and breast feeding women following World Health Organization (WHO) guidelines (Table B-1).

Table B-1: *WHO recommended PMTCT interventions* [3]

	CD4 cell count ≤ 350 cells/µl	**CD4 cell count > 350 cells/µl**
Option A	ART for life	AZT prophylaxis starting at 14 weeks gestation. sdNVP and AZT/3TC at delivery and for 7 days postpartum.
Option B	ART for life	Triple ARV prophylaxis from 14 weeks gestation until delivery or 1 week after cessation of breastfeeding
Option B+	ART for life	ART for life

Despite its known efficacy, many barriers exist to the successful implementation of ART for PMTCT. ART can only effectively prevent MTCT if women start taking treatment early enough in pregnancy and remain in care and adherent throughout the period of exposure [4]. Integrated ANC/ART services have bridged some of the barriers to ART initiation during pregnancy and have resulted in improved ART uptake for PMTCT compared to stand alone ART services [5–7]. The next step is to ensure ART adherence and retention during pregnancy and breastfeeding. For women starting lifelong ART there is the added challenge of ongoing retention in care as well as ensuring a successful transition from ART during pregnancy into general ART services. Existing evidence suggests that loss to follow up (LTF) from PMTCT programmes during pregnancy and postpartum may be common [8–10]. LTF is a major contributor to poor adherence and a significant barrier to the success of ART for PMTCT. However the factors influencing retention and adherence during pregnancy and post-delivery are not yet well understood. In the 2013 WHO PMTCT guidelines, adherence and retention to ART during pregnancy and after delivery are highlighted as key areas requiring further research [3].

This dissertation investigates retention in care following ART initiation during pregnancy. It explores factors influencing retention in the antenatal and postpartum periods, focusing in particular on integrated and non-integrated models of ART initiation for HIV-infected pregnant women. To inform this research, the objectives of this literature review are:

- To describe existing evidence regarding antenatal and postpartum adherence and LTF from HIV services following ART initiation during pregnancy.
- To compare adherence and retention in services where women are referred out for ART and where women receive integrated ART care.
- To identify barriers to retention in ART care and adherence to ART during pregnancy and after delivery

2 Search methods

PubMed and Google Scholar were searched using the search terms HIV, antiretroviral treatment, pregnancy, retention and integration, as well as their variations (See Box 1). The search was restricted to English language publications and data reported from the African continent. Titles and abstracts of resulting articles were reviewed and references of included studies and existing reviews were searched. All publications available through 28 February 2014 were included in this review.

Publications were included in the review if (i) the population of interest included HIV-infected pregnant or postpartum women, and (ii) uptake of ART during pregnancy, maternal retention in ART care or adherence to ART during pregnancy was an outcome of the study. Studies of both ART for maternal health and ART prophylaxis were included in the review. Publications focusing on optimal ARV regimen/drug efficacy, short term ARV prophylaxis (sdNVP, AZT prophylaxis), infant treatment or infant outcomes were excluded from this review. The included studies are summarised in Table B-2.

Box 1: Search strategy

HIV: Human immunodeficiency virus, mother-to-child transmission, MTCT, vertical transmission

Antiretroviral treatment: ART, PMTCT, antiretroviral

Pregnancy: pregnant, antenatal, antepartum, postnatal, postpartum, maternal

Retention: follow up, LTF, loss to follow up, attrition, linking to care, adherence, retained, loss to care

Integration: integrated, referral

3 Results

3.1 The importance of adherence and retention

Adherence to ART is closely linked to achieving viral suppression [11,12]. In turn, non-adherence leads to higher levels of viraemia that have been consistently associated with an increased risk of MTCT during pregnancy, delivery and breastfeeding [13,14]. The importance of adherence to ART is therefore heightened in the context of pregnancy as both the risk of MTCT and ongoing maternal health must be considered. Studies on ART for PMTCT specify thresholds for adequate adherence between 80-100% [15].

In order to achieve adequate adherence and ultimately viral suppression, women must regularly attend ART services to receive their treatment. Non-retention is a significant barrier to ongoing adherence. Treatment interruptions not only result in increased maternal viraemia but have also been linked to the development of treatment resistance [16]. In an MTCT setting, this poses a threat to maintaining ongoing maternal health and introduces a risk for transmission of drug resistant virus to the infant.

3.2 Retention and adherence following ART initiation during pregnancy

Pregnant women have repeatedly been shown to be at high risk for non-adherence and poor retention in ART services. Studies investigating retention in general adult ART services from across SSA have found that pregnant women are at a higher risk of being LTF compared to non-pregnant women and men [8,10,17,18]. In Gugulethu, Cape Town, Kaplan et al. found that pregnant women were significantly more likely to be LTF both pre- and post- treatment initiation when compared to non-pregnant women, however mortality was lower among pregnant women [17]. Working in other parts of South Africa, Boyles et al. and Wang et al. found a more than

three-fold increased hazard of being LTF among pregnant women compared to non-pregnant women and men [8,10].

The literature suggests that among women starting ART during pregnancy, levels of maternal ART adherence and/or retention in care vary during the antenatal and postpartum periods. In a meta-analysis focusing on adherence to ARVs during pregnancy and postpartum, Nachega et al. reported a higher pooled estimate of adequate adherence (defined as >80% adherent) in the antenatal period (76%) compared to the postpartum period (53%) [15]. Estimates from Kenya and Nigeria suggest that about 80% of women had adequate adherence (defined as >95% adherent) to ART during pregnancy [11,19]. In South Africa, Black et al. found that 28% of ARV naïve women initiating ART during pregnancy in an integrated ANC/HIV service were LTF before six weeks postpartum [20]. Clouse et al. [9] also examined LTF during pregnancy and after delivery in South Africa. They reported that 77% of women who initiated ART during pregnancy returned for at least one postpartum visit. Of those women who returned, 83% were still in care six months after ART initiation [9]. Other studies from South Africa and Kenya have found that approximately two thirds of women remain adherent and in care until delivery [21,22] and up to 28 days postpartum [23].

Definitions of retention, LTF and adherence are not standard, making it difficult to compare findings in different settings. Okonji et al. assessed adherence to triple ARV prophylaxis among pregnant women in Kenya using pill counts, participant-maintained drug calendars and self-reported three day and one month adherence [11]. They found that 84% of women had >95% adherence over the study period. No significant difference in the level of adherence or viral suppression was detected at delivery, 14 and 24 weeks postpartum [11]. At an urban HIV treatment centre in Nigeria, 80% of women had >95% adherence to ART during pregnancy

based on three day recall [19]. Ayuo et al. measured disengagement from care during pregnancy in Kenya and found that overall 32% of women disengaged from care at some time prior to delivery [21].

Overall, the literature suggests multiple challenges to adherence and retention during and after pregnancy, and that these issues are more prominent postpartum. Many of the identified barriers have been present across both the antenatal and postpartum periods, however much of the literature does not extend far past delivery. Available literature does suggest that adherence and retention in ART care is worse after delivery than during pregnancy [15,24].

Referral and successful linkage to HIV care following identification in ANC is a major barrier to ART uptake during pregnancy as well as continued retention in care. Several studies have recognized the difficulties of successful referral to ART services outside of ANC [25–28]. MacPherson et al. investigated referral to ART care among a general adult population in Malawi and found that pregnant women were less likely to be referred directly to ART services than non-pregnant women and men [25]. In a Zimbabwean study investigating referral of ART eligible women from PMTCT services in an ANC clinic to a general adult ART clinic, only 65% of women who were referred for ART successfully registered for the ART programme. Of these only 37% initiated ART and a further 37% were being monitored for ART eligibility. The study also found that only 16% of all referrals had been correctly documented at the ANC clinic completing the referral [27]. Watson-Jones et al. noted that referral to ART services following positive HIV tests during ANC, delivery or postpartum was poor [26]. The study found that 30% of health workers did not correctly refer women to ART care and that only 32% of women referred had actually been assessed for ART four months following the referral.

Few interventions have been investigated to improve ART uptake. Data from Malawi have shown that facility based interventions to improve service linkage for ART eligible pregnant women are able to improve ART uptake and retention [29]. Retention at six months on ART improved from 17% pre-intervention to 65% [29]. In South Africa, a targeted quality improvement campaign among health workers improved referral for and uptake of ART by eligible pregnant women [30]. Integrated ART services have removed the need for referral to stand alone ART services during the antenatal period and have significantly improved ART uptake during pregnancy [5,6]. These interventions have resulted in fewer losses between ART screening and ART initiation, however after successful ART initiation women must still negotiate the barriers to ongoing adherence and retention in care.

3.3 Barriers to or enablers of retention and adherence during pregnancy/postpartum

Adherence to ART and retention in ART care is an ongoing challenge for women initiating treatment during pregnancy. Stinson & Myer comment on a "triple burden" of firstly dealing with pregnancy and motherhood, secondly accepting the HIV diagnosis and thirdly coming to terms with the need to start lifelong treatment to protect from MTCT as well as for ongoing maternal health [31]. Studies have identified many barriers to ART adherence and to retention in ART care including individual-level, socioeconomic and service- related factors.

Individual-level factors

Several of the demographic associations with retention in non-pregnant/postpartum adult populations have also been documented in pregnant women. For example, younger age is often associated with increased risk of LTF and studies of ART use in the antenatal and postpartum periods have found that older women were less likely to be lost from care or to have poor adherence compared to younger women [9,10,21]. The evidence regarding gestational age and

retention is unclear. Earlier gestational age at ART initiation has been shown to be associated with increased risk of disengagement from care prior to delivery [21] and there is also evidence that late gestational age at presentation for ANC increases the likelihood of being LTF prior to delivery [9].

Women's motivations for using ART during pregnancy may act as an additional barrier to adherence and retention. Ngarina et al. found an increasing prevalence of unsuppressed viral load with increasing time postpartum among women who had initiated ART during pregnancy in Tanzania [24]. Among women with detectable viraemia at 24 months postpartum there was a decreased motivation to take ART after delivery and after weaning the infant [24]. The primary motivation for taking ART documented in the study was to protect from MTCT. Stigma, poverty, daily demands and the need to keep treatment a secret have been highlighted as significant barriers to adherence, both in the antenatal and postpartum periods [22,24]. A peer mentoring intervention in a PMTCT programme in South Africa led to women reporting better social support and reduced depression scores [32]. Women who received the intervention were more likely to return for follow up visits [32]. In Nigeria, having a treatment supporter has also been shown to improve adherence to PMTCT [19].

Among clinical characteristics, disease severity is thought to be a correlate of retention and adherence in both general adult populations and among pregnant women. Higher CD4 cell count, indicating a better baseline health status, was associated with higher odds of disengaging from care in a sample of pregnant women receiving ART for PMTCT in Kenya [21]. Similarly, better perceived health was found to be associated with poor ART adherence among postpartum women in Tanzania [24]. Pregnant women in general have a better baseline health and higher CD4 cell counts at the time of ART initiation than new initiates in the general adult population

[8,10,18]. One hypothesis is that healthier individuals are less motivated to take medication for their own health with no obvious signs of illness. In the antenatal setting this may be overcome by the increased motivation to adhere to treatment to prevent infant HIV infection, however when a woman enters the postpartum period her own perceived health may influence her motivation to remain in ART care [24].

Knowledge and understanding of HIV and PMTCT has also been shown to influence retention in care. Women in Ghana with poor knowledge of PMTCT were more likely to default in the first six months of treatment compared to women with good knowledge of PMTCT [33]. In Kenya, women who reported believing that ART was effective were more likely to access ART services [34]. Misunderstandings and misconceptions about PMTCT were reported as a major reason for non-adherence in rural South Africa [22]. Along with general knowledge about PMTCT and HIV, knowledge of the local programme systems is also important. Muchedzi et al. found that pregnant women in Zimbabwe who understood the PMTCT/ART referral systems were much more likely to successfully access care following referral from ANC [27].

Socioeconomic factors

Relationship status and partner influence on ART adherence and retention during pregnancy and postpartum have been widely investigated. Ayuo et al. found that in Kenya, women who were married were at a higher risk of LTF than single women [21]. Other studies have found that fear of disclosure to a partner as well as limited partner support and trust were significant barriers to adherence and retention [35,36]. In general, partner involvement in antenatal care as well as PMTCT programmes appears to be low in many parts of SSA and in South Africa in particular. A recent review of the literature noted that one of the main barriers to male involvement in PMTCT is the perception that antenatal care and PMTCT is an activity only for women [37,38].

This socio-cultural perception results in women navigating the ANC and PMTCT systems without partner support. Otieno et al. found that Kenyan women who had discussed referral for ART care with their partner were more likely to access care than women who did not [34]. Duff et al. examined barriers to ART from a partner perspective by interviewing husbands of women enrolled in a PMTCT programme in Uganda [39]. Men reported that they did not feel sufficiently involved in the PMTCT process. They identified disclosure and stigma, as well as low levels of PMTCT knowledge among men and low partner testing rates, as significant barriers to ART in pregnancy [39]. Similar barriers were identified by women and their husbands in Malawi [36].

In addition, economic concerns are important barriers to accessing HIV and maternal and child health services in most settings. During both the antenatal and postpartum periods, financial concerns have been found to hinder ART adherence and retention [24,34,40]. For instance, Duff et al. reported that a pregnant woman's dependence on her partner for financial support was a significant barrier to accessing care [40]. Theft of ARVs by relatives and domestic violence have also been noted as reasons for poor adherence [22].

Service-level factors

There is growing attention in the literature to the features of health care services that may influence ART adherence and/or retention during pregnancy and postpartum. Poor patient-provider relationships tend to increase the risk of disengagement from care [40]. Lack of trust in the health care provider, fear of disclosure and lack of confidentiality have been shown to increase the risk of women disengaging from care [27,34,41]. Long waiting times and overall dislike of the ART facility have been noted as barriers to adherence and retention [27,34,40]. Good health education, counselling and compassion from providers have been reported to encouraged attendance of ART services [34,38]. A mixed methods study investigating success

of referral to stand alone ART clinics from ANC in Tanzania, noted that ongoing HIV care was not covered in HIV education sessions in the ANC clinic [26]. With policies shifting to ART for all pregnant and breastfeeding women, the inclusion of information on HIV and postpartum ART care in general education sessions will be very important. The physical location, opening hours and accessibility of services have also been found to be barriers to ART uptake [38,42,43]. Retention in ART care was improved in Kenya by the use of an active defaulter tracing system. Active tracing of women who had missed a visit by two or more weeks resulted in 60% of PMTCT patients returning to care [43].

3.4 Integrated ANC & ART

Integrating ART services into routine ANC is becoming an important feature of PMTCT programmes across Africa. The WHO and South African National PMTCT guidelines now recommend immediate ART initiation for all HIV-infected pregnant women. Integrating ART services into existing ANC facilities will be required to achieve this rapid initiation in all pregnant HIV-infected women.

Uptake and retention

Integrated services have been repeatedly shown to significantly increase the uptake of ART prior to delivery [5–7]. In a recent report of routine programme data from Malawi, where Option B+ was implemented in the second half of 2011, ART uptake among pregnant and breastfeeding women increased 748% after one year of B+ implementation [7]. There has however been some concern that the rapid initiation of ART facilitated by integrated services may negatively impact long term retention and other outcomes. Pre-ART preparation has been a focus of preventing poor-adherence and promoting retention [44–46]. Fewer counselling sessions and reduced preparation time with rapid ART initiation in pregnancy may have implications for adherence

and retention. There are few data available to address this however the few existing studies have found similar outcomes among women in integrated and non-integrated services. In 2010, Killam et al. found that retention in care at three months on treatment was equivalent among women initiating ART in an integrated service (87%) and those referred out to separate ART services (91%) [6]. An early report from Malawi showed that retention at 12 months on ART, following implementation of option B+, was 77% [7]. This was in line with the national general ART retention rates. More recently, Myer et al. found that delays between screening and ART initiation, intended to further prepare women for the challenges of ART for PMTCT and for life, did not improve outcomes of retention in care at 12 months on treatment or improve levels of viral suppression at each ART visit [47].

Acceptability

Another concern regarding integrated ART and rapid ART initiation during pregnancy is acceptability for both pregnant HIV-infected women as well as the health care providers who are required to implement the guidelines. In 2012, a survey from Kenya found satisfaction with services to be higher among women attending integrated ART services (79%) compared to among women attending standalone ART services (54%) [48]. Another Kenyan study explored integrated ART services from a provider perspective [41]. During in-depth interviews, providers noted that integration of ART and ANC services meant less time for patients in health facilities but also raised concerns about increased provider time with each patient and an increased workload. Improved patient-provider relationships, confidentiality and less stigma in an integrated service compared to stand alone ART services were thought to improve the uptake of ART during pregnancy [41].

Timing

Although faster ART initiation as a result of integrated services has been highlighted as a concern, it also offers a significant advantage in the context of pregnancy. The literature suggests that the optimal time on ART prior to delivery is 8-13 weeks to ensure viral suppression and minimize the risk of MTCT [12,23,49,50]. In integrated ART services there are fewer delays between being identified as ART eligible and ART initiation. Women therefore start ART earlier and have a longer time on ART prior to delivery, improving their chances of reaching viral suppression by delivery and maximizing the benefit of ART for PMTCT [5,50–52].

3.5 Areas for further research

We know that ART is a very effective intervention for PMTCT, however we also know that pregnant and postpartum women are vulnerable to being lost to care. There is a need to better understand the challenges around ART that are particular to pregnant and postpartum women. Further knowledge on the timing of LTF and the most vulnerable points on the PMTCT cascade will help to inform interventions to improve ART adherence and support retention.

Globally, PMTCT policy is shifting to integrated same day ART initiation within ANC clinics. Existing literature suggests that rapid, integrated ART initiation does not negatively impact on future retention [6,47], however LTF and adherence remain a concern. Most women who initiate ART in an integrated ANC/ART service will ultimately be transferred to general adult ART services post-delivery. Successful linkage to care following referral out in the postpartum period is required to ensure ongoing retention in care. There are few data investigating linkage to ongoing ART care following initiation of lifelong ART in an integrated ART service. Given the

appreciable challenges of linking to care in the absence of integrated services, there is a need for research focusing on postpartum linkage to ongoing ART care.

This literature review underscores the need for additional research into the frequency and timing of LTF from ART services following ART initiation. Following from this, the proposed study aims to further our knowledge of the rate of LTF in the antenatal and postpartum periods and to investigate predictors of LTF both during pregnancy and after delivery. The knowledge generated will contribute to the body of literature on ART services for PMTCT and maternal health, and aims to inform the development of appropriate and timely interventions to promote retention in ART care throughout pregnancy and breastfeeding.

Table B-2: Summary of included studies

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV Regimen	Outcomes measured	Cascade point	Key Findings	Definition of adherence or retention outcome (if applicable)
Mixed method studies									
[34]	Boateng, 2013	Ghana, urban	Descriptive cross sectional (n=229 women, n=14 health workers)	HIV -infected women of reproductive age who had been on treatment at least 6 months	ART for own health or AZT prophylaxis	Defaulter rate, ART & PMTCT knowledge	Antenatal & postpartum	Women with inadequate ART & PMTCT knowledge were 3.5 times more likely to default ART. Defaulter rate was 27%.	**Defaulter**: missed two or more ART appointments within the previous two months
[54]	Lach Dean, 2012	South Africa, urban	Evaluation of pilot intervention (n=7)	Pregnant women newly diagnosed with HIV.	ART for own health or AZT prophylaxis	Usage and usability of an SMS support group	Antenatal	SMS support may be an acceptable support option for PMTCT	
[26]	MacPherson, 2012	Malawi, urban	Prospective cohort (n=280)	Adults undergoing HIV testing & counselling	ART for own health	Referral for ART	Linking to care	ART eligibility assessment was suboptimal as was referral to ART services. HIV-infected pregnant women were significantly less likely to be referred directly for ART than non-pregnant women and men.	
[23]	Mepham, 2011	South Africa, rural	Retrospective cohort supplemented with face-to-face unstructured interviews (n=100)	HIV-infected pregnant women	Randomized to short course AZT prophylaxis and ART prophylaxis	Adherence & reasons for poor adherence	Antenatal	61% of women had good adherence and there was no difference between the two treatment groups. Reasons for poor adherence therapy included misconceptions/misunderstandings, interruptions to routine, ARVs taken by relatives, domestic violence, poverty and issues relating to disclosure and stigma.	**Good adherence**: (>95%) based on pill count.

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV Regimen	Outcomes measured	Cascade point	Key Findings	Definition of adherence or retention outcome (if applicable)
[35]	Otieno, 2010	Kenya, urban	Cross sectional survey (n=195)	HIV-infected women located after referral to HIV care postpartum	ART - for own health	Accessing HIV care postpartum	Linking to care & postpartum	74% of women reported attending the referral HIV care site. Barriers to attending were lack of money, concern about confidentiality and dislike of the facility. Women who discussed the referral with partner and those who believed HAART was effective were more likely to access care. Enabling were health education, counselling, free services and compassion from the provider.	
[27]	Watson-Jones, 2012	Tanzania, urban	Prospective cohort (n=403), direct observation (n=9 ANC HIV education settings), in-depth interviews (n=30 health workers)	HIV-infected pregnant women and health care workers	ART for own health or AZT prophylaxis	Referral to and registration at an ART service & reasons for non-attendance	Linking to care	70% of health workers did refer women to HIV care. ANC HIV education did not cover ongoing HIV care. Only 32% of women followed for 4 months had attended and been assessed for ART eligibility. Non-attendance was linked to fewer ANC visits, nondisclosure, poor PMTCT compliance, non-Sukuma ethnicity.	
Qualitative studies									
[36]	Awiti, 2011	Kenya, rural	Narrative structuring (n=28)	HIV-infected pregnant women already on ART at time of incident pregnancy	ART	ART adherence during pregnancy	Antenatal	Fear of stigma was a reason for non-adherence in both urban and rural women. Importance of partner trust was highlighted. Importance of fulfilling home responsibilities results in women favoring a birth assistant over clinic delivery.	
[37]	Chinkonde, 2009	Malawi, urban-rural	In-depth interviews and focus group discussions (women n=28, husbands n=12)	Pregnant HIV-infected women who had joined the PMTCT programme and husbands	ART for own health or AZT prophylaxis	Factors associated with retention and drop out	Antenatal	Disclosure, confidentiality, stigma, lack of partner support, difficulty accessing care were the main reasons provided for dropout.	

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV Regimen	Outcomes measured	Cascade point	Key Findings	Definition of adherence or retention outcome (if applicable)
[41]	Duff, 2010	Uganda, rural	In-depth interviews and focus group discussions (n=45)	HIV-infected pregnant women	ART - for own health	Factors associated with retention and drop out	Linking to care & antenatal	Economic concern represented the greatest barrier to accessing ART. Stigma and non-disclosure to partner, clinic waiting times and patient provider interactions were also significant barriers.	
[40]	Duff, 2012	Uganda, rural	Qualitative descriptive exploratory using thematic analysis (n=40)	Married men with a female partner of reproductive age	PMTCT and ART during pregnancy	Barriers to ART as perceived by husbands	Linking to care & antenatal	Disclosure and stigma were two major obstacles, low male knowledge of PMTCT and low testing rate were thought to be barriers to women accessing treatment. Men felt not sufficiently involved in PMTCT.	
[39]	Lubega, 2013	Uganda, rural	Key informant interviews, in-depth interviews and focus group discussions	Patients retained and LTF from a PMTCT programme, caretakers and relatives of PMTCT patients	ART for own health or AZT prophylaxis	Reasons for LTF from PMTCT programmes	Antenatal	Reasons for LTF included sex inequality, high transport costs to access the services, inadequate posttest counseling, lack of HIV status disclosure, and the location of the ART clinic.	
[25]	Ngarina, 2013	Tanzania, urban	Qualitative cross-sectional semi-structured interviews following on from the Mitra plus study (n=23)	HIV-infected women with detectable viral load at 24 months postpartum	ART - for own health	Barriers to ART post-delivery	Postpartum	Motivation to take ART decreased after delivery and weaning as they no longer needed to protect the baby, feeling well and feeling hopeless was associated with poor adherence. Everyday demands, poverty, stigma and need to keep ARVs a secret were significant barriers to adherence	
[32]	Stinson, 2012	South Africa, urban	Qualitative - structured interviews (n=28 HIV-infected pregnant or postpartum women, n=21 service providers)	HIV-infected pregnant and postpartum women, & health care providers	ART - for own health	Barriers to initiating lifelong ART in pregnancy and retention in care postpartum	Linking to care	Key challenge to ART initiation: denial of HIV status, fear of disclosure, late presentation, treatment side effects, lifelong commitment to ART. Another challenge is dealing with pregnancy, HIV diagnosis and the need for lifelong treatment.	

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV Regimen	Outcomes measured	Cascade point	Key Findings	Definition of adherence or retention outcome (if applicable)
[42]	Winestone, 2012	Kenya, rural	In-depth interviews and thematic analysis (n=36)	ANC healthcare providers in facilities randomized to provide integrated ANC/HIV services or non-integrated services	ART for own health or AZT prophylaxis (Option A)	Health care provider perspectives on integrated ANC/HIV care services	Antenatal	Providers noted that integration meant less patient time spent in health facilities, increased efficiency and better patient-provider relationships. Increased confidentially and decreased stigma would mean more women will initiate ART if services were integrated. Some providers concerned that increased visit duration would lead to inadvertent disclosure. Need to consider impact on workload and quality of care.	
Quantitative studies									
[22]	Ayuo, 2013	Kenya, urban & rural	Retrospective cohort (n=4284)	ART naïve adult pregnant women	ART for own health	Clinician initiated change/stop of regimen, disengagement, self-reported adherence	Antenatal follow up	89% of women reported taking all medication at all visits. 31.9% of women disengaged from care. Disengagement was associated with decreasing age and decreasing gestational age at ART initiation	**Disengagement:** Early - more than 30days late but returned prior to delivery. Late - no visit within 30 days of delivery
[21]	Black, 2008	South Africa, urban	Retrospective cohort (n=689)	ART naïve pregnant women	ART for own health	Maternal health outcomes, HIV-transmission.	Antenatal and postnatal follow up	27% of women were considered LTF by 6 weeks postpartum	**LTF:** Women who did not attend the 6 week postpartum follow-up visit.
[52]	Black, 2013	South Africa, urban	Prospective evaluation of a pilot intervention (n=134)	Pregnant ART eligible women at ANC	ART for own health	ART uptake and time between screening and initiation of ART	Linking to care	During the rapid ART initiation intervention 97% of eligible women started ART and 90.8% started on the same day as screening	
[9]	Boyles, 2011	South Africa, rural	Prospective cohort (n=1803)	Adults who have initiated ART	ART for own health	Mortality and retention in care	Antenatal and postpartum follow up	Initiating ART while pregnant was an independent predictor of LTF in a general adult population. Follow up period of 4 years	**LTF:** no patient contact for more than 6 months. Censored at date of last contact
[50]	Chibwesha, 2011	Zambia, urban	Retrospective cohort (n=1813)	HIV-infected pregnant women who started HAART antenatally and had an infant PCR	ART - for own health	Infant HIV infection an duration of antenatal ART	Antenatal follow up	Maximum effect of PMTCT is achieved by initiating ART at least 13 weeks prior to delivery	

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV Regimen	Outcomes measured	Cascade point	Key Findings	Definition of adherence or retention outcome (if applicable)
[8]	CDC 2013	Malawi	Programme evaluation using national routine programme data	HIV-infected pregnant women	ART - option B+	ART uptake and retention up to 12 months on treatment	Linking to care and overall follow up	ART uptake per quarter increased 748% after 1 year of B+. Retention at 12months in facility of initiation was 77% (excluding those who transferred care). Highlight need for integrated care and staff training	Definition of retention not stated.
[10]	Clouse, 2013(a)	South Africa, urban	Retrospective cohort study	Newly diagnosed HIV-positive pregnant women	ART for own health or AZT prophylaxis (Option A)	Attrition at steps along the PMTCT cascade from HIV testing to 6 months on ART	Linking to care, antenatal and postpartum follow up	40.5% of ART eligible women cumulatively retained through to 6 months on ART. 20.5% were lost before delivery overall, and of those still in care after delivery 47.9% were LTF within 6 months of delivery. Women booking later for ANC were more likely to be LTF prior to delivery. Older age was protective of LTF after delivery.	**LTF:** not returning to the clinic within 1 month after the last scheduled visit
[19]	Clouse, 2013(b)	South Africa, urban	Retrospective cohort (n=1430)	General adult population	ART - for own health	LTF within 1 year of starting ART	Antenatal follow up	Overall pregnant women had higher baseline CD4 cell counts. Different CD4 categories had no effect on LTF among pregnant women. Among non-pregnant women and men, lower CD4 cell counts were associated with increased risk of LTF. Overall, pregnant women were the most likely to be LTF.	**LTF**: not returning to the clinic within 3 months of the patient's last missed scheduled visit
[20]	Ekama, 2012	Nigeria, urban	Cross sectional. Semi structured questionnaire (n=170)	HIV-infected pregnant women	ART for own health or AZT prophylaxis (Option A)	ARV adherence during pregnancy	Antenatal follow up	After controlling for confounders, HIV disclosure and having a treatment supporter were associated with good adherence. 80% reported good adherence	**Adherence**: (≥95%) using 3 day recall
[43]	Ferguson, 2012(a)	Kenya, rural and urban	Retrospective cohort (n=1129)	Women testing HIV-positive in pregnancy	ART for own health or AZT prophylaxis (Option A)	Attrition between ANC HIV testing and long term HIV services	Linking to care	<50% of known eligible women initiated ART. Registration of clients, cost and opening hours of services hampered uptake. Attendance of more ANC visits was associated with attendance at HIV care	
[55]	Ferguson, 2012(b)	Sub-Saharan Africa	Systematic review (n=20 studies)	Women testing HIV-positive in pregnancy	ART - for own health	Attrition between ANC HIV testing and long term HIV services	Linking to care	38-88% of known eligible women fail to initiate ART. Family focused, integrated care seems to improve ART uptake. Financial constraints and stigma are barriers to uptake.	

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV Regimen	Outcomes measured	Cascade point	Key Findings	Definition of adherence or retention outcome (if applicable)
[51]	Fitzgerald, 2010	South Africa, urban	Retrospective cohort (n=367)	ART naïve, ART eligible pregnant women	ART for own health or AZT prophylaxis (Option A)	ART uptake and HIV transmission	Linking to care and antenatal follow up	72% of women commenced ART before delivery. 13% of ART eligible women were lost to follow up. Transmission rate was 5.1%. No transmission among women on ART for >=8weeks prior to delivery	LTF not defined
[33]	Futterman, 2010	South Africa, urban	Prospective cohort evaluation of pilot intervention (n=160)	HIV-infected pregnant women	ARV prophylaxis	Transmission risk behavior and emotional functioning	Antenatal and postpartum follow up	Women in the Mamekhaya intervention arm had reduced depression scores and improved social support. They were more likely to attend follow up visits and had a significantly increased HIV knowledge score, compared to women in the control clinic.	
[18]	Kaplan, 2008	South Africa, urban	Retrospective cohort (n=2131)	ART naïve women referred for ART	ART - for own health	Mortality and LTF	ART uptake and long term follow up	Crude pre-treatment LTF was 13.2% among pregnant women compared to 6% for non-pregnant women. At 3 years on ART LTF rates were 32% and 13% respectively. Pre-treatment mortality was significantly lower among pregnant women (0.3% vs. 4.7 %)	**On treatment LTF** defined as not attending the clinic for 12 or more weeks.
[7]	Killam, 2010	Zambia, urban & rural	Stepped-wedge intervention evaluation (n=1566)	HIV-infected ART eligible pregnant women	ART - for own health	ART uptake in an integrated and non-integrated ART service	Art uptake	44.4% of women in the intervention cohort initiated ART while pregnant and within 60 days of diagnosis, compared to 25.3% in the control cohort. Integrated ART in ANC can double the proportion of eligible women starting treatment. Gestational age at initiation and retention at 90 days on AR were similar in both cohorts.	**Patient retention**: the number of women initiated on treatment and still on treatment (not LTF, dead, or transferred out) in the first 90 days of treatment. LTF not defined.
[56]	Kumwenda, 2011	Malawi, urban	Secondary analysis of PEPI-Malawi data to assess barriers to postpartum ART (n=803)	HIV-infected pregnant women eligible for ART	ART - for own health	Received ART postpartum	Linking to care	No differences in demographics found between women who did and did not initiate ART. Suggest barriers associated with health system delivery, space, personnel.	

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV Regimen	Outcomes measured	Cascade point	Key Findings	Definition of adherence or retention outcome (if applicable)
[28]	Muchedzi, 2010	Zimbabwe, urban	Cross sectional survey (n=147)	HIV-infected pregnant women	ART - for own health	Referral to and registration at an ART service	Linking to care	65% of women registered at an ART programme but referral was only documented for 16% of women. Participants who understood the referral system and those enrolled in HIV support groups were more likely to access HIV care. Women living with a male partner were less likely to access treatment. Barriers to accessing care were waiting times and competing life priorities. Among those who did access care, challenges included waiting times, irregular lab testing and transport costs.	
[48]	Myer, 2012(a)	South Africa, urban	Retrospective cohort (n=490)	HIV-infected pregnant women referred for ART	ART - for own health	ART initiation, delay from referral to initiation. Retention an viral suppression at 4,8 and 12 months	Antenatal and postpartum follow up	78% of eligible women initiated ART before delivery. 75% of women were retained at 12months and 91% of women were virally suppressed at each follow up visit. Delay between screening and ART initiation was not associated with retention/viral suppression in the first year on ART	**LTF:** having 60 days elapsed since the last scheduled visit.
[53]	Myer,2012(b)	South Africa, urban	Evaluation of a pilot intervention for rapid initiation of ART in pregnancy (RAP) (n=221)	HIV-infected pregnant women referred for ART	ART - for own health	Initiating ART during pregnancy	Linking to care	With RAP in place, 97% of women started ART during pregnancy	
[31]	Ngidi, 2013	South Africa, urban & rural	prospective, non-randomized controlled study (n=2 matched health districts)	HIV-infected pregnant women	ART - for own health	Referral for ART and initiating ART during pregnancy	Linking to care	There was a significant increase in the numbers of pregnant women referred for ART and the number of women initiating ART while pregnant in the intervention district. There was no improvement noted in the control district. A targeted campaign amongst health workers can improve access to ART	

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV Regimen	Outcomes measured	Cascade point	Key Findings	Definition of adherence or retention outcome (if applicable)
[12]	Okonji, 2012	Kenya	Prospective cohort (n=434)	HIV-infected pregnant women still enrolled in the KiBS study at 24 months postpartum	ART prophylaxis	CD4, viral load and adherence	Antenatal and postpartum	Adherence and duration on ART were associated with reaching viral suppression.	**Adherence**: (≥ 95%) by pill count, drug calendar and 3 day & 1 month self report
[57]	Stinson, 2010	South Africa, urban	Retrospective cohort (n=14987)	Women presenting for ANC	ART - for own health	Initiating ART during pregnancy	Linking to care	51% of eligible women initiated ART before delivery. Early gestational age at booking was the strongest predictor of initiating ART during delivery	
[6]	Stinson, 2013	South Africa, urban	Retrospective cohort comparing 3 models for ART initiation (n=14617)	Women presenting for ANC	ART - for own health	Initiating ART during pregnancy	Linking to care	Women in the integrated model were significantly more likely to initiate ART antenatally compared to women in the distal model.	
[58]	Tenthani, 2014	Malawi	Analysis of nationwide facility level data (n=21939) Analysis of individual patient data (n=11534)	HIV-infected pregnant and breastfeeding women	ART (option B+)	Retention up to 6 months on ART	Antenatal and postpartum follow up	Using national data, 17% of women were LTF 6 months after ART initiation. Women who started ART during pregnancy under B+ were 5 times more likely to be LTF compared to women eligible for ART for their own health (CD4<=350/WHO stage 3 or 4). LTF was highest among B+ women who started ART on the same day as HIV diagnosis. There was considerable variation of rates of LTF between facilities.	**LTF:** missed an appointment and did not return to care for more than 60 days.
[29]	Theuring, 2013	Tanzania, urban	Retrospective cohort (n=60)	HIV-infected pregnant women eligible for ART	ART for own health or AZT prophylaxis	ART initiation prior to delivery, duration of ART prior to delivery	Antenatal	39 women (65%) started ART before delivery. Median duration of ART prior to delivery was 59 days. Lower CD4 cell count was associated with antenatal Art initiation and earlier enrolment for ANC was associated with longer duration of Art prior to delivery	

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV Regimen	Outcomes measured	Cascade point	Key Findings	Definition of adherence or retention outcome (if applicable)
[44]	Thomson, 2011	Kenya, urban	Retrospective analysis of routine programme data	Active tracing attempts for patients in HIV, PMTCT, TB and HIV/TB programmes (n=1066 total, n=269 PMTCT)	ART for own health or AZT prophylaxis	Impact of Active defaulter tracing system	Antenatal follow up	59.4% of all patients and 60.2% of PMTCT patients traced returned to the clinic. Common barriers given to attending care were increased distance to the clinic due to moving/traveling, as well as the schedule and location of employment.	**LTF of HIV patients:** does not return to the clinic within six months **LTF of PMTCT patients:** does not return within two months.
[24]	Van Schalkwyk, 2013	South Africa, urban	Retrospective cohort (n=250)	Women initiating ART during pregnancy	ART - for own health	Initiating ART during pregnancy	Antenatal and postpartum follow up	Median gestation at ART initiation was lowest in 2010, meaning longer time on ART before delivery. HIV transmission was also lowest in 2010. Women on ART for <8weeks before delivery were more likely to transmit. 37.6% of women were LTF within 28 days of delivery	Not clearly defined
[49]	Vo, 2012	Kenya, rural	Cross sectional patient satisfaction survey following on from a cluster randomized controlled trial comparing integrated to non-integrated HIV and ANC services (n=326)	Pregnant women who had been randomized to integrated and non-integrated HIV care services	ART for own health or AZT prophylaxis	Patient satisfaction	Linking to care	79% of women in fully integrated clinics were very satisfied with the care they received, compared to 54% of women in non-integrated clinics. HIV-negative women did not report any significant differences in satisfaction with their ANC care.	

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV Regimen	Outcomes measured	Cascade point	Key Findings	Definition of adherence or retention outcome (if applicable)
[11]	Wang, 2011	South Africa, urban-rural	Prospective cohort (n=925)	HIV-infected adults who initiated ART	ART - for own health	LTF within 6months of starting ART	Antenatal & postpartum	Younger age and pregnancy were significantly associated with higher rates of LTF.	**Patient based LTF:** Failure to return for a scheduled consultation or medication pick-up within 6 months after ART initiation. **Data-based definition LTF:** if no information was recorded with respect to the date of the 6-month follow-up visit & there was no laboratory testing (CD4 or HIV RNA tests) within 6 months of ART initiation.
[30]	Weigel, 2012	Malawi, urban	Operational cohort (n=612)	HIV-infected women eligible for ART	ART - for own health	completion of referral, initiation and retention up to 6 months	Linking to care and antenatal follow up	47% of eligible women started ART during pregnancy. 43% were alive on ART or transferred out at 6months. Median delay from screening to initiation fell from 2006-2009, and proportions of women initiating ART and retained at 6months improved significantly. Still delays between taking CD4 and referral for ART.	not clearly defined

4 References

[1] World Health Organisation. Countdown to zero: global plan for the elimination of new HIV infections among children by 2015 and keeping their mothers alive. Geneva, Switzerland: World Health Organisation; 2011 [cited 2014 February 2]. Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/20110609_jc2137_global-plan-elimination-hiv-children_en.pdf

[2] Joint United Nations Programme on HIV/AIDS. 2013 Progress Report on the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS; 2013 [cited 2014 February 2]. Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2013/20130625_progress_global_plan_en.pdf

[3] World Health Organisation. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a publich health approach. Geneva: World Health Organization; 2013 [cited 2014 February 2]. Available from: http://www.who.int/hiv/pub/guidelines/arv2013/download/en/

[4] Goga A, Dinh T, Jackson D, for the SAPMTCTE study group. Evaluation of the effectiveness of the National Prevention of Mother-to-Child Transmission (PMTCT) programme measured at six weeks postpartum in South Africa, 2010. South African Medical Research Council, National Department of Health of South Africa and PEPFAR/US Centers for Disease Control and Prevention; 2012 [cited 2014 February 2]. Available from: [http://www.mrc.ac.za/healthsystems/SAPMTCTE2010.pdf]

[5] Sturt A, Dokubo E, Sint T. Antiretroviral therapy (ART) for treating HIV infection in ART-eligible pregnant women. Cochrane Database Syst Rev 2010;3. Art. No.: CD008440

[6] Stinson K, Jennings K, Myer L. Integration of antiretroviral therapy services into antenatal care increases treatment initiation during pregnancy : a cohort study. PLoS One 2013;8:e63328.

[7] Killam WP, Tambatamba BC, Chintu N, Rouse D, Stringer E, Bweupe M, et al. Antiretroviral therapy in antenatal care to increase treatment initiation in HIV-infected pregnant women: a stepped-wedge evaluation. AIDS 2010;24:85–91.

[8] CDC. Impact of an innovative approach to prevent Mother-to-Child Transmission of HIV — Malawi, July 2011–September 2012. Morb Mortal Wkly Rep 2013;62:148–51.

[9] Boyles TH, Wilkinson LS, Leisegang R, Maartens G. Factors influencing retention in care after starting antiretroviral therapy in a rural South African programme. PLoS One 2011;6:e19201.

[10] Clouse K, Pettifor A, Shearer K, Maskew M, Bassett J, Larson B, et al. Loss to follow-up before and after delivery among women testing HIV-positive during pregnancy in Johannesburg, South Africa. Trop Med Int Health 2013;18:451–60.

[11] Wang B, Losina E, Stark R, Munro A, Walensky RP, Wilke M, et al. Loss to follow-up in a community clinic in South Africa-roles of gender, pregnancy and CD4 count. South African Med J 2011;101:253–7.

[12] Okonji JA, Zeh C, Weidle PJ, Williamson J, Akoth B, Masaba RO, et al. CD4, viral load response, and adherence among antiretroviral-naive breast-feeding women receiving triple antiretroviral prophylaxis for prevention of mother-to-child transmission of HIV in Kisumu, Kenya. J Acquir Immune Defic Syndr 2012;61:249–57.

[13] Denoeud-Ndam L, Fourcade C, Ogouyemi-Hounto A, Azon-Kouanou A, D'Almeida M, Azondékon A, et al. Predictive factors of plasma HIV suppression during pregnancy: a prospective cohort study in Benin. PLoS One 2013;8:e59446.

[14] O'Shea S, Newell ML, Dunn DT, Garcia-Rodriguez MC, Bates I, Mullen J, et al. Maternal viral load, CD4 cell count and vertical transmission of HIV-1. J Med Virol 1998;54:113–7.

[15] Tubiana R, Le Chenadec J, Rouzioux C, Mandelbrot L, Hamrene K, Dollfus C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). Clin Infect Dis 2010;50:585–96.

[16] Nachega JB, Uthman O, Anderson J, Peltzer K, Wampold S, Cotton MF, et al. Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis. AIDS 2012;26:2039–52.

[17] Paredes R, Marconi VC, Lockman S, Abrams EJ, Kuhn L. Impact of antiretroviral drugs in pregnant women and their children in Africa: HIV resistance and treatment outcomes. J Infect Dis 2013;207 Suppl :S93–100.

[18] Kaplan R, Orrell C, Zwane E, Bekker L-G, Wood R. Loss to follow-up and mortality among pregnant women referred to a community clinic for antiretroviral treatment. AIDS 2008;22:1679–81.

[19] Clouse K, Pettifor A, Maskew M, Bassett J, Van Rie A, Gay C, et al. Initiating antiretroviral therapy when presenting with higher CD4 cell counts results in reduced loss to follow-up in a resource-limited setting. AIDS 2013;27:645–50.

[20] Ekama SO, Herbertson EC, Addeh EJ, Gab-Okafor C V, Onwujekwe DI, Tayo F, et al. Pattern and determinants of antiretroviral drug adherence among Nigerian pregnant women. J Pregnancy 2012;2012:851810.

[21] Black V, Hoffman RM, Sugar CA, Menon P, Venter F, Currier JS, et al. Safety and efficacy of initiating highly active antiretroviral therapy in an integrated antenatal and HIV clinic in Johannesburg, South Africa. J Acquir Immune Defic Syndr 2010;49:276–81.

[22] Ayuo P, Musick B, Liu H, Braitstein P, Nyandiko W, Otieno-Nyunya B, et al. Frequency and factors associated with adherence to and completion of combination antiretroviral therapy for prevention of mother-to-child transmission in western Kenya. J Int AIDS Soc 2013;16:17994.

[23] Mepham S, Zondi Z, Mbuyazi a, Mkhwanazi N, Newell ML. Challenges in PMTCT antiretroviral adherence in northern KwaZulu-Natal, South Africa. AIDS Care 2011;23:741–7.

[24] Van Schalkwyk M, Andersson MI, Zeier MD, La Grange M, Taljaard JJ, Theron GB. The impact of revised PMTCT guidelines : a view from a public sector ARV clinic in Cape Town , South Africa. J Acquir Immune Defic Syndr 2013;63:234–8.

[25] Ngarina M, Popenoe R, Kilewo C, Biberfeld G, Ekstrom AM. Reasons for poor adherence to antiretroviral therapy postnatally in HIV-1 infected women treated for their own health: experiences from the Mitra Plus study in Tanzania. BMC Public Health 2013;13:450.

[26] MacPherson P, Lalloo DG, Choko AT, Mann GH, Squire SB, Mwale D, et al. Suboptimal patterns of provider initiated HIV testing and counselling, antiretroviral therapy eligibility assessment and referral in primary health clinic attendees in Blantyre, Malawi. Trop Med Int Health 2012;17:507–17.

[27] Watson-Jones D, Balira R, Ross DA, Weiss HA, Mabey D. Missed opportunities: poor linkage into ongoing care for HIV-positive pregnant women in Mwanza, Tanzania. PLoS One 2012;7:e40091.

[28] Muchedzi A, Chandisarewa W, Keatinge J, Stranix-chibanda L, Woelk G, Mbizvo E, et al. Factors associated with access to HIV care and treatment in a prevention of mother-to-child transmission programme in urban Zimbabwe. J Int AIDS Soc 2010;13:38.

[29] Theuring S, Sewangi J, Nchimbi P, Harms G, Mbezi P. The challenge of referring HIV-positive pregnant women with treatment indication from PMTCT to ART services: a retrospective follow-up study in Mbeya, Tanzania. AIDS Care 2013;Epub:ahead of print.

[30] Weigel R, Hosseinipour MC, Feldacker C, Gareta D, Tweya H, Chiwoko J, et al. Ensuring HIV-infected pregnant women start antiretroviral treatment: an operational cohort study from Lilongwe, Malawi. Trop Med Int Health 2012;17:751–9.

[31] Ngidi W, Reddy J, Luvuno Z, Rollins N, Barker P, Mate KS. Using a campaign approach among health workers to increase access to antiretroviral therapy for pregnant HIV-infected women in South Africa. J Acquir Immune Defic Syndr 2013;63:e133–9.

[32] Stinson K, Myer L. Barriers to initiating antiretroviral therapy during pregnancy : a qualitative study of women attending services in Cape Town , South Africa. African J AIDS Res 2012;11:65–73.

[33] Futterman D, Shea J, Besser M, Stafford S, Desmond K, Comulada WS, et al. Mamekhaya: a pilot study combining a cognitive-behavioral intervention and mentor mothers with PMTCT services in South Africa. AIDS Care 2010;22:1093–100.

[34] Boateng D, Kwapong GD, Agyei-Baffour P. Knowledge, perception about antiretroviral therapy (ART) and prevention of mother-to-child-transmission (PMTCT) and adherence to ART among HIV-positive women in the Ashanti Region, Ghana: a cross-sectional study. BMC Womens Health 2013;13:2.

[35] Otieno PA, Kohler PK, Bosire RK, Brown ER, Macharia SW, John-Stewart GC. Determinants of failure to access care in mothers referred to HIV treatment programs in Nairobi, Kenya. AIDS Care 2010;22:729–36.

[36] Awiti Ujiji O, Ekström AM, Ilako F, Indalo D, Wamalwa D, Rubenson B. Reasoning and deciding PMTCT-adherence during pregnancy among women living with HIV in Kenya. Cult Health Sex 2011;13:829–40.

[37] Chinkonde JR, Sundby J, Martinson F. The prevention of mother-to-child HIV transmission programme in Lilongwe, Malawi: why do so many women drop out. Reprod Health Matters 2009;17:143–51.

[38] Morfaw F, Mbuagbaw L, Thabane L, Rodrigues C, Wunderlich A-P, Nana P, et al. Male involvement in prevention programs of mother-to-child transmission of HIV: a systematic review to identify barriers and facilitators. Syst Rev 2013;2:5.

[39] Lubega M, Musenze IA, Joshua G, Dhafa G, Badaza R, Bakwesegha CJ, et al. Sex inequality, high transport costs, and exposed clinic location: reasons for loss to follow-up of clients under prevention of mother-to-child HIV transmission in eastern Uganda - a qualitative study. Patient Prefer Adherence 2013;7:447–54.

[40] Duff P, Rubaale T, Kipp W. Married men's perceptions of barriers for HIV-positive pregnant women accessing highly active antiretroviral therapy in rural Uganda. Int J Womens Health 2012;4:227–33.

[41] Duff P, Kipp W, Wild TC, Rubaale T, Okech-Ojony J. Barriers to accessing highly active antiretroviral therapy by HIV-positive women attending an antenatal clinic in a regional hospital in western Uganda. J Int AIDS Soc 2010;13:37.

[42] Winestone LE, Bukusi EA, Cohen CR, Kwaro D, Schmidt NC, Turan JM, et al. Acceptability and feasibility of integration of HIV care services into antenatal clinics in rural Kenya: a qualitative provider interview study. Glob Public Heal 2012;7:149–63.

[43] Ferguson L, Lewis J, Grant AD, Watson-Jones D, Vusha S, Ong'ech JO, et al. Patient attrition between diagnosis with HIV in pregnancy-related services and long-term HIV care and treatment services in Kenya: a retrospective study. J Acquir Immune Defic Syndr 2012;60:e90–7.

[44] Thomson KA, Cheti EO, Reid T. Implementation and outcomes of an active defaulter tracing system for HIV, prevention of mother-to-child transmission of HIV (PMTCT), and TB patients in Kibera, Nairobi, Kenya. Trans R Soc Trop Med Hyg 2011;105:320–6.

[45] Coetzee D, Boulle A, Hildebrand K, Asselman V, Cutsem G Van, Goemaere E. Promoting adherence to antiretroviral therapy : the experience from a primary care setting in Khayelitsha , South Africa. AIDS 2004;18 Suppl 3:S27–31.

[46] Gebrekristos HT, Mlisana KP, Karim QA. Patients' readiness to start highly active antiretroviral treatment for HIV. BMJ 2005;331:772–5.

[47] Kwaan L, Kindra G, Mdutyana L, Coutsoudis A. Prevention is better than cure – the art of avoiding non-adherence to antiretroviral treatment. South Afr J HIV Med 2010;11:8–10.

[48] Myer L, Zulliger R, Bekker L, Abrams E. Systemic delays in the initiation of antiretroviral therapy during pregnancy do not improve outcomes of HIV-positive mothers : a cohort study. BMC Pregnancy Childbirth 2012;12:94.

[49] Vo BN, Cohen CR, Smith RM, Bukusi EA, Onono MA, Schwartz K, et al. Patient satisfaction with integrated HIV and antenatal care services in rural Kenya. AIDS Care 2012;24:1442–7.

[50] Chibwesha C, Giganti M, Putta N, Chintu N, Mulindwa J, Benjamin J, et al. Optimal Time on HAART for Prevention of Mother-to-Child transmission of HIV. J Acquir Immune Defic Syndr 2013;58:224–8.

[51] Fitzgerald FC, Bekker L-G, Kaplan R, Myer L, Lawn SD, Wood R. Mother-to-child transmission of HIV in a community-based antiretroviral clinic in South Africa. S Afr Med J 2010;100:827–31.

[52] Black S, Zulliger R, Myer L, Marcus R, Jeneker S, Taliep R, et al. Safety , feasibility and efficacy of a rapid ART initiation in pregnancy pilot programme in Cape Town , South Africa. South African Med J 2013;103:557–62.

[53] Myer L, Zulliger R, Black S, Pienaar D, Bekker L-G. Pilot programme for the rapid initiation of antiretroviral therapy in pregnancy in Cape Town, South Africa. AIDS Care 2012;24:986–92.

[54] Lach Dean A, Makin JD, Kydd AS, Biriotti M, Forsyth BWC. A pilot study using interactive SMS support groups to prevent mother-to-child HIV transmission in South Africa. J Telemed Telecare 2012;18:399–403.

[55] Ferguson L, Grant AD, Watson-Jones D, Kahawita T, Ong'ech JO, Ross DA. Linking women who test HIV-positive in pregnancy-related services to long-term HIV care and treatment services: a systematic review. Trop Med Int Health 2012;17:564–80.

[56] Kumwenda J, Matchere F, Mataya R, Chen S, Mipando L, Li Q, et al. Coverage of highly active antiretroviral therapy among postpartum women in Malawi. Int J STD AIDS 2011;22:368–72.

[57] Stinson K, Boulle A, Coetzee D, Abrams EJ, Myer L. Initiation of highly active antiretroviral therapy among pregnant women in Cape Town, South Africa. Trop Med Int Health 2010;15:825–32.

[58] Tenthani L, Haas AD, Tweya H, Jahn A, van Oosterhout JJ, Chimbwandira F, et al. Retention in care under universal antiretroviral therapy for HIV-infected pregnant and breastfeeding women (’Option B+') in Malawi. AIDS 2014;28:589–98.

C. MANUSCRIPT

Retention in care among HIV-infected women initiating antiretroviral therapy during pregnancy: a cohort study

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Keywords: Antiretroviral therapy, Pregnancy, Postpartum, Retention, Prevention of mother-to-child transmission (PMTCT), HIV/AIDS, South Africa

[*] As per the MPH dissertation guidelines, co-authors are not listed on the journal ready manuscript. The contribution of collaborators and supervisors is listed in the acknowledgments section of this dissertation. This article is written according to the requirements in the Instructions for Authors for the Journal of the International AIDS Society (JIAS). These instructions are included as Appendix D, following dissertation guidelines.

Abstract

Background: Recent international guidelines call for universal use of triple-drug antiretroviral therapy (ART) in HIV-infected women during pregnancy and postpartum. There are however concerns regarding potentially high levels of non-adherence and/or loss to follow-up (LTF) that may attenuate the benefits of ART for HIV transmission and maternal health. We investigated missed visits and LTF among women initiating ART during pregnancy in Cape Town, South Africa.

Methodology: A cohort study was conducted of women starting ART, January 2011-September 2012, at a large primary care antenatal clinic. Eligible women were identified in PMTCT services based on CD4 ≤350 cells/μL, and women initiated a regimen of tenofovir, lamivudine and efavirenz. Outcomes were measured up to six months postpartum: (i) LTF (no attendance within 56 days of a scheduled visit) and (ii) missed visit (returning to care 14-56 days late for a scheduled visit).

Results: A total of 358 women (median age, 28 years; median gestational age at initiation, 26 weeks) initiated ART during pregnancy. By six months postpartum 24% of women (n=86) had missed at least one visit and 32% (n=115) were LTF. Overall, 49% of women had either missed a visit or were LTF by six months postpartum. LTF was more than twice as frequent postpartum compared to in the antenatal period (6.2 vs 2.4 per 100 woman-months, respectively; p=0.0004). In a proportional hazards model, later gestational age at initiation (HR: 1.04; 95% CI: 1.00-1.07; p=0.030) and being newly diagnosed with HIV (HR: 1.57; 95% CI: 1.07-2.33; p=0.022) were significant predictors of LTF after adjusting for patient age, starting CD4 cell count and site of ART initiation. Site of ART initiation was not a significant predictor of LTF.

Conclusions: These results demonstrate that missed visits and LTF occur frequently among HIV-infected women initiating ART during pregnancy, particularly post-delivery. Further research is required to understand reasons for non-adherence and LTF and the implications thereof in the context of pregnancy. Women newly diagnosed with HIV and those presenting at later gestational ages may be particularly vulnerable and there is an urgent need for interventions to promote retention among all HIV-infected women during pregnancy and after delivery.

1 Introduction

Mother-to-child transmission (MTCT) of human immunodeficiency virus (HIV) is the main contributor to new HIV infections in children globally. In 2012, 260 000 children were newly infected with HIV and 90% of these new infections occurred in Sub-Saharan Africa (SSA) [1]. In South Africa in particular, 30% of all women presenting for antenatal care (ANC) are HIV-infected [2]. Vertical transmission can take place *in utero*, intrapartum and postpartum through breastfeeding; and throughout, maternal viral load is a key determinant of MTCT risk. Antiretroviral therapy (ART) is known to be a highly effective method of achieving viral suppression and is highly efficacious in preventing MTCT, in addition to having well-known benefits for maternal health [3,4]. Use of ART by HIV-infected pregnant women is currently the standard of care worldwide and the latest South African national PMTCT guidelines recommend immediate ART initiation in all pregnant and breastfeeding women [5].

The success of ART for PMTCT hinges on eligible women starting treatment timeously during pregnancy and maintaining ongoing adherence to ART throughout pregnancy and breastfeeding. Uptake of ART during pregnancy has improved dramatically with the introduction of ART services integrated into ANC [6–9]. Integrated ART has also resulted in earlier ART initiation, increasing the time on treatment prior to delivery and further reducing the risk of MTCT [10–14]. Poor ART adherence and loss to follow-up (LTF) undermine the potential benefits of maternal ART use during pregnancy and/or breastfeeding and confer increased risk of both MTCT as well as maternal morbidity and mortality [15].

Several studies have suggested that levels of ART adherence may be lower, and/or LTF higher, in pregnant and postpartum women compared to non-pregnant adults initiating ART [16–19]. There is a particular concern regarding adherence and LTF in the postpartum period [7,20,21],

when women may encounter multiple barriers to remaining in care and adherent to treatment [21–24]. These concerns, coupled with new policies that call for expanded access to lifelong ART in HIV-infected pregnant women [15], mean that there is an urgent need for additional data on ART adherence and retention in care among women initiating ART during pregnancy.

This study investigated retention in care, including LTF and missed ART dispensing visits, following ART initiation by pregnant women in Cape Town, South Africa. The first objective was to describe the occurrence of LTF and missed visits from ART services during pregnancy and up to six months postpartum. The second objective was to investigate socio-demographic, obstetric and clinical characteristics, as well as health services factors, in particular integrated and non-integrated ART initiation sites, as possible predictors of retention in ART services.

2 Methods

2.1 Study setting

We conducted a retrospective cohort study at a large primary health care antenatal clinic in Gugulethu, Cape Town. Historically, all women found to be ART eligible during ANC were referred to a nearby general adult ART clinic for treatment initiation [10,14,25]. In January 2012, integrated nurse-initiated and managed ART (NIMART) services were introduced at the antenatal clinic. From this time onwards, all eligible women started ART in the ANC facility where they continued to receive their ART care along with ANC throughout the antenatal period. Following delivery, women were transferred to general adult ART services after the latter of either 20 weeks on treatment or when the infant HIV status had been determined at six weeks of age. Clinical protocols did not differ between the general ART service and the ANC-based ART service but there were slight variations in pre-ART counselling procedures: Women who were

referred to the general ART service received two counselling sessions at weekly intervals prior to initiation, while women starting ART in the ANC clinic received one pre-ART counselling session 1-2 weeks before initiation, with additional counselling on the day of initiation. Pre-ART counselling was provided by the same team of counsellors working at both services.

Throughout the study period, pregnant HIV-infected women who were eligible for ART were started on a combination of tenofovir with lamivudine and either nevirapine or efavirenz [26]. ART eligibility was based on CD4 cell count of ≤350 cells/µl or WHO stage III/IV disease throughout the review period. At both ART sites women received a 30 day supply of ART for the first four months on treatment and 30-60 day supply thereafter. Visits were scheduled every 28 or 56 days depending on the quantity of ART dispensed.

2.2 Data collection

Data for this analysis come from a review of routine medical records for all women who initiated ART during pregnancy between January 2011 and September 2012. Demographic, obstetric and clinical characteristics, as well as the ART initiation site and details of visit attendance (including dates of clinic visits, scheduled visits and quantity of ART supplied at each visit) were abstracted from routine medical records at both ART facilities using standardized data abstraction tools (see Appendix A & B). Data were abstracted up to 12 months on ART and missing data were obtained from the National Health Laboratory Service (NHLS) database.

2.3 Data analysis

Data were entered into a Microsoft Access database and analysed using Stata 12.0 (Stata Corporation, College Station, USA). Descriptive statistics were used to summarise the baseline characteristics of the study population. Bivariate associations were calculated using chi-squared tests for categorical variables and the Wilcoxon rank-sum test for independent samples of

continuous variables. The primary exposure of interest was the site of ART initiation, analysed as a binary variable denoting general adult ART initiation or ART initiation integrated into ANC. The quantity of ART supplied at each visit was used to determine the next expected visit date and the number of days late were calculated as the difference between the expected ART visit and the date the visit was attended.

We used time-to-event analysis to investigate LTF in the antenatal and postpartum periods. The primary outcome LTF was defined as having 56 days elapsed since the last scheduled visit with no evidence of attendance, treatment collection or transfer out (TFO) [10,27,28].[1] For the purpose of this analysis, women transferred out during the analysis period were considered retained and were censored at the time of transfer out[2]. Secondary analyses focused on missed visits as a marker of non-adherence, defined as being more than 14 days late for a visit but returning to care within 56 days. Antenatal person-time was accrued from ART initiation to the first of: (i) Delivery; (ii) TFO or (iii) LTF. For women remaining in care postpartum, person-time accrued from the date of delivery up to the first of: (i) The end of the study period; (ii) TFO or (iii) LTF. The date assigned to LTF was the date of the last expected visit. Kaplan Meier curves were generated to explore retention in the antenatal and postpartum periods and between the two ART initiation sites. Predictors of LTF overall, as well as restricted to the antenatal or postpartum periods, were examined using Cox proportional hazards models, with results reported as adjusted hazard ratios (aHR) with 95% confidence intervals (CI). Time-varying covariates were used to examine the impact of pregnancy status (antenatal versus postpartum) on retention.

[1] In a sub-analysis, LTF was defined as having 28 days elapsed since the last scheduled visit. These results are presented in the appendix however they did not differ substantively from those presented based on LTF as 56 days elapsed since the last scheduled visit.

[2] Descriptive characteristics stratified by outcomes retained, transferred out and LTF are presented in the appendix.

Ethical approval to abstract data and conduct this analysis was provided by the Human Research Ethics Committee of the University of Cape Town. As part of the routine services in this setting, all women screened for ART also complete an informed consent document allowing their anonymous health care information to be used in research.

3 Results

A total of 358 women initiated ART in pregnancy during the study period and were included in the analysis. The median age and gestational age at ART initiation were 28 years (IQR 26-33) and 26 weeks (IQR 21-31), respectively (Table C-1). Most women had at least secondary level education and only 28% of women were employed. Overall, 207 women (58%) were newly diagnosed as HIV-infected in the current pregnancy. Among the 315 women (88%) for whom relationship status was available, 77% reported being in a relationship and the majority of women had disclosed their HIV status to at least one person at the time of ART initiation. The median CD4 cell count at the time of screening for ART eligibility was 233 cells/µl (IQR 157-287) and 88% of women were classified as WHO clinical stage I or II at the time of ART initiation. Among women for whom parity was available (94%), 19% were primigravid and the median parity was 1 (IQR 1-2). History of antiretroviral (ARV) use was available for 350 women (98%) of whom 45% were ARV naïve, 5% had defaulted ART previously and 50% had previous exposure to ARV prophylaxis for PMTCT only.

Table C-1: *Demographic, obstetric and clinical characteristics of 358 participants stratified by site of ART initiation*

	General adult ART initiation site		ANC ART initiation site		p-value*	Total	
	n (%) or median (IQR)		*n (%) or median (IQR)*			*n (%) or median (IQR)*	
Number of women	142	(40)	216	(60)	-	358	
Total woman months of observation	1077	(44)	1369	(56)	-	2446	
Demographics							
Age (years)	28	(25-33)	28	(26-33)	0.829	28	(26-33)
Level of education							
Primary	13	(9)	10	(5)	0.100	23	(6)
Secondary/Tertiary	128	(90)	199	(92)		327	(91)
Missing	1	(1)	7	(3)		8	(2)
Employment status					0.838		
Employed	42	(30)	59	(27)		101	(28)
Missing	2	(1)	26	(12)		28	(8)
Relationship status[3]					0.014		
In a relationship	115	(81)	160	(74)		275	(77)
Missing	2	(1)	41	(19)		43	(12)
HIV history							
Time of HIV diagnosis							
Diagnosed in current pregnancy	75	(53)	132	(61)	0.068	207	(58)
Missing	0	(0)	5	(2)		5	(1)
Disclosure status							
Disclosed	129	(91)	174	(81)	0.021	303	(85)
missing	1	(1)	6	(3)		7	(2)
Previous ARV use							
No exposure	44	(31)	114	(53)	<0.001	158	(44)
Previous ART	9	(6)	10	(5)		19	(5)
PMTCT only	88	(62)	87	(40)		175	(49)
missing	1	(1)	5	(2)		6	(2)
WHO stage at screening							
I/II	120	(85)	194	(90)	0.135	314	(88)
III/IV	22	(15)	22	(10)		44	(12)
CD4 cell count at screening	233	(157-285)	230.5	(157-291)	0.944	233	(157-287)
Obstetric characteristics							
Parity	1	(1-2)	1	(1-2)	0.195	1	(1-2)
Primigravid	28	(20)	40	(19)		68	(19)
Missing	19	(13)	2	(1)		21	(6)
Gestational age at initiation	28	(23-32)	25	(20-30)	0.006	26	(21-31)

ARV, antiretroviral; ART, antiretroviral therapy; WHO, World Health Organization
*Bivariate comparisons using chi-squared and Wilcoxon rank sum tests. Missing data excluded.

[3] Relationship status has only been included in descriptive tables. It has been omitted from models due to inconsistencies and missing values in the data.

In total, 142 women started ART in a general adult ART service while 216 women started ART within the ANC clinic. There was no significant difference in age, parity, education or employment status in the two groups. Compared to pregnant women who started ART in a general ART clinic, women who started ART in the ANC clinic were more likely to be ARV naïve ($p<0.001$). Among women starting ART in the ANC clinic, 61% had been newly diagnosed with HIV in the current pregnancy compared to 53% of women referred out to start ART ($p=0.068$). Women starting ART in the ANC clinic also tended to have a lower WHO clinical stage at ART initiation ($p=0.036$), although there was no significant difference in screening CD4 cell count between the two groups. Disclosure was common in both groups, however the proportion of women who had disclosed was significantly higher among women initiating in a general adult ART clinic compared to women starting within ANC ($p=0.021$).

Descriptive characteristics of all women stratified by their final retention status in the primary analysis are displayed in Table C-2. Of 358 women included in the analysis, 115 women (32%) were LTF while 243 (68%) were either still in care at the ART initiation site or had been transferred out (TFO) before six months postpartum. Demographic characteristics were similar between women retained and those LTF. Among the women retained in care, 54% had been newly diagnosed with HIV, compared to 65% new diagnoses among women LTF ($p=0.060$). Median gestational age at ART initiation was lower among women who were retained (25 weeks IQR: 20-30), compared to those LTF (28 weeks IQR: 21-32).

Table C-2: *Demographic, obstetric and clinical characteristics of 358 participants stratified by final retention status*

	Lost to follow up *n (%) or median (IQR)*		**Retained** *n (%) or median (IQR)*		**p-value***
Number of women	115	(32)	243	(68)	-
Total woman months of observation	508	(21)	1938	(79)	-
Integrated ANC/ART initiation site	66	(57)	150	(62)	0.433
Demographics					
Age	28	(24-33)	28	(26-33)	0.576
Level of education					
Primary	6	(5)	17	(7)	0.568
Secondary/Tertiary	104	(91)	223	(92)	
missing	5	(4)	3	(1)	
Employment status					
Employed	38	(33)	63	(26)	0.155
missing	9	(8)	19	(8)	
Relationship status					
In a relationship	85	(74)	190	(78)	0.277
missing	21	(18)	22	(9)	
HIV history					
Time of HIV diagnosis					
Diagnosed in current pregnancy	75	(65)	132	(54)	0.060
missing	1	(1)	4	(2)	
Disclosure status					
Disclosed	99	(86)	204	(84)	0.629
missing	2	(2)	5	(2)	
Previous ARV use					
No exposure	51	(44)	107	(44)	0.640
Previous ART	8	(7)	11	(5)	
PMTCT only	55	(48)	120	(49)	
missing	1	(1)	5	(2)	
WHO stage at screening					
I/II	100	(87)	214	(88)	0.765
III/IV	15	(13)	29	(12)	
CD4 cell count at screening	248	(151-290)	228	(159-285)	0.568
Obstetric characteristics					
Parity	1	(1-2)	1	(1-2)	0.719
Primigravid	24	(21)	44	(18)	
Missing	9	(8)	12	(5)	
Gestational age at initiation	28	(21-32)	25	(20-30)	0.027

ARV, antiretroviral; ART, antiretroviral therapy; WHO, World Health Organization

*Bivariate comparisons using chi-squared and Wilcoxon rank sum tests. Missing data excluded.

Outcomes by ART initiation site are displayed in Table C-3. In the primary analysis, 32% of women were LTF (having 56 days elapsed from the last scheduled visit and no evidence of attendance) and 24% of women experienced a missed visit (returning to care 14-56 days after the scheduled visit date). Overall, 49% of women were either LTF or had at least one missed visit before six months postpartum. Rates of LTF were lower in the antenatal period (2.41 per 100 woman months) compared to postpartum (6.17 per 100 woman months). The difference between postpartum and antenatal rates of LTF was higher among women who started ART in the ANC clinic (Rate ratio 4.09) compared to those starting at a general adult service (Rate ratio 1.42).

Table C-3: *Outcomes stratified by site of ART initiation*

	General adult ART initiation site		**ANC ART initiation site**		**Total**	
	n (%) or rate (95% CI)		*n (%) or rate (95% CI)*		*n (%) or rate (95% CI)*	
Overall analysis period (ART initiation to six month postpartum)						
Number of women	142	(40)	216	(60)	358	
Total woman months of observation	1077	(44)	1369	(56)	2446	
Retained (including TFO)	93	(65)	150	(69)	243	(68)
Lost to follow-up	49	(35)	66	(31)	115	(32)
Rate of LTF per 100 woman months	4.55	(3.44-6.02)	4.82	(3.79-6.14)	4.70	(3.92-5.64)
One or more missed visit	50	(35)	36	(17)	86	(24)
Antenatal period (ART initiation to delivery)						
Number of women	142		216		358	
Total woman months of observation	340		616		956	
Retained (including TFO)	130	(92)	205	(95)	335	(94)
Lost to follow-up	12	(8)	11	(5)	23	(6)
Rate of LTF per 100 woman months	3.53	(2.00-6.22)	1.79	(0.99-3.23)	2.41	(1.60-3.62)
One or more missed visit	7	(5)	11	(5)	18	(5)
Postpartum period (delivery to six months postpartum)						
Number of women	127		205		332	
Total woman months of observation	737		753		1490	
Retained (including TFO)	90	(71)	150	(73)	240	(72)
Lost to follow-up	37	(29)	55	(27)	92	(28)
Rate of LTF per 100 woman months	5.02	(3.64-6.93)	7.30	(5.61-9.51)	6.17	(5.03-7.57)
One or more missed visit	43	(34)	27	(13)	70	(21)

ART, antiretroviral therapy; TFO, transfer out; LTF, loss to follow-up

Retention in care by site of treatment initiation is presented in Kaplan Meier curves for the overall, antenatal and postpartum periods (Figure C-1). Among women LTF after delivery, the

median time to loss was 57 days postpartum (IQR 9-97). Rates of LTF appeared similar in women who started ART in the general ART clinic compared to those initiated in the ANC overall (Figure C-1a) and postpartum (Figure C-1c). During the antenatal period, LTF appeared higher among those who started ART in a general ART clinic, though this difference was not statistically significant (p=0.054; Figure C-1b). Retention in care in the antenatal and postpartum periods is shown by model of ART initiation in Figure C-2, where the bold lines represent initiation at the general ART initiation site and the thin lines represent integrated ART initiation at the antenatal clinic. Overall, the cumulative probability of LTF was higher in the postpartum period regardless of the model of ART initiation (p=0.0004).

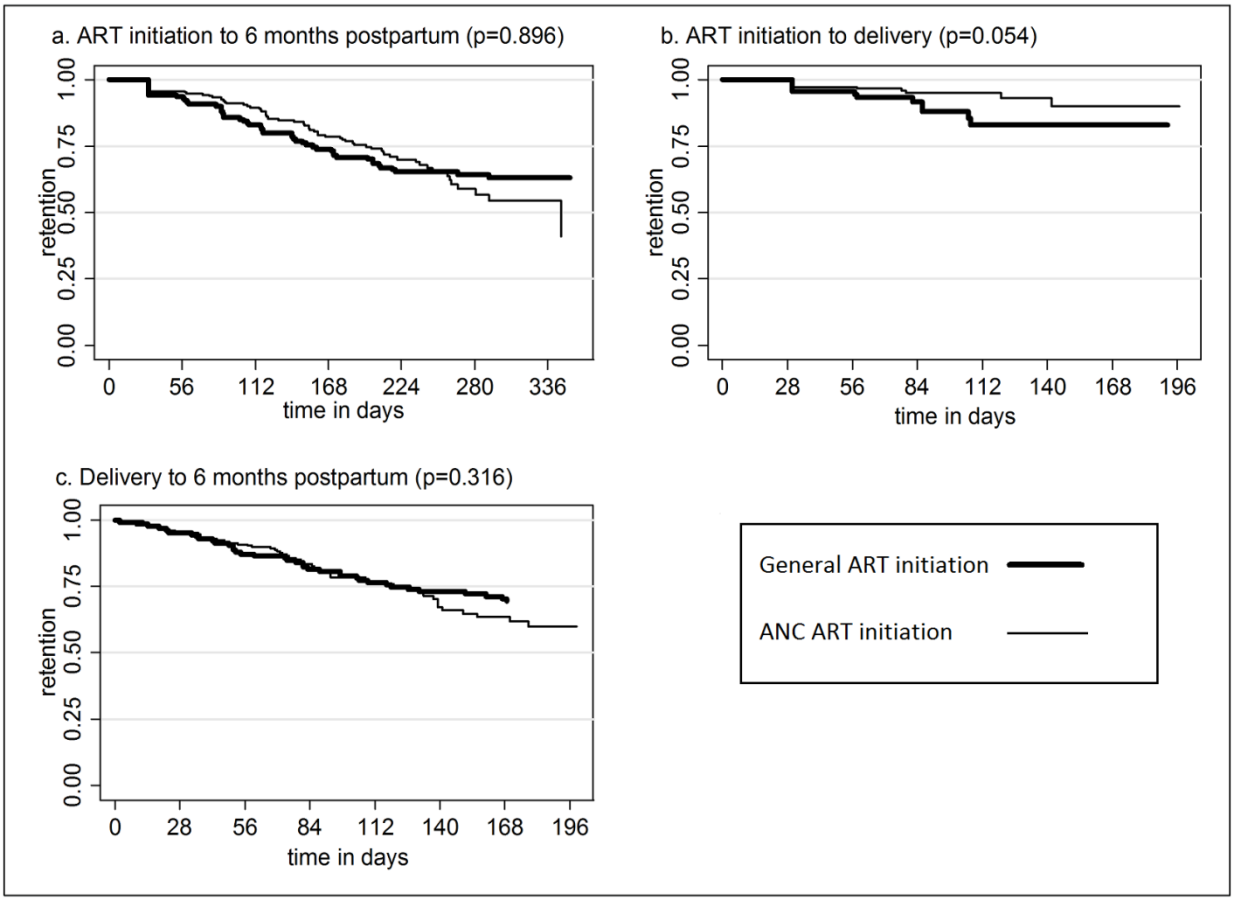

Figure C-1: *Kaplan Meier curves of the probability of retention in care for a) ART initiation to six months postpartum, b) ART initiation to delivery and c) delivery to six months postpartum. (log rank p-values presented)*

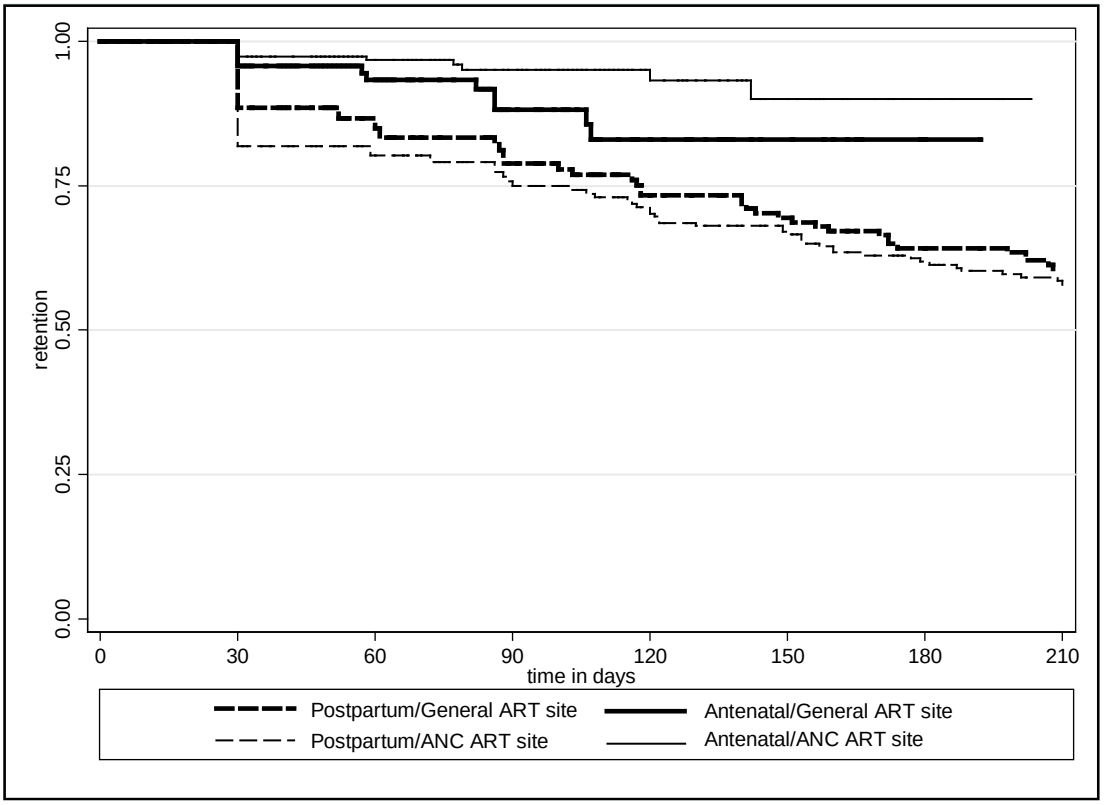

Figure C-2: *Kaplan Meier curve of retention during the antenatal and postpartum periods by ART initiation site*

In proportional hazard models (Table C-4) the site of ART initiation was not a significant predictor of LTF overall, antenatally or in the postpartum period. Only gestational age at ART initiation and time of HIV diagnosis were identified as significant predictors of LTF overall and after delivery. Overall, after adjusting for age, time of HIV diagnosis, CD4 cell count at screening, site of initiation and being in the postpartum period, a one week increase in gestational age at ART initiation was associated with a 4% increased hazard of being LTF by six months postpartum (aHR: 1.04 CI: 1.00-1.07). Women newly diagnosed with HIV in the current pregnancy had a 57% increased hazard of LTF overall compared to women with known HIV infection (aHR: 1.57 CI: 1.07-2.33). There was an almost four fold increase in the hazard of being LTF postpartum compared to that found in the antenatal period (aHR: 3.93 CI: 1.25-12.31). When restricted to the antenatal period, there were no significant predictors of LTF.

Table C-4: *Proportional hazard models predicting LTF according to participant demographic, obstetric and clinical characteristics in (a) the overall analysis period, and restricted to (b) the antenatal period and (c) the postpartum period*

	A) Crude associations			B) Adjusted associations[4]		
	HR	(95% CI)	p-value	aHR	(95% CI)	p-value
a) Overall analysis period (ART initiation to six month postpartum)						
Age	0.99	(0.95-1.02)	0.517	0.99	(0.95-1.03)	0.554
Employed	0.80	(0.54-1.19)	0.263			
Diagnosed in current pregnancy	1.56	(1.06-2.30)	0.024	1.57	(1.07-2.33)	0.022
Have not disclosed	0.96	(0.55-1.68)	0.879			
ARV history						
No exposure	1	(ref)				
Previous ART	1.11	(0.53-2.35)	0.778			
PMTCT only	1.02	(0.70-1.50)	0.912			
WHO clinical stage III/IV	0.97	(0.74-1.27)	0.802			
Screening CD4	1.00	(0.999-1.003)	0.570	1.00	(0.999-1.003)	0.453
Parity	0.98	(0.79-1.20)	0.824			
Gestational age	1.05	(1.02-1.08)	0.001	1.04	(1.00-1.07)	0.030
Integrated ART	1.03	(0.70-1.49)	0.897	1.14	(0.77-1.69)	0.506
Postnatal	2.75	(1.56-4.88)	0.001	3.93	(1.25-12.31)	0.019
b) Antenatal (ART initiation to delivery)						
Age	0.99	(0.91-1.08)	0.866	0.99	(0.91-1.08)	0.860
Employed	2.24	(0.65-7.63)	0.199			
Diagnosed in current pregnancy	1.25	(0.52-2.98)	0.613	1.28	(0.53-3.09)	0.576
Have not disclosed	0.58	(0.14-2.48)	0.462			
WHO clinical stage III/IV	0.59	(0.22-1.62)	0.307			
Screening CD4	1.00	(0.99-1.00)	0.449	1.00	(0.99-1.00)	0.514
Parity	1.04	(0.66-1.64)	0.863			
Gestational age	1.06	(0.98-1.16)	0.145	1.06	(0.97-1.15)	0.193
Integrated ART	0.45	(0.19-1.04)	0.062	0.48	(0.21-1.13)	0.093
c) Postpartum (delivery to six months postpartum)						
Age	0.98	(0.94-1.02)	0.391	0.99	(095-1.03)	0.472
Employed	0.68	(0.44-1.04)	0.077			
Diagnosed in current pregnancy	1.58	(1.03-2.44)	0.038	1.59	(1.03-2.46)	0.038
Have not disclosed	1.08	(0.59-1.99)	0.796			
ARV history						
No exposure	1	(ref)				
Previous ART	1.25	(0.59-2.67)	0.562			
PMTCT only	0.92	(0.60-1.41)	0.691			
WHO clinical stage III/IV	1.04	(0.78-1.38)	0.788			
Screening CD4	1.00	(0.999-1.004)	0.291	1.00	(0.999-1.004)	0.236
Parity	0.95	(0.74-1.20)	0.651			
Gestational age	1.04	(1.01-1.08)	0.012	1.05	(1.01-1.08)	0.008
Integrated ART	1.24	(0.81-1.89)	0.318	1.31	(0.85-2.02)	0.224

ART, antiretroviral therapy; ARV, antiretroviral; prevention of mother-to-child transmission, PMTCT; WHO, World Health Organization

[4] Multivariate models were adjusted for age, ART initiation site, gestational age at ART initiation, screening CD4 cell count and time of HIV diagnosis. Pregnancy status (antenatal/postnatal) was included as a time varying covariate in the overall multivariate analysis. ARV history was excluded from the antenatal model as there were insufficient observations in each category.

4 Discussion

This analysis suggests that by six months postpartum, almost half of women had either missed at least one scheduled visit or were LTF after initiating ART during pregnancy and that LTF was substantially more common postpartum compared to before delivery. In the context of pregnancy and PMTCT, these gaps in care have serious implications for the risk of vertical transmission as well as maternal health.

While outcome definitions vary between studies, these findings are broadly consistent with the results of previous studies indicating high levels of non-retention and/or non-adherence, particularly postpartum [21,27]. Two significant predictors emerged for risk of LTF in this analysis. Firstly, women newly diagnosed with HIV in pregnancy were more likely to be LTF than women who had previously been diagnosed with HIV. This echoes previous research suggesting substantial challenges related to coping with an HIV diagnosis in pregnancy [23,28,29]. In turn, this points to the need for interventions that support women newly diagnosed with HIV during pregnancy. Secondly, later gestational age at initiation was found to be a predictor of LTF through six months postpartum. While the mechanisms underlying this require further investigation, it is possible that late gestation at ART initiation reflects suboptimal health-seeking behavior more generally [30,31]. This would suggest that women who seek ANC and/or initiate ART late in pregnancy are a high-risk population that requires special attention throughout the postpartum period of breastfeeding.

Women receiving care in the integrated service started ART earlier in gestation. Earlier gestational age at initiation was found to be a predictor of retention in this analysis, however levels of LTF were similar among women in both ART initiation groups overall. In the antenatal period the rate of LTF was lower among women who received integrated ART compared to

women who were referred out for ART (1.82 and 3.59 women LTF per 100 women months respectively, p=0.054). This may be explained by a lower burden of health care visits as well as improved relationships with health care providers in an integrated ART/ANC service [32,33]. Further research is required to fully explore the impact of timing of ART initiation and integrated service delivery on retention in care both during pregnancy and after delivery.

Linking women to ART care from ANC services is known to be a challenge. Although women in this analysis were considered to be retained in care at the time of TFO, it is important to note that women transferred in the early postpartum period may be particularly vulnerable to LTF. Studies, including the presented analysis, have found that women are at a higher risk of LTF and/or non-adherence post-delivery compared to during pregnancy [21,27]. This, coupled with the known challenges of linking women to general adult ART care, may be cause for concern [22,34]. Research on postpartum linkage to general ART services is necessary in the context of integrated antenatal ART.

Several important limitations should be considered with the presented findings. The sample size may limit the power of the analysis to detect small associations involving measured covariates. All data were collected from review of routine medical records and not all covariates were routinely measured and recorded in this setting. Related to this, recording of reasons for late or missed visits is not routine and it was not possible to explore reasons for late visit attendance. The retrospective design of this study made it possible to include two sequential cohorts of women initiating ART, first at general adult ART services and then in an integrated antenatal ART service. However, without randomization or simultaneous enrolment at the two ART sites, changes in care provision over time could not be controlled for in this analysis.

This analysis is limited to a cohort of women known to have initiated ART during pregnancy; a select group who successfully linked from ANC to ART services. LTF prior to ART initiation in pregnancy is known to be high [8,35] and our estimates of LTF and missed visits are likely to be an underestimation as a result of this selection bias. The rate of LTF in this analysis may be an overestimate if women who were considered LTF have returned to care after the end of the study period or moved to other facilities without formal transfer. Recent studies have suggested that not all patients considered LTF are truly no longer in care [24,36]. Kranzer et al. found that approximately one third of patients thought to be LTF returned to care in a general adult ART programme in South Africa [36]. In addition, this analysis focused on missed visits and LTF but there are other important PMTCT outcomes, in particular infant HIV-infection, which we have not examined.

Despite the limitations of routinely collected medical records, this study took place in a large, representative primary health care facility where visit attendance and pharmacy records were well completed. In turn, these data represent a 'real-world' estimate of the timing of disengagement from primary care services in this setting, however further research into the frequency, predictors and prevention of LTF from ART care during pregnancy and postpartum are clearly required.

In conclusion, these results demonstrate that missed visits and LTF occur frequently among HIV-infected women who have initiated ART during pregnancy, particularly in the post-partum period. With the promotion of breastfeeding and a shift to lifelong ART for all pregnant HIV-infected women in SSA, these data highlight the importance of promoting postpartum adherence for PMTCT as well as for ongoing maternal health. While additional research is required, women newly diagnosed with HIV and those presenting for ANC or ART at later gestational ages may

be particularly vulnerable and there is an urgent need for interventions to promote adherence and retention among all HIV-infected women during pregnancy and after delivery.

5 References

[1] Joint United Nations Programme on HIV/AIDS. 2013 Progress Report on the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS; 2013 [cited 2014 February 2]. Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2013/20130625_progress_global_plan_en.pdf

[2] Barron P, Pillay Y, Doherty T, Sherman G, Jackson D, Bhardwaj S. Eliminating mother-to-child HIV transmission in South Africa. Bull World Health Organ 2013;91:70–4.

[3] Sturt A, Dokubo E, Sint T. Antiretroviral therapy (ART) for treating HIV infection in ART-eligible pregnant women. Cochrane Database Syst Rev 2010;3. Art. No.: CD008440

[4] Kumwenda J, Matchere F, Mataya R, Chen S, Mipando L, Li Q, et al. Coverage of highly active antiretroviral therapy among postpartum women in Malawi. Int J STD AIDS 2011;22:368–72.

[5] National Department of Health. The South African antiretroviral treatment guidelines. Pretoria, South Africa: National Department of Health; 2013 [cited 2014 February 2]. Available from: http://www.kznhealth.gov.za/medicine/2013_art_guidelines.pdf

[6] Ferguson L, Grant AD, Watson-Jones D, Kahawita T, Ong'ech JO, Ross DA. Linking women who test HIV-positive in pregnancy-related services to long-term HIV care and treatment services: a systematic review. Trop Med Int Health 2012;17:564–80.

[7] Myer L, Zulliger R, Black S, Pienaar D, Bekker L-G. Pilot programme for the rapid initiation of antiretroviral therapy in pregnancy in Cape Town, South Africa. AIDS Care 2012;24:986–92.

[8] Killam WP, Tambatamba BC, Chintu N, Rouse D, Stringer E, Bweupe M, et al. Antiretroviral therapy in antenatal care to increase treatment initiation in HIV-infected pregnant women: a stepped-wedge evaluation. AIDS 2010;24:85–91.

[9] Stinson K, Jennings K, Myer L. Integration of antiretroviral therapy services into antenatal care increases treatment initiation during pregnancy : A cohort study. PLoS One 2013;8:e63328.

[10] Myer L, Zulliger R, Bekker L, Abrams E. Systemic delays in the initiation of antiretroviral therapy during pregnancy do not improve outcomes of HIV-positive mothers : a cohort study. BMC Pregnancy Childbirth 2012;12:94.

[11] Chibwesha C, Giganti M, Putta N, Chintu N, Mulindwa J, Benjamin J, et al. Optimal Time on HAART for Prevention of Mother-to-Child transmission of HIV. J Acquir Immune Defic Syndr 2013;58:224–8.

[12] Van Schalkwyk M, Andersson MI, Zeier MD, La Grange M, Taljaard JJ, Theron GB. The impact of revised PMTCT guidelines : a view from a public sector ARV clinic in Cape Town , South Africa. J Acquir Immune Defic Syndr 2013;63:234–8.

[13] Denoeud-Ndam L, Fourcade C, Ogouyemi-Hounto A, Azon-Kouanou A, D'Almeida M, Azondékon A, et al. Predictive factors of plasma HIV suppression during pregnancy: a prospective cohort study in Benin. PLoS One 2013;8:e59446.

[14] Fitzgerald FC, Bekker L-G, Kaplan R, Myer L, Lawn SD, Wood R. Mother-to-child transmission of HIV in a community-based antiretroviral clinic in South Africa. S Afr Med J 2010;100:827–31.

[15] World Health Organisation. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a publich health approach. Geneva: World Health Organization; 2013 [cited 2014 February 2]. Available from: http://www.who.int/hiv/pub/guidelines/arv2013/download/en/

[16] Wang B, Losina E, Stark R, Munro A, Walensky RP, Wilke M, et al. Loss to follow-up in a community clinic in South Africa-roles of gender, pregnancy and CD4 count. South African Med J 2011;101:253–7.

[17] MacPherson P, Lalloo DG, Choko AT, Mann GH, Squire SB, Mwale D, et al. Suboptimal patterns of provider initiated HIV testing and counselling, antiretroviral therapy eligibility assessment and referral in primary health clinic attendees in Blantyre, Malawi. Trop Med Int Health 2012;17:507–17.

[18] Boyles TH, Wilkinson LS, Leisegang R, Maartens G. Factors influencing retention in care after starting antiretroviral therapy in a rural South African programme. PLoS One 2011;6:e19201.

[19] Kaplan R, Orrell C, Zwane E, Bekker L-G, Wood R. Loss to follow-up and mortality among pregnant women referred to a community clinic for antiretroviral treatment. AIDS 2008;22:1679–81.

[20] Ngarina M, Popenoe R, Kilewo C, Biberfeld G, Ekstrom AM. Reasons for poor adherence to antiretroviral therapy postnatally in HIV-1 infected women treated for their own health: experiences from the Mitra Plus study in Tanzania. BMC Public Health 2013;13:450.

[21] Nachega JB, Uthman O, Anderson J, Peltzer K, Wampold S, Cotton MF, et al. Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis. AIDS 2012;26:2039–52.

[22] Watson-Jones D, Balira R, Ross DA, Weiss HA, Mabey D. Missed opportunities: poor linkage into ongoing care for HIV-positive pregnant women in Mwanza, Tanzania. PLoS One 2012;7:e40091.

[23] Stinson K, Myer L. HIV-infected women's experiences of pregnancy and motherhood in Cape Town, South Africa. Vulnerable Child Youth Stud 2012;7:36–46.

[24] Muchedzi A, Chandisarewa W, Keatinge J, Stranix-chibanda L, Woelk G, Mbizvo E, et al. Factors associated with access to HIV care and treatment in a prevention of mother-to-child transmission programme in urban Zimbabwe. J Int AIDS Soc 2010;13:38.

[25] Bekker L, Myer L, Orrell C, Lawn S, Wood R. Rapid scale-up of a community-based HIV treatment service. Programme performance over 3 consecutive years in Guguletu, South Africa. South African Med J 2006;96:315–20.

[26] National Department of Health; South African National AIDS Council. Clinical guidelines: PMTCT (Prevention of Mother-to-Child Transmission). Pretoria, South Africa: National Department of Health; 2010 [cited 2014 February 2]. Available from: http://www.sahivsoc.org/upload/documents/NDOH_PMTCT.pdf

[27] Clouse K, Pettifor A, Shearer K, Maskew M, Bassett J, Larson B, et al. Loss to follow-up before and after delivery among women testing HIV-positive during pregnancy in Johannesburg, South Africa. Trop Med Int Health 2013;18:451–60.

[28] Tenthani L, Haas AD, Tweya H, Jahn A, van Oosterhout JJ, Chimbwandira F, et al. Retention in care under universal antiretroviral therapy for HIV-infected pregnant and breastfeeding women ('Option B+') in Malawi. AIDS 2014;28:589–98.

[29] Stinson K, Myer L. Barriers to initiating antiretroviral therapy during pregnancy : a qualitative study of women attending services in Cape Town , South Africa. African J AIDS Res 2012;11:65–73.

[30] Myer L, Harrison A. Why do women seek antenatal care late? Perspectives from rural South Africa. J Midwifery Womens Health 2003;48:268–72.

[31] Ebeigbe PN, Ndidi EP, Igberase GO, Oseremen IG. Reasons given by pregnant women for late initiation of antenatal care in the niger delta, Nigeria. Ghana Med J 2010;44:47–51.

[32] Vo BN, Cohen CR, Smith RM, Bukusi EA, Onono MA, Schwartz K, et al. Patient satisfaction with integrated HIV and antenatal care services in rural Kenya. AIDS Care 2012;24:1442–7.

[33] Suthar AB, Hoos D, Beqiri A, Lorenz-Dehne K, Duncombe C, McClure C. Integrating antiretroviral therapy into antenatal care and maternal and child health settings: a systematic review and meta-analysis. Bull World Health Organ 2013;91:46–56.

[34] Theuring S, Sewangi J, Nchimbi P, Harms G, Mbezi P. The challenge of referring HIV-positive pregnant women with treatment indication from PMTCT to ART services: a retrospective follow-up study in Mbeya, Tanzania. AIDS Care 2013;Epub:ahead of print.

[35] Stinson K, Boulle A, Coetzee D, Abrams EJ, Myer L. Initiation of highly active antiretroviral therapy among pregnant women in Cape Town, South Africa. Trop Med Int Health 2010;15:825–32.

[36] Kranzer K, Lewis JJ, Ford N, Zeinecker J, Orrell C, Lawn SD, et al. Treatment interruption in a primary care antiretroviral therapy programme in South Africa: cohort analysis of trends and risk factors. J Acquir Immune Defic Syndr 2010;55:17–23.

D. APPENDICES

Appendix A: Data abstraction forms

Form 1: Baseline, ART screening and initiation

Item	Response
Year (by CD4 count on referral)	
HCTC Folder number	
Provincial Folder number	
DOB	
Level of education	(1) Primary, (2) Secondary, (3) Tertiary
Hx of ARV	(1) Naïve, (2) Non-naïve, (3) PMTCT
Employment	(1) Employed, (2) Unemployed
Disclosure status	(1) Yes, (2) No
Disclosure to whom	(1) Partner, (2) Other family member, (3) Employer (4) Community, (5) Other household member, (6) Friend, (7) Other
Relationship status	(1) Single (2) Married (3) Separated (4) Widowed
Partner tested	(1) Yes, (2) No
Partner status	(1) Positive, (2) Negative
Partner on ARVs	(1) Yes, (2) No
WHO stage	(1) I, (2) II, (3) III, (4) IV
Gestational age	
Date of 1st HIV diagnosis?	
Newly diagnosed with HIV?	
Date of 1st CD4 (booking)	
CD4 count (1st)	
Date of 2nd CD4 (-4-2)	
CD4 count (2nd)	
Viral load (if available)	
Date of referral letter from MOU/other	
Date of ARV screening (-4-2)	
Date of HAART initiation	
Not screened until postpartum?	(1) Yes
Did not initiate treatment until postpartum?	(1) Yes
Other reasons causing potential delays	
Previous defaulter?	(1) Yes
Referred from site **other than Gugs MOU**?	(1) Yes, (2) No
If so, referral Source	
Notes	

Form 2 – page 1: ART visits and delivery outcomes

Maternal ART retention
Data Abstraction Form V1.4

Site Name:		Data collected by:	
Linkage phase: routine / EL / NIMART		Date of data collection: __ __/__ __ __/ __ __ __ __ (D D M M M Y Y Y Y)	
1. Folder #		2. DOB:	__ __/__ __ __/ __ __ __ __ (D D M M M Y Y Y Y)
3. ART care site at initiation?	HC=1 Gugulethu MOU = 2	4. Gestational age at initiation(week 0)	
Pregnancy details			
5. Gravidity & Parity	G ___ P___	6. Pregnancy outcome	Live Birth = 1 Still Birth = 2 NR= 5
7. Date of delivery	__ __/__ __ __/ __ __ __ __ (D D M M M Y Y Y Y) NR = 5	8. Delivery Site	Gugulethu MOU = 1 MMH = 2 GSH = 3 Other = 4, specify: NR= 5
Retention status			
9. Date of last contact	__ __/__ __ __/ __ __ __ __ (D D M M M Y Y Y Y)	10. Status at last contact	Documented death = 1 Transferred out = 2 Stopped treatment = 3 Unknown = 4 Retained = 5
11. Pregnancy status at last contact	Still pregnant = 1 Delivered = 2 Unable to determine = 5	12. If transferred: Date of transfer out of MOU (DD/MM/YY)	__ __/__ __ __/ __ __ __ __ (D D M M M Y Y Y Y)
13. Referred to:	Clinic name:	14. Other comments:	
Infant PCR			
15. Infant 6week PCR	Nonreactive = 0 Reactive = 1 NR = 5	16. PCR date	__ __/__ __ __/ __ __ __ __ (D D M M M Y Y Y Y)

Form 2- page 2: ART visits and delivery outcomes

Folder #:_____

Date of data abstraction: __ __/__ __ __/ __ __ __ __ Person abstracting data:_____

Instructions: *List all ART visits from ART screening and the result of any routine bloods. Note if the participant is a known defaulter, was transferred out at that visit or any other points of interest (maternal death, loss of pregnancy)*

1. ART VISITS	2. Date visit (DD/MM/YY)	3. WHO Stage	4. CD4	5. Viral Load	6. ART supply dispensed (eg 1/12)	7. Known defaulter	8. Comment: Note any reasons given for missed visits
-4-2							

Appendix B: Ethics approval forms

UCT HREC 359/2002

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Annual Progress Report

REC REF Number	359/2002
Title	Data collection at the Hannan Crusaid ART treatment Centre in Gugulethu and at the Masiphumelele ART roll-out sites
Principal	Catherine Orrell, Robin Wood

List of documentation

- **Updated FHS016 form – January 2013**
- **Cover letter listing current collaborators – January 2013.**

HUMAN RESEARCH ETHICS COMMITTEE
21 JAN 2013
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

HREC office use only (FWA00001637; IRB00001938)

☑ Approved	This serves as notification of annual approval, including all documentation described above.		
☐ Not approved	See attached comments.		
Type of review	☐ Expedited	☐ Full committee	
Expiry date			
Signature Chairperson of the HREC		Date	22/1/2013

UCT HREC 391/2010

UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE
22 OCT 2012
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	22/8/2013
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	23/10/12

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	18/10/12		
HREC REF Number	391/2010	Current Ethics Approval was granted until	29/8/11
Protocol title	Optimizing strategies for PMTCT in South Africa		
Protocol number (if applicable)			
Principal Investigator	A/Prof B L Myer, SPH&FM		
Department / Office Internal Mail Address	SPH&FM, Falmouth Bldg, FHS		

1.1 Does this protocol receive US Federal funding?	☐ Yes	☑ No
1.2 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	☐ Yes	☑ No

2. List of documentation

Cover letter

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

UCT HREC/REF: 669/2

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

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
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Website: www.health.uct.ac.za/research/humanethics/forms

14 November 2013

HREC/REF: 669/2013

Miss T Phillips
c/o A/Prof L Myer
School of Public Health & Family Medicine
Room 5.46 Level 5
Falmouth Building
FHS

Dear Miss Phillips

Project Title: RETENTION IN MATERNAL ART SERVICES: A COMPARISON OF ART RETENTION DURING PREGNANCY AND AFTER DELIVERY AMONG WOMEN INITIATING ART UNDER TWO MODELS OF CARE

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

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

Approval is granted for one year until the 30 November 2014.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please note:-Those women, in either arm, who do not commence ART after HIV-diagnosis in pregnancy, are an important group and should not be excluded from the study, but rather considered early LTFU. They have to be accounted for in the CONSORT diagram in any case.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Hrec/ref:669/2013

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

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

Hrec/ref:669/2013

Appendix C: Sub-analysis

1. Comparison of women lost to follow-up, transferred out and retained at ART initiation site

Table D-1: *Demographic, obstetric and clinical characteristics of 358 participants stratified by final retention status*

	Lost to follow up		**Retained at ART site**		**Transferred out**		**p-value***
	n (%) or median (IQR)		*n (%) or median (IQR)*		*n (%) or median (IQR)*		
Number of women	115	(32)	97	(27)	146	(41)	-
Total woman months of observation	508	(21)	995	(41)	943	(39)	-
Integrated ANC/ART initiation site	66	(57)	17	(18)	133	(91)	<0.0001
Demographics							
Age	28	(24-33)	29	(26-33)	28	(26-32)	0.595
Level of education							
Primary	6	(5)	9	(9)	8	(6)	0.449
Secondary/Tertiary	104	(91)	88	(91)	135	(92)	
missing	5	(4)	0	(0)	3	(2)	
Employment status							
Employed	38	(33)	29	(30)	34	(23)	0.291
missing	9	(8)	2	(2)	17	(12)	
Relationship status							
In a relationship	85	(74)	78	(80)	112	(77)	0.180
missing	21	(18)	2	(2)	20	(14)	
HIV history							
Time of HIV diagnosis							
Diagnosed in current pregnancy	75	(65)	43	(44)	89	(61)	0.003
missing	1	(1)	0	(0)	4	(3)	
Disclosure status							
Disclosed	99	(86)	89	(92)	115	(79)	0.013
missing	2	(2)	2	(2)	3	(2)	
Previous ARV use							
No exposure	51	(44)	36	(37)	71	(49)	0.244
Previous ART	8	(7)	7	(7)	4	(3)	
PMTCT only	55	(48)	52	(54)	68	(47)	
missing	1	(1)	2	(2)	3	(2)	
WHO stage at screening							
I/II	100	(87)	77	(79)	137	(94)	0.003
III/IV	15	(13)	20	(21)	9	(6)	
CD4 cell count at screening	248	(151-290)	215	(147-276)	232	(173-285)	0.636
Obstetric characteristics							
Parity	1	(1-2)	1	(1-2)	1	(1-2)	0.715
Primigravid	24	(21)	18	(19)	26	(18)	
Missing	9	(8)	9	(90	3	(2)	
Gestational age at initiation	28	(21-32)	27	(22-32)	24	(20-29)	0.003

ARV, antiretroviral; ART, antiretroviral therapy; WHO, World Health Organization

*Bivariate associations were calculated using chi-squared tests for categorical variables and the Kruskal Wallis test for multiple independent samples of continuous variables.

The table presented here displays descriptive characteristics of all 358 women included in the analysis, stratified by outcome where being transferred out was treated as an independent outcome category (Table D-1). Overall, 41% of women were transferred out, 27% retained at the ART initiation site and 32% were LTF by six months postpartum. The overwhelming majority (91%) of women transferred out before six months postpartum started ART in the integrated service. This table corresponds to Table C-2 in the results section of the manuscript (Part C, page 66) where women transferred out are included in the retained group.

2. Results with an alternative definition of loss to follow-up

In this sub-analysis, loss to follow-up (LTF) was defined as having more than 28 days elapse after missing a scheduled ART visit. Table D-2 below corresponds to Table C-3 in the results section of the manuscript (Part C, page 67), where LTF is defined as being more than 56 days late for a scheduled ART visit. The results of both analyses were similar. As expected, estimates of LTF were higher using the earlier 28 day definition and LTF occurred more frequently in the postpartum period compared to the antenatal period. Overall in this analysis, 43% of women were LTF by six months postpartum.

Table D-2: *Outcomes stratified by site of ART initiation*

	General adult ART initiation site *n (%) or rate (95% CI)*		**ANC ART initiation site** *n (%) or rate (95% CI)*		**Total** *n (%) or rate (95% CI)*	
Overall analysis period (ART initiation to six month postpartum)						
Number of women	142	(40)	216	(60)	358	
Total woman months of observation	913	(42)	1285	(58)	2199	
Retained (including TFO)	71	(50)	132	(61)	203	(57)
Lost to follow-up	71	(50)	84	(39)	155	(43)
Rate of LTF per 100 woman months	7.77	(6.16-9.81)	6.53	(5.28-8.09)	7.05	(6.02-8.25)
Antenatal period (ART initiation to delivery)						
Number of women	142		216		358	
Total woman months of observation	331	(36)	599	(64)	930	
Retained (including TFO)	123	(87)	196	(91)	319	(89)
Lost to follow-up	19	(13)	20	(9)	39	(11)
Rate of LTF per 100 woman months	5.75	(3.67-9.01)	3.34	(2.15-5.17)	4.19	(3.06-5.74)
Postpartum period (delivery to six months postpartum)						
Number of women	120		196		316	
Total woman months of observation	583	(46)	686	(54)	1269	
Retained (including TFO)	68	(57)	132	(67)	200	(63)
Lost to follow-up	52	(43)	64	(33)	116	(37)
Rate of LTF per 100 woman months	8.92	(6.80-11.71)	9.33	(7.30-11.92)	9.14	(7.62-10.97)

Kaplan Meier curves displayed in Figure D-1 show that retention was consistently better among women who started ART integrated into ANC compared to women referred out for ART, however this difference was only statistically significant in the antenatal period (Figure D-1a; p=0.042). Figure D-2 shows that the probability of LTF was highest among postpartum women initiating ART in the general ART service and lowest among women in the integrated ART group in the antenatal period. Using this definition of LTF, 50% of women were LTF by three months postpartum in the referred out group. These figures correspond to Figure C-1 and Figure C-2 in the manuscript, section C of this document.

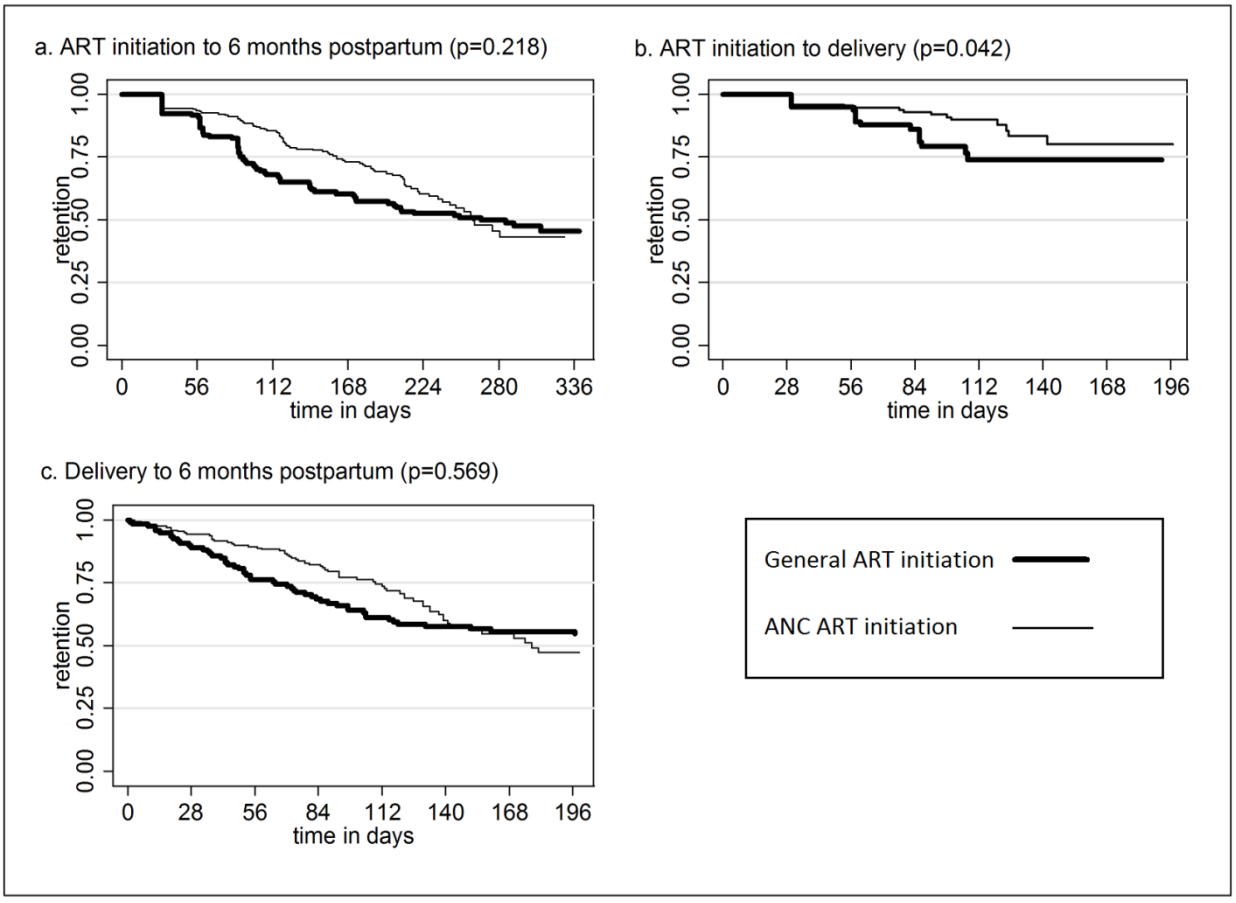

Figure D-1: *Kaplan Meier curves of the probability of retention in care for a) ART initiation to six months postpartum, b) ART initiation to delivery and c) deliver to six months postpartum. (log rank p-values presented)*

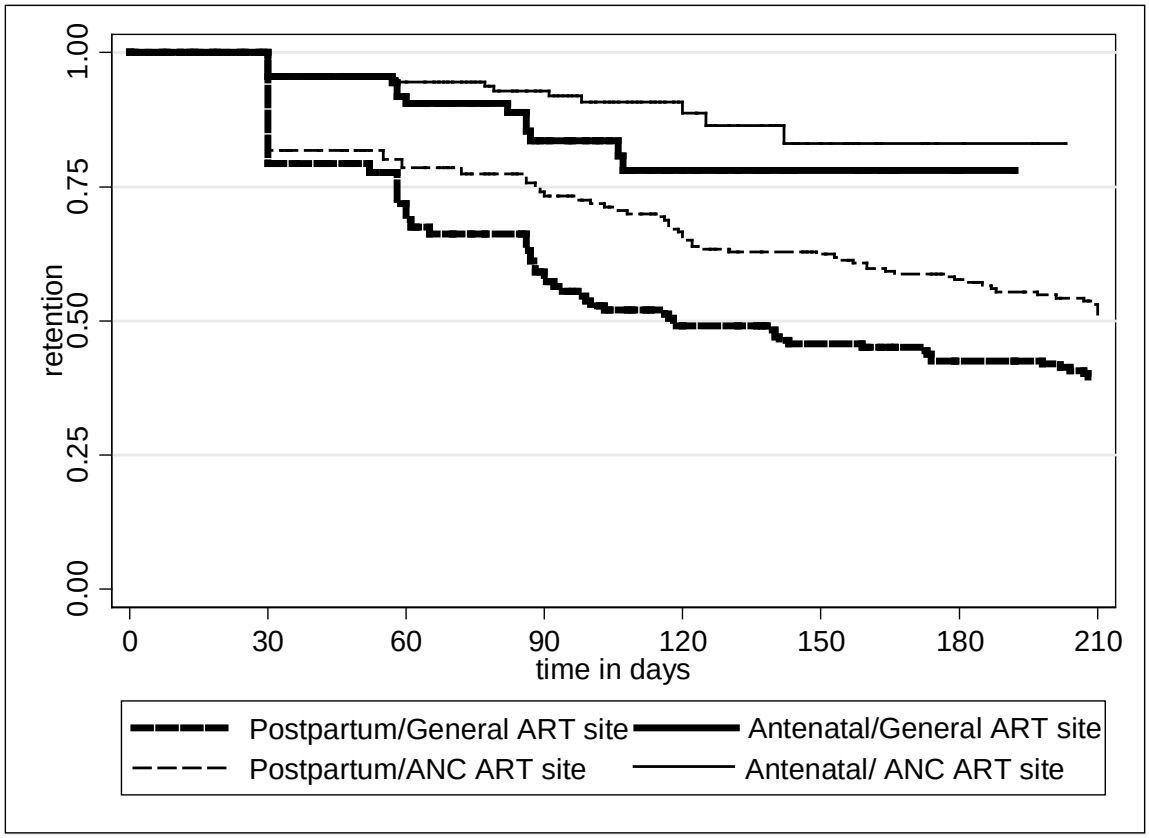

Figure D-2: *Kaplan Meier curve of retention during the antenatal and postpartum periods by ART initiation site*

Proportional hazards models for the overall time from ART initiation to six months postpartum, the antenatal and the postpartum periods are presented in Table D-3. In the overall model and a model restricted to the postpartum period, being newly diagnosed with HIV and having a previous history of ART use were identified as predictors of LTF after adjusting for age, gestational age, screening CD4 cell count and site of ART initiation. Integrated ART initiation was protective against LTF in the univariate model but was no longer significant after adjusting for age, gestational age, screening CD4 cell count, time of diagnosis and ARV history.

Table D-3: *Proportional hazard models predicting LTF according to participant demographic, obstetric and clinical characteristics in (a) the overall analysis period, and restricted to (b) the antenatal period and (c) the postpartum period*

	A) Crude associations			B) Adjusted associations[5]		
	HR	(95% CI)	p-value	aHR	(95% CI)	p-value
a) Overall analysis period (ART initiation to six month postpartum)						
Age	0.98	(0.95-1.01)	0.250	0.99	(0.96-1.02)	0.406
Employed	0.80	(0.57-1.13)	0.204			
Diagnosed in current pregnancy	1.29	(0.93-1.79)	0.127	1.50	(1.06-2.13)	0.023
Have not disclosed	1.14	(0.72-1.80)	0.590			
ARV history						
No exposure	1	(ref)		1	(ref)	
Previous ART	2.13	(1.19-3.81)	0.010	2.40	(1.28-4.48)	0.006
PMTCT only	1.26	(0.90-1.76)	0.176	1.20	(0.85-1.70)	0.305
WHO clinical stage III/IV	0.97	(0.76-1.22)	0.771			
Screening CD4	1.00	(0.999-1.002)	0.667	1.00	(0.999-1.002)	0.445
Parity	0.92	(0.76-1.10)	0.343			
Gestational age	1.04	(1.02-1.07)	0.001	1.01	(0.98-1.04)	0.474
Integrated ART	0.82	(0.59-1.13)	0.221	0.94	(0.67-1.32)	0.706
Postnatal	3.06	(1.93-4.86)	<0.001	5.85	(2.23-15.31)	<0.001
b) Antenatal (ART initiation to delivery)						
Age	0.97	(0.91-1.04)	0.349	0.97	(0.90-1.04)	0.379
Employed	1.37	(0.62-3.00)	0.438			
Diagnosed in current pregnancy	1.12	(0.58-2.15)	0.731	1.28	(0.65-2.50)	0.476
Have not disclosed	1.11	(0.46-2.65)	0.819			
ARV history						
No exposure	1	(ref)		1	(ref)	
Previous ART	2.46	(0.82-7.42)	0.110	2.06	(0.64-6.60)	0.223
PMTCT only	1.39	(0.70-2.74)	0.343	1.32	(0.65-2.67)	0.447
WHO clinical stage III/IV	0.78	(0.43-1.41)	0.414			
Screening CD4	1.00	(0.995-1.002)	0.477	1.00	(0.995-1.002)	0.564
Parity	0.92	(0.64-1.33)	0.649			
Gestational age	1.00	(0.94-1.07)	0.938	0.99	(0.93-1.06)	0.775
Integrated ART	0.53	(0.28-0.99)	0.048	0.56	(0.29-1.09)	0.086
c) Postpartum (delivery to six months postpartum)						
Age	0.98	(0.94-1.02)	0.257	0.99	(095-1.02)	0.406
Employed	0.71	(0.48-1.04)	0.082			
Diagnosed in current pregnancy	1.32	(0.91-1.94)	0.142	1.56	(1.03-2.36)	0.036
Have not disclosed	1.15	(0.67-1.98)	0.623			
ARV history						
No exposure	1	(ref)		1	(ref)	
Previous ART	2.08	(1.05-4.12)	0.036	2.55	(1.20-5.42)	0.015
PMTCT only	1.24	(0.84-1.83)	0.276	1.19	(0.80-1.79)	0.392
WHO clinical stage III/IV	1.03	(0.79-1.33)	0.834			
Screening CD4	1.00	(0.999-1.003)	0.361	1.00	(0.999-1.004)	0.175
Parity	0.88	(0.71-1.09)	0.255			
Gestational age	1.05	(1.01-1.08)	0.003	1.05	(1.01-1.08)	0.004
Integrated ART	0.90	(0.62-1.30)	0.570	1.03	(0.70-1.51)	0.893

[5] Multivariate models were adjusted for age, ART initiation site, gestational age at ART initiation, screening CD4 cell count, time of HIV diagnosis and history of ARV use. Pregnancy status (antenatal/postnatal) was included as a time varying covariate in the overall multivariate analysis.

Appendix D: Journal submission guidelines

Journal of the International AIDS Society (JIAS)

Author Guidelines

The *Journal of the International AIDS Society (JIAS)* welcomes submissions on HIV-related topics from various disciplines and accepts submissions of Original Research Articles, Short Reports, Reviews, Debates, Commentaries, Letters to the Editor and Viewpoints. Please carefully read through the Instructions for Authors and prepare your manuscript according to the guidelines; structure your manuscript based on the chosen article category. Manuscripts that do not follow the instructions may be returned to the authors for re-formatting. Submissions must be an original contribution, and the authors must guarantee that the content has not been previously published and is not considered for publication elsewhere. The JIAS levies a publication fee on all accepted articles to fund open-access publication. For information on editorial policies and processes, see the About JIAS page. For scientific writing resources and support, see Writing resources.

Structures
Chemical structures and assays
Functional genomics data (such as microarray or CHIP-Seq data)
Computational modelling
Plasmids

INFORMATION PRIOR TO SUBMISSION

Aims and scope

The JIAS welcomes submissions on HIV-related topics from across all scientific disciplines, including but not limited to:

Basic and biomedical sciences
Behavioural sciences and epidemiology
Clinical sciences
Health economics and health policy
Operations research and implementation sciences
Social sciences and humanities, including political sciences and media

The JIAS places high priority on submissions from operational research and implementation science as publication of such material can provide valuable information on various algorithms for monitoring and providing support for comprehensive, yet affordable and sustainable treatment, prevention and care programmes in different contexts.

Submission of HIV research carried out in low- and middle-income countries is strongly encouraged.

The JIAS accepts submissions in the categories of Research, Short Report, Review, Debate, Commentary and Letter to the Editor.

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Ethical approval

Experimental research described in the manuscript must have been performed with the approval of an appropriate ethics review board. Research carried out on humans must be in compliance with the Helsinki Declaration, and any experimental research on animals must have followed internationally recognized guidelines. A statement on the ethical aspects, including the consent procedure followed, must be included in the Methods section of the manuscript. The Editors may reject manuscripts where the research has not been carried out within an ethical framework. For all articles that include information or photographs relating to individuals, written and signed consent from each patient to publish must also be made available if requested by the Editors. Confidentiality of study participants must be ensured at all stages of research and reporting.

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MANUSCRIPT PREPARATION

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Guidelines on mutation nomenclature are provided by the Human Genome Variation Society, and authors should use the recommended gene name by referring to the appropriate genetic nomenclature database, for example, HUGO for human genes, and the International Committee on Standardized Genetic Nomenclature for Mice. When describing human phenotypes, please use standardized terms, such as those proposed by the Elements of Morphology working group (see http://research.nhgri.nih.gov/morphology/index.cgi).

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File formats
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manuscript needs to be prepared. Tables and figures should be inserted in the main text. Additional files, such as supporting information or large datasets, can be submitted in any file format and should be uploaded as a separate file. Footnotes are not allowed.

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Use line spacing of 1.5 and an easily readable font, for example, Times New Roman, size 12. Do not use underlining, but use of bold and italics is acceptable. Set the text unjustified to the left and use portrait page setup. Your manuscript must contain line numbers to facilitate editors' and reviewers' comments. All submissions must be in UK English (International) and UN-accepted terminology should be followed. No capitalization should be used except for grammatically correct use, official names and titles, and abbreviations. Acronyms should be used sparingly, and not in headings or in the Abstract. Only commonly known acronyms may be used, and they should be spelt out at first use followed by the abbreviation in brackets. SI units should be used, with litre and molar being permitted.

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Abstract
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Main text
More information on the different article categories is provided below, including specific section headings and word limits. Information on the different sections in the manuscript is further detailed below, as well.

Article categories
Research - full reports of data from original research studies
Headings: Introduction, Methods, Results, Discussion, Conclusions
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The Introduction section should introduce the topic to readers without specialist knowledge in that area and must clearly outline the current state of knowledge in this field, the motivation and the aim of the study or the article.

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The Methods section should include all information necessary to repeat the study, in particular, the study design, how data was collected and analyzed, clarifying the choice of methods that were made. If applicable, you should describe the setting of the study, the dates the study were conducted, and the sample or participants, as well as necessary power calculations and materials, including statistical packages, used. Interventions and programmes should be described in detail. Generic names for drugs or any molecules should be used.

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