

UNIVERSITY OF CAPE TOWN

Adherence to Antiretroviral treatment (ART) among HIV-infected pregnant women starting treatment immediately vs delayed: a cohort study

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PREAMBLE

1. Declaration

I, Nontokozo Langwenya (LNGNON004), hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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2. Acknowledgments

I would like to acknowledge the following people for their help and support in completing this thesis:

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3. Thesis abstract

Introduction: Use of highly effective antiretroviral drugs to eliminate new paediatric HIV infections is the keystone of all prevention of mother-to-child transmission (PMTCT) programmes. Time on antiretroviral treatment (ART) before delivery reduces maternal viral load and decreases the risk of transmission in utero, during labour and whilst breastfeeding. Currently, many PMTCT programmes across Africa initiate HIV-infected pregnant women on lifelong antiretroviral therapy (ART) on the first day of antenatal care (“same-day” initiation). However concerns have been raised regarding patient readiness and whether same-day initiation in pregnancy may contribute to subsequent ART non-adherence.

Methods: As part of a larger study of ART in pregnancy, consecutive ART-eligible pregnant women making their first antenatal care (ANC) visit at a primary care facility in Cape Town, South Africa were enrolled into a prospective cohort between March 2013 and June 2014. Before July 2013, eligibility was based on CD4 cell count ≤ 350 cells/ μ L (“Option A”), with a 1-2 week delay from the first ANC visit to ART initiation; thereafter all women were eligible regardless of CD4 cell count (“Option B+”) and typically offered ART on the same day as first ANC visit. All women received standardized counselling before starting a fixed-dose regimen. Study interviews were conducted separately from the ART service through one week postpartum with self-reported adherence from 30-day recall.

Results: Among 625 consecutive ART-eligible women (median age, 28 years; median gestation, 21 weeks; 55% newly diagnosed with HIV), 72% of women started ART same-day; this proportion was higher under “Option B+” versus “Option A” ($p < 0.001$). Of those with adherence assessments data available ($n=618$), 29% reported at least one missed ART dose during pregnancy. Missed doses were reported more frequently among women with previous use of PMTCT ($p=0.014$), of younger age ($p=0.029$) and starting ART under Option B+ ($p=0.019$). In women initiating ART same-day, 31% reported a missed dose compared to 23% among women who delayed ART start following first ANC visit (odds ratio, 1.07; 95% CI: 0.61 – 1.88). This finding did not vary after adjustment for demographic and clinical measures, and was consistent when restricted to women with CD4 cell counts ≤ 350 cells/ μ L.

Conclusions: These results suggest same-day ART initiation in pregnant women is not associated with increased non-adherence during the antenatal period. While these results are reassuring for ART programmes implementing “Option B+”, further research is required to examine adherence over time, particularly postpartum.

4. List of Abbreviations

3TC	Lamivudine
AIDS	Acquired Immunodeficiency Syndrome
ANC	Antenatal Care
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT	Azidothymidine
EFV	Efavirenz
FTC	Emtricitabine
HIV	Human Immunodeficiency Virus
LTFU	Lost to follow-up
MOU	Midwife Obstetric Unit
MTCT	Mother-to-child transmission
PMTCT	Prevention of mother-to-child transmission
POC	Point-of-care
Sd-NVP	Single-dose nevirapine
SES	Socio-economic status
SMS	Mobile text message
SSA	Sub- Saharan Africa
TDF	Tenofovir
UNAIDS	The Joint United Nations Programme on HIV and AIDS
WHO	World Health Organization

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A. PROTOCOL

1. Protocol Synopsis

According to the World Health Organization (WHO), there were approximately 3.2 million children under 15 years of age living with Human Immunodeficiency Virus (HIV) globally in 2013 [1]. Of these, 91% were from Sub-Saharan Africa and the majority acquired HIV infection through mother-to-child transmission (MTCT) [1]. The principle determinant of the risk of vertical transmission of HIV is viral load [2]. In the absence of any intervention, the rate of MTCT varies from 15% - 45%, with an estimated 70% of perinatal transmission occurring during delivery where exposure to the mother's blood and other bodily fluids is greatest [3, 4]. Antiretroviral Therapy (ART) reduces the risk of MTCT by suppressing maternal viral load during pregnancy, delivery and while breastfeeding [5, 6]. Thus, maximizing ART exposure through timely initiation of ART following the first presentation for antenatal care (ANC) is priority for all PMTCT programs.

In the last decade, several approaches have been adopted to facilitate rapid ART initiation during pregnancy. Use of point-of-care (POC) tests for CD4 cell enumeration have decreased delays related to CD4 testing whereas integration of ART service with ANC has eliminated delays attributable to the referral of pregnant women to adult ART clinics for ART start [7, 8]. More recently, many sub-Saharan African (SSA) countries have shifted to providing universal ART for all pregnant and breastfeeding HIV-infected women regardless of clinical indication; the World Health Organization's "Option B+" [9]. Option B+ enables immediate initiation of ART at first ANC visit, and therefore maximizes women's time on ART prior to delivery.

Timing of ART initiation is not the sole predictor of PMTCT - adherence to ART during pregnancy is equally important. Immediate ART initiation significantly reduces the time spent by both the health-care providers and the patient in preparing for lifelong treatment. Adherence to ART is associated with sustained HIV viral suppression, reduced chances of developing drug resistance and thus better survival [10]. Adequate patient preparation is considered a key determinant for treatment adherence [11]. However, studies assessing the impact of delayed ART initiation for patient preparation are few.

The primary objective of the proposed research is to compare adherence during the antenatal period of pregnancy among women starting ART immediately and those who delayed ART initiation following their ANC visit, either due to policy implementation or personal choice. The secondary objective of the study is to identify risk factors associated with non-adherence

during this period. The proposed research is a secondary analysis of women enrolled in a maternal and child health cohort study investigating HIV care service delivery during the postpartum period (MCH-ART). Women initiating ART during pregnancy were followed at three scheduled study visit intervals: once shortly after initiation, another at around 34 weeks gestation, and a final visit within 6 weeks of delivery to assess the reporting of any missed ART doses in the preceding 30 days. All women were attending antenatal care at Gugulethu Midwife Obstetric Unit (MOU), a large public health facility providing integrated HIV treatment and ANC since 2012.

The proposed study will contribute to the limited literature on the impact of immediate ART initiation during pregnancy on patient readiness and ongoing adherence to ART. Study findings will inform ART programmes considering different models for Option B+ implementation.

2. Introduction

2.1. Background

Since 2001, the number of new paediatric HIV infections has decreased by over 50% [12]. The keystone of all prevention of mother-to-child transmission (PMTCT) programmes is the use of antiretroviral therapy (ART) to eliminate new paediatric HIV infections [13]. Use of ART during pregnancy reduces the maternal viral load and decreases the risk of transmission *in utero*, during labour and whilst breastfeeding [14, 15]. However, in the year 2014, only 73% of pregnant women living with HIV in sub-Saharan African (SSA) had access to antiretroviral medication for PMTCT [16]. In South Africa, mother to child transmission (MTCT) remains a major source of child morbidity and mortality, with more than half of infant deaths related to HIV [17].

Maximizing the duration of ART before delivery is key to minimizing MTCT risk. The European Collaborative Study has shown that 93% of women initiating HAART achieved viral suppression by 15 weeks of treatment [2]. In France, the risk of MTCT decreased from 2.2% to 0.2% for those who started ART prior to pregnancy compared to those who were ART naïve at current pregnancy, consistent with other study findings from SSA [18, 19]. In Zambia, women who received ART less than 4 weeks before delivery had a 5-fold increased risk of MTCT, compared with women who received more than 12 weeks of therapy before delivery

[5]. This demonstrates that the timing of ART following first presentation for ANC is crucial to the success of PMTCT.

Historically, initiation of ART during pregnancy has required the use of CD4 cell counts to differentiate between women requiring ART for their own health and those requiring prophylaxis. If eligible for ART, pregnant women were referred to adult clinics for patient education and psychological preparation, based on the notion that pre-therapy counselling contributes to improved treatment adherence over time [11, 20, 21]. Consequently, pregnant women faced a two-six week delay to ART initiation following their first ANC visit, in spite of research showing that each additional week on treatment potentially reduces the odds of perinatal HIV transmission by 8% [5, 22, 23]. There has been an emerging interest in the possibility of providing lifelong ART to all HIV-infected pregnant and breastfeeding women, regardless of CD4 count through the World Health Organisation's (WHO) Option B+ [9].

Under Option B+, PMTCT implementation is greatly simplified by eliminating the need for access to laboratory services and placing all women on the same ARV regimen. Option B+ provides the opportunity for same-day ART initiation at first presentation for ANC, thus maximizing duration on ART prior to delivery. Furthermore, Option B+ can ensure that all eligible women initiate treatment, reducing maternal mortality and MTCT in future pregnancies [24]. Despite these prospects, there are concerns that same day initiation of ART during pregnancy may contribute to increased non-adherence due to inadequate patient preparation before ART initiation [25].

Pre-therapy preparation consists of formal education from health care providers and personal time taken by the individual to adjust to the need and lifestyle changes associated with lifelong treatment [10]. In the context of pregnancy, the argument for delaying treatment to accommodate personal time needed by patients to accept lifestyle changes may hold true. Many women may face a triple burden of physiological challenges during pregnancy: dealing with their current pregnancy while simultaneously accepting their HIV diagnosis, accepting the need to start lifelong treatment to both protect their infant from HIV infection, and to maintain their own personal health [26]. However, minimal efforts have been made to assess the risk and benefits associated with delayed ART initiation on patient preparation.

There is little agreement in research data examining the impact of patient preparation on maternal health. In a prospective cohort study, delaying ART initiation for patient preparation

among HIV-infected pregnant women was not associated with improved maternal outcomes at 12 months after initiation [27]. In Ugandan adult patients, completion of adherence counselling visits prior to antiretroviral therapy was not associated with increased adherence at 3 months post-initiation [28]. Personalized individual preparatory sessions among adults initiating ART led to a decrease in the number of ART initiation barriers identified by patients; however, the rate of continued therapy use at 12 months was comparable between those receiving counselling versus those who did not [29]. Moreover, implementation of personalised pre-therapy counselling in low- and middle-income countries may not be feasible due to limited financial and human resources.

Generally, pre-therapy preparation is viewed as a preventative measure for non-adherence, better enabling patients to overcome challenges relating to adherence once on treatment [30]. On the other hand, several authors have suggested that pre-therapy counselling may be differentially beneficial for patients at high risk of non-adherence, but not for the majority of individuals [29]. Nonetheless little evidence exists to support either premise. Therefore the mechanism by which patient preparation may contribute to better adherence requires further investigation.

2.2. Background to the proposed dissertation

The Western Cape was the first province in South Africa to adopt Option B+ in 2013 with the National Department of Health aligning with the WHO recommendations in 2015 [31]. Prior to this, pregnant women were identified as ART-eligible according to WHO “Option A” guidelines based on CD4 cell count ≤ 350 cells/ μL and/or WHO stage III/IV. Under this approach, ART-eligible women received at least two pre-therapy counselling sessions prior to ART initiation. Under Option B+, however, all HIV-infected pregnant women are initiated on lifelong ART at their first ANC visit regardless of CD4 count. This difference in policy structures has greatly reduced the time available for patient preparation prior to ART start.

2.3. Study Rationale

Although there has been a rapid successful scale-up of PMTCT in SSA, coupled with the use of highly effective ART regimens, new perinatal HIV infections remain a public health burden in many Sub-Saharan African countries. Research findings indicate that starting pregnant women on ART early in pregnancy can lead to MTCT rates below 1% [19]. However, there are concerns that women who only receive pre-therapy counselling on the day of ART initiation

may be at increased risk of ART non-adherence and/or loss to follow-up, compared to those who receive multiple pre-ART counselling sessions [25]. There is also limited evidence evaluating the impact of different PMTCT guidelines on maternal health outcomes. Moreover, determinants of adherence during and after pregnancy remain unclear, particularly around patient preparation.

3. Study aim and objectives

3.1. Study aim

The aim of the proposed study is to investigate the association between the timing of ART initiation following first antenatal care visit and subsequent adherence during pregnancy in HIV-infected pregnant women.

3.2. Objectives

Primary objective: To compare ART adherence during the antenatal period among women initiating ART at the first antenatal visit (same-day initiation) versus women with delayed ART initiation.

Secondary Objectives:

1. To describe the timing of ART initiation following first ANC care visit among ART-naïve pregnant women and identify risk factors associated with delayed ART initiation.
2. To identify risk factors associated with adherence during pregnancy.

3.3. Hypothesis

Women initiating ART at the first antenatal visit (same-day initiation) will have lower adherence levels compared to those who delay ART initiation following their first antenatal visit.

4. Methodology

4.1. Study Design

This study is a secondary analysis of data from a prospective cohort study being conducted at a large primary health care facility in Gugulethu, Cape Town since 2013. The MCH-ART study evaluates two different strategies for delivering HIV care and treatment services during the

postpartum period to HIV-infected women initiating ART during pregnancy and their HIV-exposed infants. The MCH-ART study is a three-phase study design:

Phase 1 was a cross-sectional evaluation of consecutive HIV-infected pregnant women presenting for care at the Gugulethu Midwife Obstetric Unit (first antenatal visit).

Phase 2 was a prospective observational cohort study of women from Phase 1 who were eligible for lifelong ART initiation according to local guidelines in effect at the time. This Phase followed women from their second antenatal visit until their first postpartum visit, which was usually one week after delivery.

Phase 3 was a randomized control trial evaluating two strategies for delivering ART to breastfeeding women postpartum. Women enrolled in Phase 3 of the study were observed until 18 months postpartum.

All study interviews were conducted separately from routine ART services and abstraction of routinely collected clinical information occurred periodically. Women included in this secondary analysis were enrolled in Phase 1 and 2 of the parent study (Figure A-1).

4.2. Population and Sampling

The proposed secondary analysis will be restricted to women initiating lifelong ART during their pregnancy, thus the inclusion criteria for the analysis is as follows:

Inclusion Criteria

- Age 18 years or older
- Willing and able to provide written informed consent (IC) for Phase 1 and Phase 2 of the MCH-ART study
- Has documented HIV-infection
- Confirmed pregnancy according to urine pregnancy test, ultrasound or clinical assessment
- ART eligible based on current local guidelines or, if previously receiving lifelong ART, must have not used ART for at least six months.

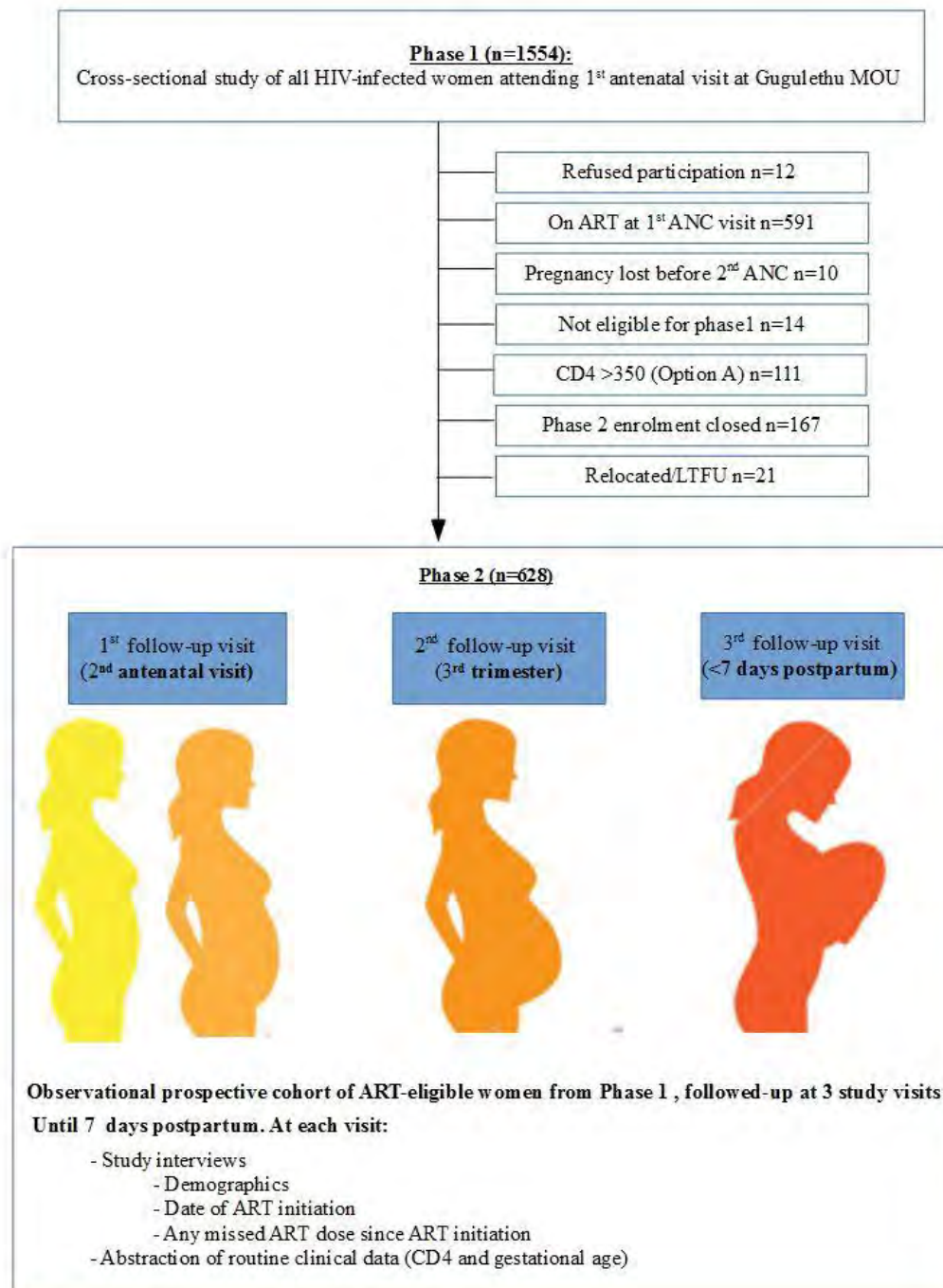


Figure A- 1: *MCH-ART study schema showing situation of the proposed research analysis*

4.3. Research setting

Since 2012 Gugulethu MOU has been providing integrated ANC/PMTCT services to women living within the Klipfontein sub-district of Cape Town in the Western Cape Province of South Africa. All women presenting and found to be eligible for ART initiation are provided with a fixed-dose combination of antiretrovirals tenofovir + efavirenz + emtricitabine (TDF+FTC+EFV) once daily and receive standardized counselling before ART initiation, per

local guidelines (39). Pregnant women receiving ART at the Gugulethu MOU return 1-2 times monthly for follow-up visits and medication refills until delivery.

PMTCT guidelines in affect during the study period were as follows:

- March 2013 – June 2013: ART initiation based on CD4 cell count and clinical stage (“Option A”). Pre-therapy counselling associated with 1-2 week delay from first ANC to ART start.
- July 2013 – June 2014: immediate ART initiation regardless of CD4 cell count (“Option B+”) and pre-therapy counselling occurring on the day of ART initiation (first ANC).

4.4. Measurements

Conceptually, ART delay is the delay following confirmation of ART eligibility to first taking ART medication. In the context of this study, confirmation of ART eligibility at first ANC visit could have been delayed due to the need for CD4 testing to confirm ART eligibility during Option A implementation. However, delays associated with CD4 testing were unlikely due to the use of POC testing that gave results within 20 minutes. Furthermore, there were no service interruptions relating to POC CD4 testing during the study period. Thus confirmation of ART eligibility at first ANC visit was equally likely during both PMTCT guidelines.

In this analysis, ART initiation refers to the self-reported date of first taking ART medication by the participant. Delay to ART initiation will be defined as the time difference between first ANC visit and when the participant reports having started taking ART. In this analysis, delay to ART initiation will be analysed as a proxy for the time available for patient preparation prior to ART initiation. In reviewing existing literature for the definitions of immediate or same-day ART initiation, we found little variation in the definition of these terms between studies. Immediate or same-day initiation often referred to the initiation of ART within 48 hours of ART dispensing and this definition is applied in this analysis [32, 33].

In contrast, diverse methods of measuring and defining adherence exist in literature. Although viral load may be influenced by multiple factors other than adherence, it is commonly used as a proxy for adherence [34]. Other measures of adherence include pill count, electronic measurements such as Medication Event Monitoring Systems (MEMS) and self-report [35]. However, self-report is the most convenient and widely used form of adherence measurement, as it provides a unique opportunity for health workers to immediately address the issue of non-adherence with the patient [36]. A systematic review of 77 studies using various self-report

measures found an 85% correlation between HIV viral load and self-report adherence, demonstrating the validity of self-reported measurements in clinical management [37].

In the proposed analysis, the exposure and outcome will be defined as follows:

1. Same-day initiation: Starting ART on the day of first presentation for ANC or the following day. It thus follows that delayed ART initiation is when a woman reports to have started ART more than 2 days after their first visit to the ANC facility.
2. Adherence: Women will be considered adherent if self-reporting that they have not missed their ART dose at any study visit following ART initiation through one week after delivery.

The study time will range from the day of first antenatal care visit up to, and including, 7 days after delivery. Censoring will occur if women experience a miscarriage or have a termination of pregnancy following the start of ART.

4.5. Data collection

The data for this secondary analysis will be taken from the MCH-ART demographics and medical case report forms (Appendices A and B), which were administered through face-to-face interviews at time of enrolment (first ANC visit) and again at each subsequent study measurement visit. At each study follow-up visit, women were asked to self-report the date of ART initiation and any missed ART doses in the 30 days prior to the study visit with the reasons for missed ART doses recorded on case report forms. Obstetric and current clinical characteristics such as CD4 cell count, gestational age and viral load were abstracted from patient records throughout the study period. Variables of interest in this analysis are listed in Table A-1.

Table A-1: *List and definition of variables to be collected for analysis*

Variable	Type	Categorical
<i>Demographics</i>		
Age (years)	Numerical - continuous	n/a
Relationship status	Categorical - binary	Married / Not married
Education	Categorical - binary	Primary / High school & above
Occupation	Categorical - binary	Scholar or Employed / Neither
Housing	Categorical - binary	Formal / Informal
Gravidity	Numerical - continuous	0-1; >1
<i>Clinical Characteristics</i>		
Timing of HIV diagnosis	Categorical - binary	Current pregnancy / Prior
Years since HIV diagnosis	Numerical - continuous	<1 year; 1 – 5 years; >5 years
Previous PMTCT exposure	Categorical - binary	Yes / No
Disclosure status	Categorical - binary	Yes / No
Gestation age in weeks	Numerical - continuous	≤12 wks; 13-28 wks; ≥29 wks
CD4 count	Numerical - continuous	<200 cell/μL; 201-350 cell/μL; 351-500 cells/μL; >500cells/μL
Viral load	Numerical - continuous	n/a

5. Data Management and Analysis Plan

Completed questionnaires from the parent study have already been entered into a password-protected Microsoft Access database. The relevant data will be transferred onto a password-protected external hard drive for the purpose of this dissertation. If not in use, the external hard drive will be kept in a secure locked area in the study office at University of Cape Town.

The data cleaning, exploration and analysis will be done using Stata 12 (Stata Corporation, College Station, Texas), with data from Phase 1 and Phase 2 of the parent study being matched using unique study participant identification fields.

5.1. Univariate and bivariate analysis

Once data has been imported into Stata, all variables will be explored to identify missing data and any patterns associated with missing data. Missing data will be addressed by review of patient records where applicable. Univariate exploration will include use of histograms, box and whisker plots and scatterplots. Study population characteristics will be summarized using descriptive statistics such as means with standard deviation, medians with interquartile ranges (IQR) and proportions, depending on the data distribution.

Bivariate analysis will include the use of rank-sum and Kruskal-wallis tests for continuous variables, and Chi-squared and Fischer tests for categorical variables. This will be done to explore any differences that may be associated with the exposure (delayed/same-day ART initiation) and outcome (any missed vs no missed ART doses) of interest. Correlation between variables will be considered and evaluated by use of scatter plots and frequency tables.

5.2. Model building

The primary outcome of interest is missed ART doses, which will be treated as a binary variable: any missed ART dose (non-adherent) vs. no missed ART doses (adherent). Logistic Regression Models will be used to identify predictors of non-adherence, with variables being included if known to be a risk factor of adherence, as indicated by existing literature, or if independently associated with the outcome of interest during bivariate analysis. Three models will be explored: one including the entire study population, one restricted to participants with CD4 cell counts below ≤ 350 cells/ μ L and another restricted to women initiating ART under Option B+. Restricting to women with baseline CD4 cell count below ≤ 350 cells/ μ L will control for the confounding effect of PMTCT policies on the study outcome, whereas restricting the analysis to women initiating ART under Option B+ will control for the confounding effect of PMTCT policies by assessing the study outcome within a sub-population. Statistical significance for all analyses will be evaluated using 95% Confidence Intervals (CI) and an α -level of 0.05.

Adherence will also be analyzed as a continuous variable; the number of self-reported missed ART doses at each study visit. This will be a count outcome that will be modelled using Poisson Regression. In a systematic review of ART use during and after pregnancy in low- and middle-income countries, three quarters (74%) of the population were found to be adherent [38]. Thus we anticipate most women will report no missed ART doses in the preceding 30 days, which will be best modelled using the zero-inflated poisson regression.

6. Potential limitations

The primary exposure and outcome of this analysis are collected using self-report measurement tools and are therefore susceptible to recall and social desirability biases. Social desirability

can lead to the over-reporting of adherence thus making it difficult to identify factors associated with study outcome (same-day ART initiation versus delayed).

Although self-report measures in the form of personal interviews or written questionnaires vary greatly in recall time periods and response tasks, they are the most commonly used method for assessing adherence in both clinical and research settings [39]. Data indicates that recall periods can vary from one–thirty day, with a greater association between self-reported adherence and viral load for recall periods greater than 3 days [40, 41]. The study used a 30 day recall period to capture non-adherence due to randomly forgetting to take ART medication and non-adherence reflective of routine behaviour.

Lastly, the reasons for delaying ART were not recorded on study documents, thus the analysis is unable to differentiate between sources of delays attributable to the health system and /or the individual, limiting the interpretation of the study findings.

7. Ethical considerations

7.1. Consent

The parent-study has had on-going ethics approval from the University of Cape Town and Columbia University since 2012. Annual renewal for the year 2015 during which this dissertation is being conducted can be found in Appendices (Appendices C and D). Although there is no direct contact with study participants, women eligible for this secondary analysis must have signed the relevant informed consent forms allowing for secondary use of study data and review of routine medical records as part of the main study measurements (Appendices E and F).

7.2. Risks

Since this is a secondary analysis, there will be no direct involvement with the participants and thus the proposed research presents minimal risk to participants enrolled in the parent study. However, data quality checks require review of clinical records for a sample of the participants, during which anonymity will be lost. Clinical records can only be accessed using patient identifying information. As the student conducting this research, I will sign a data sharing and confidentiality agreement with the principle investigator of the parent study and will undergo training in ethics and confidentiality prior to accessing any data (Appendix G). Identifying information will only be used to locate the required folders, thereafter all abstraction forms and

study documentation will be identified with the use of study participants’ unique identification numbers. Completed data abstraction forms will be kept in a locked cabinet and shredded upon completion of dissemination of this dissertation.

7.3. Benefits

This analysis provides no direct benefits to the participants enrolled in the parent study. Nonetheless, the study aims to contribute to the limited knowledge regarding same-day ART initiation and adherence during pregnancy. It seeks to provide further understanding and knowledge regarding patients’ readiness and maternal outcomes following ART initiation. Thus, the indirect benefits to participants enrolled in the parent study are the use of study findings to inform the current PMTCT guidelines and models of care for ANC/HIV service delivery in participants’ local communities.

7.4. Confidentiality

Efforts will be made to ensure confidentiality at all times. These include attendance at confidentiality and human subject protection training, the use of de-identified data as provided by the parent study and complying with necessary arrangements to ensure that all data (electronic or hardcopy) are kept in secure locked area.

8. Logistics and timetable

Table A-2: Time frame from study start to completion

	Aug’15	Sept’ 15	Oct’ 15	Nov’15	Dec’15	Jan 16	Feb’ 16
Literature review							
Data collection							
Data Management							
Data Analysis							
Results							
Write-up							

9. Budget

There is no budget needed for this study. Work is undertaken in part of completion of the Masters in Public Health degree.

10. Stakeholders and Dissemination

Given the objectives of the research project, the findings of the study are valuable to current practices in PMTCT programmes. Relevant stakeholders who are likely to be interested in these findings include the South African Department of Health, clinicians working in HIV-related health care services, women attending ANC/HIV services in South Africa and research projects investigating ART initiation during pregnancy. The results will be made available to these stakeholders by publication in a peer-reviewed journal and by presentation of the study findings at local and international conferences.

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B. LITERATURE REVIEW

1. Introduction

Between 2009 and 2013, the proportion of new HIV infections among children living in low- and middle-income countries decreased by 43% [1]. This was the result of a global scale-up of prevention of mother-to-child transmission (PMTCT) services, doubling the proportion of pregnant women living with HIV and receiving antiretroviral (ARVs) medications [2]. Despite these significant advances, in 2013, three out of ten pregnant women living with HIV did not receive antiretroviral medication for the prevention of vertical transmission of HIV during pregnancy [3, 4]. In South Africa, 30% of women attending antenatal care are HIV-infected, half of all deaths of children younger than 5 years are associated with HIV [1, 5].

Several studies have reported a reduction in the risk of MTCT with each additional week of treatment [6, 7]. Thus timely initiation of triple-drug antiretroviral therapy (ART) during pregnancy is fundamental to the success of PMTCT services. ART inhibits HIV replication, reducing viremia and the risk of HIV transmission to the HIV-exposed infant [8]. Without treatment, the risk of mother-to-child MTCT varies from 15 - 45%, occurring in *utero* (ante-partum), during labour (intrapartum) or while breastfeeding (postpartum) [9]. Identifying pregnant women who are eligible for ART initiation can be challenging in low- and middle-income countries where access to laboratory services is limited and healthcare facilities are poorly staffed (ref). Consequently, a significant proportion of women initiate ART quite late in pregnancy, if at all [10].

The global call for the elimination of new HIV infections by 2015 required pragmatic approaches in the provision of antenatal care (ANC) and HIV services to pregnant women [11]. Many resource-limited settings chose to adopt the World Health Organisation's (WHO) Option B+ PMTCT guidelines, providing lifelong ART to all HIV-infected pregnant and breastfeeding women regardless of CD4 count or WHO clinical stage [12]. Previously, the 2010 guidelines made use of CD4 cell count in differentiating women requiring ART for their own health and those requiring prophylaxis (Table B-1) [13]. The current Joint United Nations Programme on HIV/AIDS (UNAIDS) Global Plan for the elimination of new HIV infections by 2020 requires 90% of all HIV-infected persons to be on treatment, with at least 90% achieving and maintaining viral suppression [14]. With women being disproportionately affected by HIV, Option B+ provides the greatest promise to achieving this goal within the context of PMTCT.

Table B-1: WHO recommended PMTCT interventions for HIV-infected pregnant women

Year	Name	CD4 \leq 350 cells/ μ L	CD4 $>$ 350 cells/ μ L
2006	Option A	ART for life	<i>Antenatal:</i> AZT prophylaxis starting at 14 weeks gestation. <i>Labour:</i> sd-NVP <i>Postpartum :</i> AZT + 3TC for 7 days post delivery
2010	Option B	ART for life	<i>Antenatal:</i> Triple ARV prophylaxis from 14 weeks gestation until delivery <i>Postpartum:</i> Triple ARV prophylaxis until 1 week after cessation of breastfeeding
2013	Option B+	ART for life	ART for life

Different models of care are used to implement Option B+. Often, these models differ with respect to patient education and counselling sessions prior to ART initiation [15]. In many settings, under Option B+, women initiate lifelong ART on the same day as their first ANC visit, commonly referred to as immediate ART initiation [16]. Immediate ART initiation provides limited time for the individual to adjust to lifestyle changes associated with lifelong treatment, though adequate patient preparation is considered a key determinant for treatment adherence [17]. In comparison to those who delayed ART initiation under Option B+, pregnant women who started ART on the day of HIV diagnosis were twice as likely to never return to the health facility following their initial visit [18]. For example, in Ethiopia, poor counselling during initiation was reported as one reason for non-adherence among women initiating ART immediately [19]. However, there are conflicting findings regarding the benefits of delayed ART initiation on maternal health [20, 21].

Given the above, this dissertation explores the timing of ART initiation following the first ANC visit and the effects of immediate ART initiation on maternal adherence during the prenatal stage of pregnancy. It further explores structural and individual factors that may contribute to maternal ART adherence. To inform this research, the objectives of the literature review are:

- To provide an overview of ARV use in PMTCT programs
- To identify sources of delay to timely initiation of ART during pregnancy
- To present data on patient preparation and health outcomes
- To identify risk factors associated with ART adherence

2. Search Method

Pubmed, Science Direct and Google Scholar were the search engines used to locate literature for this review. The search was restricted to English language publications, with no restriction applied with reference to time period or continent. The titles and abstracts of the articles were reviewed for inclusion or exclusion in the literature review. Publications available through February 2016 were included in this review. Search terms (and their synonyms) used are listed in box C-1 and the included studies are summarised in Table B-2.

Publications were included if:

- The study population was HIV-infected and pregnant women
- Study participants initiated ART during pregnancy or prior to pregnancy
- Outcome of interest was perinatal transmission and/or adherence during pregnancy

Box C-1: Literature review search terms

Human immunodeficiency virus (HIV), Acquired Immunodeficiency Syndrome (AIDS)
Mother-to Child Transmission (MTCT), Perinatal infections, Prevention Mother-to Child
Transmission (PMTCT)
Antiretroviral therapy (ART), Antiretroviral medication (ARVs)
Pregnancy: pregnant, antenatal, postnatal, maternal, antepartum, postpartum
Adherence: missed dose, pill count, retention,

3. Epidemiology of MTCT and ART Adherence

3.1. ARV use in pregnancy

HIV transmission occurs largely through exposure to bodily fluids and it is the viral load in these fluids that determines the risk of transmission [9]. The Pediatric AIDS Clinical Trials Group 076 (PACTG 076), conducted in 1994, was the first study to demonstrate the use of ARVs in pregnancy to reduce maternal viremia and, therefore, reduce the risk of vertical HIV transmission during pregnancy [22]. In the aforementioned trial, administering zidovudine (AZT) to the mother during the second and third trimester of pregnancy, intravenously during delivery, and to the infant for first six weeks of life resulted in a 67% decreased risk of perinatal transmission at 18 months postpartum [23]. However, the requirement for frequent patient

dosing, replacement feeding and the high costs of the AZT regime restricted its application in low- and middle-income countries, where simpler and less expensive drug regimens for PMTCT prophylaxis were needed [24].

In 1999, a modified, shorter course of AZT administered late in pregnancy was hypothesized as an affordable alternative prophylactic regimen to that used in the PACTG 076 trial. Using this regimen, Thailand reported a 50% reduction in perinatal infections among women who formulae-fed for 6 months compared to 37% among those who breastfed for 3 months postpartum [25, 26]. During the same period, the use of single-dose nevirapine (sd-NVP) at onset of labour was investigated in Uganda as an alternative regimen for breastfeeding women [26]. When sd-NVP was orally administered at the onset of labour and given to the infant twice daily for the first week of life, vertical HIV transmission was reduced by 48% at 4 months postpartum [26]. SD-NVP was found to be more effective than a short-course AZT regimen among women who breastfed.

Since then, strategies for PMTCT have evolved with the development of more potent ARV medications and the extension of ARV use through the postpartum period. The efficacy of short-course AZT regimens were significantly improved when combined with sd-NVP [4, 27, 28]. Tripled-drug combined therapy was later proven to be more effective than dual therapy for the PMTCT, reducing MTCT rates to less than 1% [29, 30]. Currently, the WHO recommends tenofovir + lamivudine/emtracitabine + efavirenz (TDF + 3TC /FTC + EFV) as a fixed dose treatment for HIV-infected pregnant women requiring ARV for prophylaxis or lifelong treatment [12]. ART can be initiated as early as 14 weeks of pregnancy to ensure viral suppression at delivery and/or taken while breastfeeding.

Despite the use of potent ARVs and the global increase in PMTCT coverage, MTCT remains a burden in many resource-limited countries. In 2012, only 60% of HIV-infected pregnant women needing ART for their own health initiated ART during pregnancy in 10 priority countries [31]. In 2013, sub-Saharan Africa (SSA) accounted for almost 90% of new paediatric HIV infections, with 57% of women not receiving ART at all during prenatal or postpartum periods[1]. In 2014, 220 000 children were newly infected with HIV globally [1]. With most MTCT taking place among ART-eligible women with advanced disease, timely initiation of ART during pregnancy plays an important role in PMTCT [32].

3.2. Timing of ART initiation during pregnancy

The principle determinant of HIV transmission is HIV viral load. Consequently, the risk of transmission is greatest among women with low CD4 cell count and progressed HIV disease, who subsequently have high plasma and genital viral load [33]. The risk of MTCT is greatest during delivery when a baby passes through the birth canal and is exposed to the mother's blood [9]. Although optimal timing of ART initiation remains unclear, starting ART earlier in pregnancy increases the likelihood of obtaining an undetectable maternal viral load at delivery and thus lowers the risk of MTCT [34]. Viral suppression at delivery can be achieved after 13-15 weeks of treatment, with each additional week on treatment reducing the odds of perinatal HIV transmission by up to 10% [6, 35]. Despite this, pregnant women continue to face systematic delays to ART initiation across SSA.

3.3. Sources of ART delay during pregnancy

Historically, ART eligibility has been based on the use of CD4 cell count as an indicator of the immune function. Following confirmation of ART eligibility, women were referred to adult clinics for treatment and completion of mandatory patient preparation counselling prior to ART initiation [33]. The need for access to laboratory services for CD4 count enumeration and coordination of ANC and adult ART clinics created significant delays to ART initiation during pregnancy; yet risk of MTCT is heavily dependent on treatment duration prior to delivery and while breastfeeding [32]. Over the years, interventions targeted at reducing delays associated with CD4 testing and the referral of pregnant women has resulted in increased uptake of ART at an earlier stage in pregnancy.

Mobile text messaging (SMS) for delivery of CD4 count results and the use of point of care (POC) CD4 testing are some of the approaches adopted to decrease delays associated with CD4 screening. In Botswana, the use of SMS reduced the time between phlebotomy and the facility's receipt of CD4 count results by 16 days, but the median time to ART initiation remained the same [36]. When the results were sent directly to the patient, the median time to ART initiation decreased by five weeks [37]. In South Africa, POC CD4 testing increased the proportion of pregnant women being assessed for ART eligibility by seven percent and decreased delay to ART initiation following first ANC visit by 6 days [38]. A systematic review of studies conducted in SSA reported a 4-fold increase in the likelihood of having a CD4 count done in order to determine ART eligibility when a POC CD4 test was used in place of laboratory testing [39]. The delay from first ANC visit to CD4 testing decreased by 9 days

while the time between receiving results once CD4 test was completed decreased by 17 days [39].

Under Option B+, delays attributed to CD4 assessment are entirely eliminated. Pregnant women are initiated on lifelong ART regardless of CD4 cell count [12]. Under this policy, Malawi recorded a seven-fold increase in the number of pregnant women living with HIV receiving ART during the first two years of implementation [39]. By 2014, the total proportion of HIV-infected pregnant women in ANC accessing ART across the country had increased to 95% [40]. When ART is initiated on the first day of ANC, delay to ART initiation could be decreased by up to 4 weeks under Option B+ [20, 41]. Similar results were found in Zambia and Tanzania, with a higher proportion of pregnant women with CD4 \leq 350 cells/uL initiating ART under Option B + [42, 43].

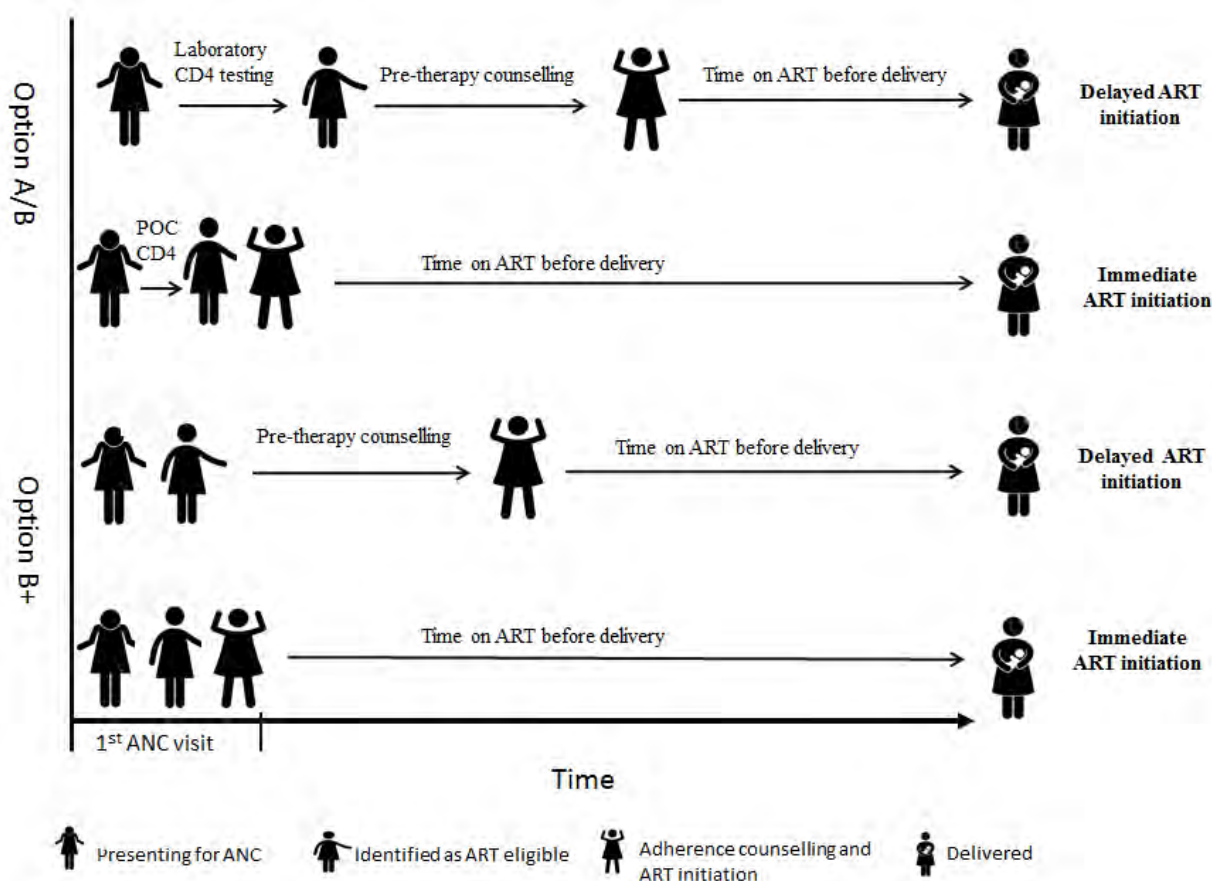


Figure B-1; *Timing of ART initiation under different PMTCT guidelines*

A number of studies have examined the impact of integrating ART and ANC services on ART initiation during pregnancy, and the results highlight the importance of decentralisation and task-shifting in ART service delivery. Findings from a systematic review showed an increase in the proportion of women initiating ART in integrated care, however this review was limited to 4 studies reporting only on retention outcomes [44]. In a cohort study comparing integrated ART and ANC services and two models of ART referral, pregnant women attending care at an integrated service were 33% more likely to initiate ART during pregnancy compared to those receiving care at a referral sites [45]. However, there was no difference in the timing of ART initiation between referral sites, of which one was located some distance from ANC and other located nearby [45]. These findings suggest that the frequency with which services are provided influence timely initiation of ART, rather than the location within the same infrastructure [45]. When counsellors were used as navigators to guide pregnant women from ANC to ART services, delays from being identified as ART eligible to initiating ART decreased by 2 weeks [46].

While there have been changes in the clinical eligibility and health systems supporting ART initiation during pregnancy, minimal efforts have been made to assess the risk and benefits associated with delayed ART initiation for patient preparation. Although all guidelines recognise that patients should not be started on ART until they are “ready”, none provide a standardised process for patient preparation or assessment of readiness.

4. Patient preparedness and ART adherence

4.1. Theories on patient preparedness

Sub-optimal adherence to treatment can compromise the effectiveness of treatment and threaten the long-term benefits of lifelong treatment. Often, patients either stop taking their medication within the first few months of treatment, or continue to take medication with regular missed doses [47]. In the context of HIV/AIDS, poor adherence as measured by viral suppression is associated with increased risk of HIV transmission to HIV exposed infant or sexual partner [48]. A number of theories have been proposed to explain adherence behaviour, not only in the context of HIV, however successful interventions based on these theories are few [49].

The health belief model describes adherence as behaviour influenced by perceived health benefits in taking treatment; referred to as “goal-directed behaviour” [49]. If health status is worsened by the lack of treatment and the goal is improved health, then the individual is more likely to be adherent [50]. This thinking is similar to the theory of planned behaviour, which further incorporates the individual’s ability to cope with external threats to adherence [51]. In the context of HIV, this includes fear of stigmatization and lack of social support. Both models apply a cognitive perspective on treatment adherence that assumes the individual is capable of foresight, decision making and self-regulation [52]. Using both these models, patient preparation prior to ART initiation should include basic HIV/AIDS education, provide confidence in treatment effectiveness, and establish an understanding of the relationship between adherence and the development of drug-resistance.

In contrast, the behavioral learning perspective focuses on environmental factors that influence adherence and encourage behaviour that seeks to manage adherence following the start of treatment [49]. This often includes the use of electronic patient reminder systems (medication alarms) or continued patient counselling following treatment initiation ref. In this model, adherence is a behaviour best learnt by doing, and the probability of adhering to medication is dependent on one’s ability to overcome external threats to adherence [51]. This premise was supported by a prospective cohort study that found that pre-therapy counselling was not associated with better ARV adherence. The authors suggested that pre-therapy preparation should be viewed as a preventative measure for non-adherence, with each clinical visit encouraging lifestyle changes to promote behaviour that enhances adherence [53]. This suggests counselling following ART initiation may be more beneficial in comparison to pre-therapy counselling.

There is little agreement in the literature comparing pre-therapy counselling to concurrent counselling. In a randomized control trial (RCT) conducted in France, there was no difference in the quality of life (including CD4 cell count and plasma viral load) at 18 months post-initiation among those who received pre-therapy counselling and those who received concurrent therapy followed by a formal education session after 12 months [54]. In contrast, patients who received at least three pre-therapy counselling sessions prior to ART initiation were 29% more likely to be adherent at 18 months post ART initiation compared to patients who received no pre-therapy counselling [21]. In South Africa, delaying initiation for patient

preparation among a cohort of HIV-infected pregnant women was not associated with improved maternal outcomes measured by the viral load at 12 months [20].

4.2. Rationale for pre-therapy preparation

On the other hand, studies examining predictors of ART adherence point to psychological factors that could be addressed through patient counselling. In Ethiopia, patients who were not depressed were two times more likely to be adherent compared to those who were depressed [55]. The fear of taking medication adversely affecting existing relationships was a common reason cited for not initiating lifelong treatment among *Zambian* women [56]. In South Africa, misunderstanding and misconception about PMTCT was a major reason for non-adherence during pregnancy whilst in Ghana, women with poor knowledge of PMTCT were more likely to default within the first year of treatment [57].

Coetzee et al. highlights the difficulties in establishing robust predictors of ART adherence as the motivation for continued intensive patient preparation before the initiation of ART [58]. This is evident in the lack of standardized patient preparation activities within one region of South Africa. Among 11 facilities offering ART services to both adult and pregnant women in Cape Town, pre-therapy counselling could involve three to seven educational sessions prior to initiation, each using different educational materials and resulting in anywhere from three to six weeks' delay to ART initiation [59]. Currently there is great variation in the materials and delivery methods used in this single metropolitan area, which is telling of the lack of an agreed upon method for achieving patient preparedness prior to ART initiation. In the context of PMTCT, delay to ART treatment must be weighed against the increased risk of MTCT.

Overall, the mechanism by which patient preparedness may contribute to positive maternal outcomes is unclear. There is a lack of consensus surrounding the activities that ought to be involved in patient preparation, and data suggests that individual factors that can negatively impact adherence may not be adequately addressed by pre-therapy counselling.

5. Barriers or enablers of ART adherence

The literature on ART adherence has focused on risk factors that can be classified into three categories: individual-level factors, clinical indicators and service-related factors.

5.1. Individual-level factors

Studies have reported that women of younger age are less likely to be adherent to ARV medication during prenatal and postnatal periods of pregnancy [60,61]. In a cohort study of HIV-infected women, a one year increase in age was associated with a three-fold increase in the odds of being adherent to ARVs [62]. It is stipulated that younger women and single women have less routine lifestyles, thus find it more challenging to take ART medication daily compared to older women or married women [63]. Two studies from Zimbabwe and Zambia also identified that a woman's education level was positively associated with adherence [64,65]. A meta-analysis of quantitative studies found that in SSA nondisclosure, fear of being stigmatized and alcohol abuse were barriers to ART adherence [66]. Pregnancy is positively associated with adherence, with women citing the protection of their unborn child from HIV infection as motivation for taking medication [62, 67].

5.2. Clinical factors

A limited number of studies have explored the relationship between gestational age and adherence during pregnancy. A retrospective cohort study of 478 HIV-infected pregnant women found that women presenting later in pregnancy achieved higher adherence levels compared to those who presented earlier for ANC [68]. But these findings did not remain statistically significant when adjusting for other factors [68].

Higher CD4 cell count at ART initiation was associated with poor ART adherence among postpartum women in Tanzania [69]. It is hypothesized that patients with higher CD4 count are less likely to take medication due to feeling well with no signs of deteriorating health status [70]. Structured interviews conducted with pregnant women in Zimbabwe found previous maternal exposure to PMCT reduced the odds of non-adherence by 80% [65].

5.3. Service-level factors

In the past, the limited availability and accessibility of ART at health care facilities was a major barrier to adherence, closely linked with patient-provider relationship [71]. Reduction in treatment costs and decentralization of ART dispensing have lessened the negative effects of health services on adherence [71]. Patient-provider relationships, such as health workers' negative attitudes were reported as barriers to both ART initiation and adherence during and/or

after pregnancy in Malawi, Uganda and South Africa [72]. Positive, “warm”, non-judgmental attitudes from health workers are considered an enabler to ART adherence [73].

6. Areas for further research

Although there has been a rapid successful scale-up of PMTCT, coupled by the use of highly effective regimens, new perinatal HIV infections remain a public health burden in Sub-Saharan Africa. The literature indicates that starting pregnant women on ART early in pregnancy can lead to MTCT rates below 1%. However, determinants of adherence during and after pregnancy remain unclear, and in particular, the impact of patient preparation prior to ART initiation on adherence to treatment is not well understood.

Review of existing literature highlights the varied activities centred on patient preparation that may exist, yet there are minimal data to support the benefits of intensive pre-therapy counselling. In contrast, there is growing evidence that women who only receive counselling on the day of ART initiation may have higher attrition rates during the postpartum period.

Following this, the proposed study aims to examine the impact of same-day ART initiation on treatment adherence during the antenatal period of pregnancy. The knowledge generated will contribute to the data assessing health benefits of pre-therapy counselling and provide insights to the potential effects of implementation of same-day ART initiation under Option B+.

Table B-2: Literature included in the review

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV regimen/s	Outcome measured	Key findings	Definition of adherence and/or patient preparation (if applicable)
Observational studies								
[64]	Albrecht, 2006	Zambia	Cross-sectional study (n=760)	HIV-infected pregnant women	Nevirapine	Adherence	Disclosure of HIV status, lack of education and couple counselling were associated with adherence.	Adherence: timely consumption of nevirapine at onset of labour
[55]	Amberbir, 2008	Ethiopia	Prospective cohort study (n=400)	HIV-infected adult patients	ARVs	Adherence	Patients who lacked social support and depressed reported more missed ART doses.	Adherence: based on 7 days recall of missed ART doses
[58]	Coetzee, 2004	South Africa	Prospective cohort study (n=287)	HIV-infected adult patients	ART	Adherence, change in plasma viral and CD4 count over time.	Higher proportion of patients achieved viral load suppression following adherence counselling with a healthcare worker.	Adherence: viral load suppression
[68]	Demas,2005	United States of America	Prospective study (n=78)	HIV-infected pregnant women	Zidovudine	Adherence	Being part of a support group and having disclosed HIV status were associated with better adherence.	Adherence: Urine sample and self-reported
[19]	Ebuy, 2014	Ethiopia	Cross-sectional study (n=277)	HIV-infected pregnant women	ART (Option B+)	Adherence, Option B+ knowledge and male involvement	Counselling on the side effects of ART was a predictor of adherence.	Adherence: self-report based on 4 questions relating to ART use over 1 month.
[35]	Fitzgerald, 2014	South Africa	Retrospective cohort study (n=367)	HIV-infected pregnant women	ART	MTCT	13% of women were LTFU during the Pre-ART period. Each additional week on ART was associated with 20% reduction in MTCT, with women with viral load >50 copies/ml, advanced WHO disease stage were at increased risk of MTCT.	

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV regimen/s	Outcome measured	Key findings	Definition of adherence and/or patient preparation (if applicable)
[67]	Henegar, 2015	South Africa	Retrospective cohort study (n=7510)	HIV-infected pregnant women	ART	Adherence	Non-pregnant women were 46% more likely to be non-adherence compared to pregnant women.	Adherence: based on pill count
[42]	Ishikawa, 2013	Zambia	Model based on health system data	HIV-infected pregnant women	ART (Option B+)	Costs and Outcomes of Option B+	Option B+ can lead to a 33% reduction in MTCT and an 80% increased risk of initiating ART during pregnancy.	
[10]	Kaplan, 2008	South Africa	Retrospective cohort study (n=2131)	HIV-infected Pregnant and non-pregnant women	ART	LTFU and mortality	Pregnant women were at an increased risk of LTFU during the pre-ART and on ART periods. No difference in the mortality rates between women enrolled on pre-ART and those receiving ART.	
[41]	Kim, 2015	Malawi	Before/After study (n=28458)	Pregnant women	ART (Option B+)	PMTCT enrolment and ART outcomes	Transitioning to Option B+ had no impact on the proportion of women initiating ART. However, time to ART initiating decreased by 48 days.	
[65]	Kounza, 2010	Zimbabwe	Cross-sectional study (n=212)	HIV-infected pregnant women	Nevirapine	Adherence	Non-adherence was associated with lack of secondary education and disclosure of HIV status.	Adherence: timely consumption of nevirapine at onset of labour
[60]	Laine, 2000	United States of America	Retrospective cohort study (n=2714)	HIV-infected pregnant women	ART	Adherence	Younger women and women on ART before pregnancy were more likely to be adherent to ART medication during pregnancy compared to older women and those initiating ART during current pregnancy.	Adherence: based on pharmacy data
[20]	Myer, 2012	South Africa	Retrospective cohort study (n=490)	HIV-infected pregnant women	ART	Viral load and LTFU	No difference in viral load suppression or retention at 4,8,12 months between those who delayed ART treatment.	

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV regimen/s	Outcome measured	Key findings	Definition of adherence and/or patient preparation (if applicable)
[46]	Myer, 2013	South Africa	Prospective cohort study (n=8752)	HIV-infected pregnant women	ARVs	ART initiation and delays	Use of lay counsellors to guide women to ART referral site increased the proportion of women initiating ART. There was a decrease in delays to ART eligibility confirmation following first ANC visit.	
[30]	Palombi, 2007	Africa	Prospective study (n=879)	HIV-infected pregnant women	ART	MTCT	At 6 months postpartum, there was no difference in MTCT rates among women who breastfed versus those who formula-fed.	
[39]	Patten, 2013	South Africa	Before/After study (n=576)	HIV-infected adult patients	ARVs	LTFU during HIV testing and assessment of ART eligibility and initiation	Use of POC CD4 test increased the likelihood of being assessed for ART eligibility. No difference in proportion of patients initiating ART, but time to ART initiation decreased by seven days.	
[70]	Rougemont, 2009	Cameroon	Retrospective cohort study	HIV-infected adult patients	ART	Adherence	Non-adherence was more frequent in women and those with higher income.	Adherence: Pharmacy-refill and self-reported missed ART doses over 30 days
[51]	Siedner, 2012	Uganda	Prospective study (n=300)	HIV-infected adult patients	ARVs	Adherence and viral load	At 3 months of treatment, there was no difference in the adherence levels in patients receiving several pre-therapy counselling sessions compared to pre-therapy counselling on the day of ART initiation.	Adherence: >90% based on pill count. Pre-therapy: each counselling session was 20 minutes long, either one-on-one or group counselling.
[37]	Siedner, 2015	Uganda	Before/After study (n=183)	HIV-infected adult patients	ARVs	Time to ART initiation and return to health facility	Time to ART initiation decreased by 5 weeks when mobile text messages were sent to patients daily for one week.	

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV regimen/s	Outcome measured	Key findings	Definition of adherence and/or patient preparation (if applicable)
[36]	Townsend, 2014	United Kingdom and France	Population based surveillance (n=11 515)	HIV-infected pregnant women	ARVs	MTCT	Initiation of ART earlier in pregnancy led to 2.1% decline in MTCT over 10 years. For all modes of delivery, MTCT was higher for women with viral load >40 copies/ml. Additional benefit of ART use lessened at 15 weeks.	
[63]	Uzochukwu, 2009	Nigeria	Cross-sectional study (n=174)	HIV-infected adults	ARVs	Adherence	Fear of social alienation, physical discomfort, higher education and being single were associated with non-adherence.	Adherence: based on 30-day recall of missed ART doses
[62]	Vaz, 2007	Brazil	Prospective cohort study (n=151)	HIV-infected women	ARVs	Adherence	Being pregnant and older was associated with increased risk of non-adherence.	Adherence: based on self-reported missed ART doses and pill count
Mixed methods								
[57]	Mephanm, 2011	South Africa	Clinical notes (n=100) and unstructured interviews (n=43)	HIV-infected pregnant women	ART	Adherence	Misconceptions of ART, violence, stigma and lack of disclosure were reasons cited for being non-adherent to ART.	Adherence: >95% based on clinical notes
[18]	Thenthani, 2014	Malawi	National level analysis (n=21939) & individual data (n=11534)	HIV-infected pregnant women & breastfeeding	ART (option B+)	LTFU	Higher proportion of women under B+ did not return to the clinic following ART initiation. LTFU was higher among those initiating ART at the first ANC visit.	

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV regimen/s	Outcome measured	Key findings	Definition of adherence and/or patient preparation (if applicable)
[15]	Van lethow, 2014	Malawi	Facility survey (n=141) & retrospective cohort of patients records	Healthcare workers & ART eligible HIV-infected pregnant women	ART	LFTU and adherence	Four models of care for B+ implementation differed in proximity to ANC & duration of pre-therapy counselling. Retention was lowest among those referred for ART & pre-therapy counselling on day of ART eligibility confirmation.	Adherence counselling: counselling concerning ART use prior to ART dispensing
Systematic Review								
[73]	Hogson, 2014	Developed and developing countries	Systematic review	HIV-infected women	ART	Adherence	Restricted access to health services and negative attitudes from health workers were negatively associated with ART adherence.	Adherence: based on self-report, pharmacy records and electronic monitoring of pill intake
[72]	Mills, 2006	Developed and developing countries	Systematic review	HIV-infected	HAART	Adherence	Use of reminder tools, understanding adverse effects of non-adherence and decreased family responsibility were positively associated with adherence.	Adherence: based on self-report, pharmacy records and electronic monitoring of pill intake
[66]	Nachega, 2012	Low-, middle- and high-income countries	Meta-analysis (n=20 153)	HIV-infected pregnant women	ART	Adherence	Emotional stress, SES, ART dose frequency and pill burden were associated with non-adherence.	Adherence: based on self-report, pill count, pharmacy data and viral load.
[61]	Reda, 2012 ⁵	Africa	Systematic review	HIV-infected adult	ART	Adherence	Adherence levels reported in Africa were comparable to those in developed countries. Barriers to adherence included younger age, substance abuse and lack of transport money.	Adherence: based on self-report, pill count, pharmacy data and viral load.

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV regimen/s	Outcome measured	Key findings	Definition of adherence and/or patient preparation (if applicable)
[44]	Suthar, 2012	Africa and Jamaica	Systematic review	HIV-infected pregnant women	ART	Timing of ART initiation	Higher proportion of women initiating ART in integrated care. No difference in the retention rates between integrated and referral ART clinics.	
[39]	Wynberg, 2014	Sub-Sahara Africa	Systematic review	HIV-infected patients	ARVs	CD4 enumeration	Use of POC CD4 tests resulted in a 4-fold increase in the completion of CD4 testing. The likelihood of receiving CD4 result increased by 3-folds, with time to receiving CD4 result decreasing by 17 days.	
Option or Commentary								
[33]	Abrams, 2007	Developing countries	Review	HIV-infected pregnant women	ARVs	PMTCT and HIV care delivery	Need to strengthen linkage between PMTCT and HIV care services to reduce vertical transmission of HIV to infants.	
[17]	Gebrekrastos, 2005	South Africa	Opinion piece	ART eligible patients	ART	Patient readiness	No consensus on activities around patient preparation for ART. Current methods for patient preparation may not adequately address barriers to ART adherence.	
[71]	Kagee, 2011	Southern Africa	Opinion piece	HIV-infected patients	ART	Adherence	Structural barriers to ART adherence include limited access to mental-health services, overburden health care facilities and inadequate counselling at ART initiation	Adherence: based on self-report, pharmacy records and electronic monitoring of pill intake.
[32]	Myer, 2011	Sub-Sahara Africa	Editorial	HIV-infected pregnant women	ART	Timing of ART initiation	In settings with limited access to laboratory services and late presentation to ANC, timely initiation of ART is crucial.	

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV regimen/s	Outcome measured	Key findings	Definition of adherence and/or patient preparation (if applicable)
[16]	Shaffer, 2014	Developing countries	Review	ART eligible patients	ART	PMTCT services	There is a need to assess quality of pre-therapy counselling due to high attrition rates following ART initiation under B+ in Malawi	
[43]	Schouten, 2011	Low-and middle-income countries	Viewpoint	HIV-infected pregnant women	ARVs	PMTCT	Option B+ offers the opportunity to fully integrate HIV to PMTCT services.	
Qualitative studies								
[56]	Murray, 2009	Zambia	Unstructured interviews	HIV-infected women	ART	Barriers to ART adherence	Medication side effects, lack of ART knowledge and depression were barriers to ART adherence.	Adherence: taking ART as prescribed with no missed ART doses.
[59]	Myer, 2012	South Africa	Interviews	Healthcare facilities (n=11)	ART	Pre-therapy activities	Number of patient education sessions ranged from 3-7 and lasted from 3-6 weeks. Materials used for patient education include posters, flipcharts and pamphlets.	
[69]	Ngarina, 2013	Tanzania	Semi-structured interviews (n=23)	HIV-infected women	ART	Adherence	Feeling well was cited as barrier to adherence while motivation to protect unborn child from HIV infection during pregnancy was mentioned as the main reason for taking ART during pregnancy	Adherence: taking ART as prescribed with no missed ART doses.
Experimental studies								
[22]	Connor, 1994	United States and France	RCT (n=477)	HIV-infected pregnant women	AZT vs placebo	MTCT at 18 months postpartum	Use of AZT has a 68% reduction in vertical transmission of HIV during pregnancy.	

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV regimen/s	Outcome measured	Key findings	Definition of adherence and/or patient preparation (if applicable)
[21]	Chung, 2011	Kenya	RCT (n=400)	ART-naïve adults	ART	Adherence, viral load, CD4 cell count & mortality	Patients who received counselling were more adherent, no effect on adherence with the use of medication alarms.	Adherence measured by monthly pill counts
[36]	Dryden-Peterson, 2015	Botswana	RCT (n=316)	HIV-infected pregnant women	ARVs	Time to ART initiation	Mobile text reduced time to CD4 receipt at the clinic by 10 days. No change in the timing of ART initiation.	
[29]	Fowler, 2015	Africa	RCT (n=1230)	HIV-infected pregnant women	AZT/NVP vs AZT/3TC/LP V-r vs TRV/LPV-r	MTCT	MTCT rate was 0.55 in triple drug arm compared to 1.8 in ZDV/NVP arm and lower risk of neonatal deaths	
[54]	Goujard, 2003	France	RCT (n=367)	HIV-infected adult patients	ARVs	Adherence, HIV knowledge	Educational intervention resulted in increased adherence levels at 6, 12 and 18 months.	Adherence: based on a validated self-report questionnaire scoring 0-100.
[26]	Guay, 1999	Uganda	RCT	HIV-infected pregnant women and breastfeeding	AZT vs sd-NVP	MTCT at 6-8 weeks	Efficacy of sd-NVP was 47%. There was no difference in the side effects of the two ARV regimens	
[27]	Kumwenda, 2008	Malawi	RCT	HIV-infected pregnant women	AZT + sd-NVP	MTCT at 9 months	Extension of nevirapine with or without AZT for first 14 weeks of life reduced postnatal HIV perianal infection by over 5%.	
[25]	Shaffer, 1999	Thailand	RCT	HIV-infected pregnant women	AZT vs placebo	MTCT and viral load at 2 & 6 months	80% of the reduced MTCT were explained by viral load suppression. Efficacy of short term AZT started at 36 weeks was 50% if formula-fed.	

In text citation	Author, year	Setting	Study design (sample size)	Population	ARV regimen/s	Outcome measured	Key findings	Definition of adherence and/or patient preparation (if applicable)
[28]	Shapiro, 2010	Botswana	RCT	HIV-infected pregnant women	AZT vs AZT+ sd-NVP vs AZT+3TC+sd-NVP	MTCT at 4-6 weeks	Triple drug therapy was most effective, followed by dual therapy & lastly use of AZT only.	
[24]	Wiktor, 1999	Cote D'Ivoire	RCT (n=280)	HIV-infected pregnant women and breastfeeding	AZT vs placebo	MTCT at 3 months postpartum	Efficacy of short course AZT at 36 week was 44% among breastfeeding women.	

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C. MANUSCRIPT

Same-day versus delayed initiation of antiretroviral therapy in pregnancy is not associated with antiretroviral adherence: a cohort study

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Abstract

Introduction: Many prevention of mother-to-child HIV transmission (PMTCT) programmes across Africa initiate HIV-infected pregnant women on lifelong antiretroviral therapy (ART) on the first day of antenatal care (“same-day” initiation). However concerns have been raised regarding patient readiness and whether same-day initiation in pregnancy may contribute to subsequent ART non-adherence.

Methods: As part of a larger study of ART in pregnancy, consecutive ART-eligible pregnant women making their first antenatal care (ANC) visit at a primary care facility in Cape Town, South Africa were enrolled into a prospective cohort between March 2013 and June 2014. Before July 2013, eligibility was based on CD4 cell count ≤ 350 cells/ μL (“Option A”), with a 1-2 week delay from the first ANC visit to ART initiation; thereafter all women were eligible regardless of CD4 cell count (“Option B+”) and typically offered ART on the same day as first ANC visit. All women received standardized counselling before starting a fixed-dose regimen. Study interviews were conducted separately from the ART service through one week postpartum with self-reported adherence from 30-day recall.

Results: Among 625 consecutive ART-eligible women (median age, 28 years; median gestation, 21 weeks; 55% newly diagnosed with HIV), 72% of women started ART same-day; this proportion was higher under “Option B+” versus “Option A” ($p < 0.001$). Of those with adherence assessments data available ($n=618$), 29% reported at least one missed ART dose during pregnancy. Missed doses were reported more frequently among women with previous use of PMTCT ($p=0.014$), of younger age ($p=0.029$) and starting ART under Option B+ ($p=0.019$). In women initiating ART same-day, 31% reported a missed dose compared to 23% among women who delayed ART start following first ANC visit (odds ratio, 1.07; 95% CI: 0.61 – 1.88). This finding did not vary after adjustment for demographic and clinical measures, and was consistent when restricted to women with CD4 cell counts ≤ 350 cells/ μL .

Conclusions: These results suggest same-day ART initiation in pregnant women is not associated with increased non-adherence during the antenatal period. While these results are reassuring for ART programmes implementing “Option B+”, further research is required to examine adherence over time, particularly postpartum.

1. Introduction

Use of triple-drug antiretroviral therapy (ART) during pregnancy reduces maternal viral load and decreases the risk of transmission *in utero*, during labour and while breastfeeding [1-3]. Historically, eligibility criteria for ART initiation in pregnant women has mirrored that used in adults, with CD4 cell count as a marker of advanced disease requiring treatment [4, 5]. If eligible for ART, pregnant women were referred to ART services for patient education and pre-treatment counselling [6]. The need for CD4 cell counts and pre-ART counselling contributed to significant delays in ART initiation in pregnancy, although each additional week on ART may reduce the odds of perinatal HIV transmission by up to 10% [7-9].

In the last five years, there has been a progressive shift to provide lifelong ART to all HIV-infected pregnant and breastfeeding women regardless of health status (the World Health Organization's "Option B+"), eliminating the need for CD4 cell counts [4, 10]. In parallel, there have been major advances in integrating ART provision into antenatal care (ANC), removing the referral of women to separate ART services [11]. Together, these developments have contributed to reductions in the time taken to initiate ART in HIV-infected pregnant women. In particular, "Option B+" has introduced the possibility of same-day ART initiation: that HIV-infected pregnant women could commence lifelong ART on the day of their first ANC visit [4].

Same-day ART initiation in pregnancy has several distinct advantages, but also potential limitations; and data on this question are few. By maximising the duration of ART during pregnancy, same-day initiation may contribute to an increased likelihood of achieving viral suppression prior to delivery and reduced HIV transmission [12]. Same-day initiation may also reduce attrition in the ART initiation 'cascade' by increasing the proportion of HIV-infected pregnant women who start ART [13]. However, same-day initiation also reduces the opportunity for pre-ART patient education and counselling, which are traditionally a core component of ART services [14]. This pre-treatment counselling is often thought to play an important role in preventing non-adherence on ART, though the evidence for this is limited [15].

In Malawi under "Option B+", pregnant women who were offered ART same-day were five times less likely to return for an ART follow-up visit, citing limited understanding of the initial ART education session as one reason for being LTFU [16]. These findings persisted regardless

of the degree of integration of ANC and ART services [17]. In contrast, one South African analysis found that in a system with CD4-based ART eligibility, delaying ART initiation for patient preparation among HIV-infected pregnant women was not associated with improved maternal outcomes at 12 months after initiation [18].

Given the paucity of data on this question, we examined the associations between delay of ART initiation in ANC and missed ART doses during pregnancy among ART-eligible pregnant women in Cape Town, South Africa.

2. Methods

This study is a secondary analysis of an ongoing prospective cohort study evaluating strategies to optimize antiretroviral therapy services for maternal & child health (MCH-ART) in Gugulethu, South Africa. The study took place at a large primary health care facility which has been providing integrated antenatal and PMTCT services to women living within the Klipfontein sub-district since 2012. Between March 2013 and June 2014, consecutive HIV-infected, ART-eligible pregnant women, older than 17 years of age seeking care at the local ANC service were enrolled into this cohort study on the day of their first antenatal care visit.

2.1. ART services

Before July 2013, pregnant women were identified as ART-eligible according to World Health Organisation (WHO) “Option A” guidelines based on CD4 cell count ≤ 350 cells/uL and/or WHO stage III/IV. Under this approach, ART-eligible women received at least two pre-therapy counselling sessions: the first being one to two weeks before initiation and second on the day of ART dispensing. After July 2013, lifelong ART was provided at first antenatal care visit irrespective of CD4 cell count or WHO clinical stage, per WHO’s Option B+, with all women receiving one pre-therapy counselling on the day of their first antenatal care visit. Under both Option A and Option B+, counselling was provided by trained counsellors during a 15 minute group session covering dose schedules, treatment side effects, adherence and prevention of drug resistance; further one-on-one counselling was provided at dispensing by clinic nurse. Women received ongoing counselling and support at subsequent ART refill visits. Throughout the study period, women received fixed dose combination of tenofovir, emtricitabine and efavirenz (TDF+FTC+EFV) to be taken once daily, with a month’s supply of treatment being

provided for the first four months of treatment. Thereafter, women received one to two months' supply of treatment at the discretion of the provider.

2.2. Data collection

In this secondary analysis, women were followed from the first antenatal visit to seven days after delivery with study interviews conducted separately from the ART service at the second antenatal visit then again during the late third trimester and within the first week postpartum. During each study visit, data on demographic characteristics, clinical history, ART initiation and ART use were collected through face-to-face interviews conducted in the local language, isiXhosa. Viral load was taken at first ANC and at each subsequent visit. At each study visit, women were asked to self-report any missed ART doses in the last 30 days prior to the study visit, with reasons for any missed doses investigated. Obstetric and current clinical characteristics such as CD4 cell count were abstracted from patient records throughout the study duration.

Ethical approval to abstract data and conduct this analysis was provided by the Human Research Ethics Committee of the University of Cape Town and the Institutional Review Board of Columbia University Medical Centre. All women enrolled in the study completed a written informed consent form for study participation and abstraction of routine health care records.

2.3. Analysis

Data were analysed using Stata Version 12 (Stata Corporation, College Station, USA). The primary exposure of interest was delay to ART initiation from first antenatal booking. We defined time delay to ART initiation as the difference in days from the first ANC visit to the date on which participants first took an ART dose. In this analysis, delay to ART initiation after first antenatal visit was analysed as a proxy of the time available for patient preparation, with all women receiving at least one pre-therapy counselling session on the day of ART initiation. Same-day ART initiation was defined as starting ART within 48 hours of first presentation for ANC. This variable was analysed both as a continuous variable and categorized into 'same-day', 3-14 days, 15-28 days and ≥ 29 days.

The principle outcome of interest was ART non-adherence, defined as any self-reported missed ART doses at any study follow-up visit. The primary outcome of missed ART doses was treated as a binary variable; any reported missed doses versus none. Women with no adherence

assessment following ART initiation were excluded from the analysis. The analysis is therefore limited to women who completed at least one ART adherence assessment.

The cohort's characteristics were summarized using descriptive statistics such as means with standard deviation, medians with interquartile range (IQR) and proportions, depending on the data distribution. Bivariate analysis used rank-sum and Kruskal Wallis tests for continuous variables and Chi-squared and Fischer tests for categorical variables. We investigated the association between delay to ART initiation and reported missed ART doses during pregnancy using logistic regression, reporting odds of missing a dose with 95% confidence intervals (CI). Variables were included in the model if known to be a confounder of missed ART dose during pregnancy as indicated by literature or if independently associated with the outcome during bivariate analysis. Model fitting was examined using likelihood ratio test and the Akaike Information Criterion (AIC).

3. Results

Baseline characteristics

Overall, 628 HIV-positive pregnant women were enrolled into the parent study. Of these, three women reported not having initiated ART by seven days postpartum and are excluded from analysis. The baseline characteristics of the cohort and timing of ART initiation are shown on Table C-1. Among those initiating ART (n=625) the median gestational age at first ANC visit was 21 weeks (IQR 16-26). The majority of women were less than 30 years of age (61%), had completed primary education (96%) and were living in informal housing (53%). Overall, 55% of the women were newly diagnosed as HIV-infected during this current pregnancy and 81% initiated ART under Option B+. Among those diagnosed HIV-infected prior to the current pregnancy (n=283), half were diagnosed during a previous pregnancy and 91% reported to have disclosed their HIV status to at least one individual. More than half (52%) of those diagnosed prior to the current pregnancy had exposure to ARV prophylaxis for PMTCT. The median CD4 cell count at first antenatal visit was 343 cells/ μ L (IQR 235-506) with half of the cohort (52%) having a CD4 cell count \leq 350 cells/ μ L.

Timing of initiation of antiretroviral therapy

Seventy-two percent (n=450) of the cohort initiated ART same-day. Among 175 women (28%) who delayed ART initiation for two or more days, the median delay to ART initiation was seven days (IQR 3-102; range 1-98). There were no significant differences in age, gravidity, level of education or marital status between the two groups. However, women who started ART on the same day presented at the clinic at a later gestational age compared to women with delayed ART initiation ($p<0.001$). Women who initiated ART same-day were also more likely to be unemployed or not attending school and living in informal housing. The majority of women who initiated ART same-day were enrolled under Option B+ and had a higher median CD4 cell count ($p<0.001$) at first antenatal visit.

Table C-1: Baseline description of 625 women who initiated ART during pregnancy, by delay in days from first antenatal visit to ART initiation

	Total	Delay from first Antenatal visit to ART initiation				P value
		same day	3-14 days	15-28 days	>29 days	
Number of participants	625	450 (72%)	101 (16%)	30 (5%)	44 (7%)	
Demographics						
Age in years	28 (24 - 32)	28 (24-32)	28 (25 -32)	27 (23-31)	27 (26-31)	0.840
Level of education						
Primary school	26 (4)	17 (3)	6 (6)	0 (0)	3 (7)	
High school& above	599 (96)	433 (97)	95 (94)	30 (100)	41 (93)	0.384
Occupation						
Not scholar/employed	387 (62)	289 (64)	64 (64)	16 (53)	19 (43)	
Scholar/Employed	238 (38)	161 (36)	37 (36)	14 (47)	25 (57)	0.037
Housing						
Informal (shack)	332 (53)	234 (52)	59 (59)	11 (36)	29 (66)	
Formal (house/hostel)	293 (47)	216 (48)	42 (39)	19 (64)	15 (34)	0.068
Relationship status						
Single/Not married	474 (76)	342 (76)	78 (77)	20 (67)	34 (77)	
Married	151 (24)	108 (24)	23 (23)	10 (33)	10 (23)	0.673
Gravidity						
Nulli /Prima	373 (60)	263 (58)	59 (58)	24 (80)	27 (61)	
Multi	252 (40)	187 (42)	42 (42)	6 (20)	17 (39)	0.136
Timing of HIV diagnosis						
Current pregnancy	342 (55)	258 (57)	49 (49)	14 (47)	21 (48)	
Before current pregnancy	283 (45)	192 (43)	52 (51)	16 (53)	23 (52)	0.216
Among those previously diagnosed (n=283)						
Years since HIV diagnosis						
0 – 5 years	183 (65)	123 (64)	36 (69)	8 (50)	16 (70)	
6 years or more	100 (35)	69 (46)	16 (31)	8 (50)	7 (30)	0.522
Reason for testing at HIV diagnosis						
Pregnancy (PMTCT)	146 (52)	103 (54)	26 (50)	6 (38)	11 (46)	
VCT	76 (27)	56 (29)	8 (15)	6 (38)	6 (27)	
Medical (TB/STI/sick)	61 (21)	33 (17)	18 (35)	4 (24)	6 (27)	0.102
Disclosed HIV status						
No	26 (9)	21 (11)	2 (4)	1 (6)	2 (9)	
Yes	257 (91)	171 (89)	50 (96)	15 (94)	21 (91)	0.448
Exposure to ARV at previous pregnancy						
No	112 (40)	69 (36)	22 (42)	10 (63)	11 (48)	
Yes	171 (60)	123 (64)	30 (58)	6 (37)	12 (52)	0.145
Clinical						
Median Gestation ¹ (weeks)	21 (16 - 26)	22 (18 - 28)	20 (15-24)	13.5 (9 – 25)	11.5 (7 -21)	<0.001
Median Viral load (log ₁₀ copies/ml)	3.99 (3.40 – 4.64)	3.92 (3.2 - 4.6)	4.38 (3.9 - 4.8)	3.78 (3.4 - 4.4)	4.01 (3.4 - 4.7)	<0.001
Median CD4 count ² (cells/uL)	343 (235 - 506)	378.5 (246 - 546)	265 (189 - 355)	289.5 (217 - 403)	346 (271 - 470)	<0.001
≤350 cells/uL	315 (52)	198 (46)	75 (74)	20 (67)	22 (51)	<0.001
PMTCT						
Option A	119 (19)	21 (5)	65 (64)	12 (40)	21 (48)	
Option B+	506 (81)	429 (95)	36 (36)	18 (60)	23 (52)	<0.001

*Bivariate comparison using Kruskal Wallis test, Fischer test and chi-squared test

1 missing data for 4 participants

2 missing data for 17 participants

Missed dose among those initiating ART during pregnancy

Of the 628 women initiating ART, seven women did not have adherence assessments at follow-up visits although reporting having started ART. Among the 618 women initiating ART and with missed ART doses data available, 29% (n=178) reported missing at least one dose within the last 30 days prior to the interview and the median missed doses per month was 1 (IQR 0.67-2.13) in this group. There was no difference in the reporting of missed ART doses and timing of ART initiation (70% versus 78% among same-day initiators; $p=0.236$). Table C-2 shows the characteristics of all women who had data available on ART adherence stratified by self-reported missed ART doses. Those who reported a missed ART dose within the last month were more likely to be younger ($p=0.027$), live in formal housing ($p=0.002$) and be currently single or with a partner but not married ($p=0.02$). Among those diagnosed with HIV prior to the current pregnancy, those with who did not miss any ART doses were more likely to have had ARV prophylaxis exposure during previous pregnancy (65% vs 49%; $p=0.014$), but there was no difference in disclosure status between the two groups ($p=0.842$). A higher proportion of missed ART doses was reported by women enrolled under Option A versus Option B+ ($p=0.021$).

Table C-2: Demographic, obstetric and clinic characteristics of 618 women stratified by missed ART dose status

	Total* n=618	No ART dose missed n=440	Missed ART dose/s n=178	P value
Demographics				
Age in years	28 (24-32)	28 (25-32)	27 (23-31)	0.027
Level of education				
Primary school	25 (4.0)	18 (4)	7 (4)	
High school& above	593 (96.0)	422 (96)	171 (96)	0.924
Occupation				
Not scholar/employed	383 (62)	269 (61)	114 (64)	
Scholar/Employed	235 (38)	171 (39)	64 (36)	0.487
Housing				
Informal (shack)	330 (53)	252 (57)	78 (44)	
Formal (house/hostel)	288 (47)	188 (43)	100 (56)	0.002
Relationship status				
Single/Not married	469 (76)	322 (73)	147 (83)	
Married	149 (24)	118 (27)	31 (17)	0.013
Gravidity				
Nulli /Prima	369 (60)	255 (58)	114 (64)	
Multi	249 (40)	185 (42)	64 (36)	0.162
Timing of HIV diagnosis				
Current pregnancy	336 (54)	243 (55)	93 (52)	
Before current pregnancy	282 (46)	197 (45)	85 (48)	0.501
Among those previously diagnosed (n=283)				
Years since HIV diagnosis				
0 – 5 years	183 (65)	126 (64)	57 (67)	
6 years or more	99 (35)	71 (36)	28 (33)	0.617
Reason for testing at HIV diagnosis				
Pregnancy (PMTCT)	145 (52)	108 (55)	37 (44)	
VCT	76 (27)	46 (23)	30 (35)	
Medical (TB/STI/sick)	61 (21)	43 (22)	18 (21)	0.099
Disclosed HIV status				
No	26 (9)	18 (9)	8 (9)	
Yes	256 (91)	179 (91)	77 (91)	0.942
Exposure to ARV at previous pregnancy				
No	112 (40)	69 (35)	43 (51)	
Yes	170 (60)	128 (65)	42 (49)	0.014
Clinical				
Median Gestation ¹ (weeks)	21 (16-26)	21 (16-26)	20 (17-26)	0.942
Median Viral load (log10 copies/ml)	3.99 (3.4-4.6)	4.00 (3.2-4.62)	4.01 (6.5-4.6)	0.186
Median CD4 count ² (cells/uL)	342.5 (235 - 509)	343 (234 - 513)	340.5 (236.5-502.5)	0.923
≤350 cells/uL	313 (52)	223 (52)	90 (52)	0.918
PMTCT				
Option A	115 (19)	92 (21)	23 (13)	
Option B+	503 (81)	348 (79)	155 (87)	0.021
Median days on ART	121 (78-153)	121 (71-152)	121 (89-153)	0.199
ART initiation delay (days)				
0-2	447 (72)	308 (70)	139 (78)	
3-14	99 (16)	76 (17)	23 (13)	
15- 28	29 (5)	22 (5)	7 (4)	
29 and above	43 (7)	34 (8)	9 (5)	0.236

* Seven women did not have adherence assessments at follow-up visits although reporting having started ART

**Use Wilcoxon ran sum test and chi-squared test

1 missing data for 5 participants

2 missing data for 16 participants

Predictors of reporting any missed dose during pregnancy are presented in Table C-3. After adjusting for demographic and clinical characteristics, the delay to ART initiation after a woman's first antenatal visit was not associated with reported missed ART doses (OR=1.07; CI=0.61–1.88), and this lack of an association persisted across all of the ART delay groups (Appendix D-1). The findings did not vary in a sub-analysis restricted to those with a CD4 count ≤ 350 cells/ μ L, who would have been eligible to start ART under either PMTCT guideline (Table C-4). Age at first antenatal care visit and type of housing were significant predictors of reporting missed ART doses during pregnancy. A one year increase in age was associated with 4% reduced odds of reporting a missed dose (OR=0.96; CI=0.93-0.98). Women who resided in informal housing were found to have 58% increased odds of reporting a missed ART dose compared to those living in an informal settlement (OR=1.58; CI=1.08-2.27). In addition, women initiating ART under Option B+ were twice as likely to report a missed ART dose compared to those initiating under Option A (OR=1.92; CI=1.02-3.64). However, when the analysis was restricted to all women with CD4 cell count ≤ 350 cells/ μ L, who would have been eligible to start ART under either PMTCT guidelines, the odds of reporting a missed ART dose did not differ between the two PMCT guidelines (OR= 0.93; CI=0.38-2.30). Moreover, when the analysis was restricted to women initiating ART under Option B+, delay to ART initiation after a woman's first antenatal visit was still not associated with reported missed ART doses (OR=1.14; CI=0.61–2.16) (Appendix D-2).

Table C-3: Unadjusted and adjusted logistic regression models of association between timing of ART initiation and any missed ART dose in pregnancy

	Unadjusted			Adjusted		
	OR	95 % CI	P value	aOR	95% CI	P value
Age in years	0.96	0.92 - 0.99	0.012	0.96	0.93 - 0.98	0.031
Scholar /employed	0.88	0.60 - 1.27	0.481	0.88	0.60 - 1.29	0.517
Informal housing	1.68	1.17 - 2.41	0.004	1.58	1.08 - 2.27	0.015
Diagnosed HIV+ before current pregnancy	1.18	0.83 - 1.69	0.344	1.28	0.87 - 1.88	0.196
Gestation (weeks)	1.00	0.98 - 1.03	0.859	1.02	0.99 - 1.06	0.181
CD4 (cell/ μ L) 0 -250	1	(ref)		1	(ref)	
251-350	0.67	0.403 - 1.11	0.125	1.21	0.71 - 2.08	0.489
351-500	0.71	0.30 - 1.69	0.435	1.00	0.56 - 1.81	0.991
>500	0.52	0.23 - 1.15	0.110	0.90	0.51 - 1.59	0.712
PMTCT Option A	1	(ref)		1	(ref)	
Option B+	1.86	1.12 - 3.08	0.016	1.92	1.02 - 3.64	0.044
Median days on ART	1.00	1.00 - 1.06	0.056	1.00	0.99 - 1.01	0.354
Delay to ART initiation						
Delayed (>2 days)	1	(ref)		1	(ref)	
Same-day (0-2 days)	1.56	1.03 - 2.37	0.034	1.07	0.61 - 1.88	0.808

Table C-4: Restricted to women with baseline CD4 < 350 cell/uL (n=312): Unadjusted and adjusted logistic regression models of association between timing of ART initiation and any missed ART dose in pregnancy

	Unadjusted			Adjusted		
	OR	95 % CI	P value	aOR	95% CI	P value
Age in years	0.96	0.91 - 0.99	0.045	0.95	0.91 - 1.00	0.066
Scholar /employed	0.86	0.51 - 1.42	0.550	0.86	0.50 - 1.450	0.604
Informal housing	1.66	1.02 - 2.76	0.038	1.56	0.93 - 2.61	0.094
Diagnosed HIV+ before current pregnancy	1.43	0.88 - 2.34	0.153	1.62	0.96 - 2.72	0.073
Gestation (weeks)	1.00	0.98 - 1.03	0.899	1.00	0.95 - 1.06	0.945
CD4 (cell/ μ L) 0 -250	1	(ref)		1	(ref)	
251-350	1.18	0.70 - 2.00	0.522	1.21	0.70 - 2.10	0.476
PMTCT Option A	1	(ref)		1	(ref)	
Option B+	1.42	10..79 - 2.54	0.245	0.93	0.38 - 2.30	0.879
Median days on ART	1.00	0.99 - 1.01	0.262	1.00	0.99 - 1.01	0.893
Delay to ART initiation						
Delayed (>2 days)	1	(ref)		1	(ref)	
Same-day (0-2 days)	1.53	0.96 - 2.59	0.111	1.86	0.79 - 4.37	0.154

4. Discussion

This analysis suggests that delayed ART initiation for patient preparation is not associated with improved maternal adherence during the antenatal period. Among pregnant women with delays to ART initiation of up to 4 weeks, adherence levels did not differ compared to those initiating same-day. Given the need to maximize the duration on ART prior to delivery and thus prevent vertical transmission of HIV, our findings have important implications for the design of PMTCT services for ART eligible pregnant women.

These findings support previous studies that have indicted no appreciable benefits of delaying ART initiation for pre-therapy counselling either during pregnancy or among non-pregnant adults. A French randomised controlled trial found no difference in the quality of life and health outcomes, including CD4 cell count and plasma viral load at 18 months post initiation among those who received pre-therapy counselling and those who received concurrent therapy followed by formal education sessions after 12 months [19]. More recently, completing adherence counselling prior to ART initiation was not associated with better adherence at 3 months among Ugandan adult patients initiating ART due to low CD4 cell count [20]. In South Africa, one study found that delaying initiation for patient preparation among HIV-infected pregnant women was not associated with improved maternal outcomes, measured by viral load at 12 months on ART [18]. Nonetheless, any levels of non-adherence during pregnancy are concerning as they increase the risk of HIV transmission to the exposed infant.

In these data, patients initiating ART under Option B+ were more likely to be offered same-day ART initiation compared to women starting ART under Option A, and the independent effect of this difference in program structure cannot be entirely isolated from this analysis. Despite this, we conducted a sub-analysis restricted to women with CD4 \leq 350 cells/ μ L who would have been eligible to start ART under both PMTCT guidelines, and the lack of an association between delayed ART initiation and adherence persisted in this sub-analysis.

Two significant predictors for reporting missed ART doses were identified. First, being younger was associated with increased odds of reporting a missed dose, which is consistent with findings reported by previous studies of adherence in pregnancy [21,22]. It is plausible that, related to a range of circumstances, younger women may have less routine lifestyles and thus find it more challenging to take ART medication daily in comparison to older women. Second, women living in informal housing appeared to be at increased odds of reporting a

missed ART dose. Although the mechanisms underlying the observed association between housing and missed ART doses is not clear, it is likely that housing is a proxy of socio-economic status (SES) with women of higher SES being more likely to be residing in formal housing, though data on SES and adherence are mixed [23].

Several limitations need to be considered when interpreting these findings. Data on the primary exposure (delay to ART initiation since first antenatal care visit) and outcome (missed ART doses in the last 30 days) were self-reported by study participants. All interviews were conducted by trained staff, separate from routine care. However, these measures could be susceptible to social desirability bias leading to an overestimation of adherence levels among same-day ART initiators and those who delayed ART initiation and pulling the association towards the null. Nevertheless, the observed high levels of adherence during pregnancy are comparable to similar studies conducted in low- and middle-income countries; with a systematic review of ART use during and after pregnancy reporting three quarters (74%) of the population as being adherent [24-25].

It is also important to note that the reasons for delayed ART initiation were not recorded, and thus it is unclear if the delays in ART initiation were due to participant choice or as a result of clinical indication (i.e. TB diagnosis) identified at the first antenatal care visit. With delays being observed under both PMTCT guidelines, we believe sources of delays were a combination of the two influences, and further research is required to understand how different sources of delays to ART initiation may impact on subsequent adherence, positively or negatively. The study design employed could not control for unknown and unmeasured confounders, which may account for the observed null association. Nonetheless, secondary analyses such as this offers the best available information given randomization control trial are unlikely to be conducted. Finally, the generalizability of these findings should be treated with caution, as ART adherence and patient preparation are likely to be context-specific, and vary with the health service and patient population.

In this analysis, delay to ART initiation after the first antenatal visit was used as a proxy for the time available for patient preparation before starting ART. Although treatment beliefs and knowledge were not included in this analysis, , the results can be interpreted to support a behavioral learning theory (BLT) of medication adherence that sees adherence is a behavior

best learned through practice and not necessarily founded on cognitive variables such as treatment beliefs and knowledge [26]. In addition, it is useful to note that same-day ART initiation in pregnancy can help to maximise the proportion of women starting ART in pregnancy by reaching women who may not have returned to care following their first antenatal visit, helping to close a gap in the PMTCT cascade. Few studies have reported a high proportion of pregnant women being lost to follow-up (LTFU) during the pre-therapy counselling period and therefore receiving no ARVs prior to delivery [27, 28]. Data on this issue are mixed, however, one Malawian study found that pregnant women who were offered ART initiation same-day were five times less likely to return for an ART following visit [16], and further research is clearly required.

This evidence from the context of PMTCT may have important implications for the implementation of universal ART policies for non-pregnant adults [29]. The transition in PMTCT services to providing lifelong treatment to all pregnant women regardless of clinical indication can be viewed as implementation of the “Test and Treat” strategy proposed by Granich et al [30]. The findings here of no difference in missed doses by pre-ART delays, and no observed difference in self-reported missed dose between those diagnosed in the current pregnancy versus previously, provide preliminary suggestions that HIV-infected individuals might accept immediate initiation of lifelong treatment and be adherent to ART even when identified as ART-eligible (and possibly HIV-infected) on the same day. While evidence from PMTCT services should be extrapolated with caution, this possibility is an important avenue for future research.

Given the urgency for timely initiation of ART during pregnancy, randomized controlled trials may be difficult to implement for this scientific question. While secondary analyses such as this may have limitations, they may also represent the best available information.

5. Conclusion

In summary, these findings do not support the hypotheses that delaying ART initiation in pregnancy for patient preparation contributes to improved maternal outcomes. While these results are reassuring for ART programmes implementing immediate ART initiation during pregnancy, and may have implications for the roll-out of universal adult treatment, further research is required to examine long term adherence in care, particularly postpartum.

6. References

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D. APPENDICES

Appendix A: Phase 1 Demographic and Medical History Questionnaire

Phase 1 Demographics & Medical History Questionnaire

MCH-ART: Demographics & Medical History, Phase 1
Xhosa-English of Version 3.0, 15 October 2013

PID: 1 - _____ - _____

		Visit Date: ____/____/____
1.	Mingaphi iminyaka yakho <i>What is your age?</i>	Age: _____ Iminyaka/years
2.	Uloluphi uhlanga <i>What population group do you belong to?</i>	UmAfrika African = 1 Indiya Indian = 2 Umntu webala Coloured = 3 Umlungu White = 4 Olunye = 5, cacisa: _____ <i>Other specify</i>
3.	Uthetha oluphi ulwimi ekhayai? <i>What language do you speak at home?</i>	isiXhosa = 1 isiZulu = 2 isiBhulu Afrikaans = 3 isiNgesi English = 4 Olunye = 5, cacisa: _____ <i>Other specify</i>
4.	Lelephi elona banga liphezulu oliphumeleleyo? <i>What is the highest level of schooling/education that you have completed?</i>	Umgangatho/Grade: _____ Okanye/or Ibanga/ Standard: _____ Imfundo enomsila/ Postsecondary: _____
5.	Ngoku uyasebenza okanye uyafunda <i>Are you currently working and /or studying?</i>	Hayi No = 0 → Gqithela ku Q7 SKIP to Q7 Ewe Yes = 1
6.	Ukuba nguEwe, yeyephi kwezi zilandelayo echaza, bhetele ukuba wenza ntoni? <i>If yes, which of one the following best describes what you do?</i> Khetha ibenye /Choose one only	Ndiphangela isigxina = 1 <i>Employed full-time</i> Ndiphangela mangqaphangqapha = 2 <i>Employed part-time</i> Ndiphangela izingxungxo/ ndingumatheng 'ethengisa = 3 <i>Informal job/hawker</i> Uhamba isikolo/ ungumfundi = 4 <i>Attending school/learner</i> Uhamba isikolo semfundo enomsila = 5 <i>Attending tertiary education facility</i>
7.	Ngowuphi owona mthombo wemali kwikhaya lakho? <i>What is the MAJOR source of income for your household?</i> Khetha ibenye /Choose one only	Ayikho =0 <i>None</i> Umsebenzi osisigxina =1 <i>Full-time employment</i> Umsebenzi wamaangqaoha-ngqapha =2 <i>Part-time employment</i> Umsebenzi wezingxungxo/ umthengisi =3 <i>Informal employment</i> Imali yesibonelelo sokukhuba zeka karhulumente= 4 <i>Disability grant</i> Imali yesibonelelo karhulumente =5 <i>Social grant</i> Umhlala phantsi =6 <i>Pension</i> Olunye imali yesibonelelo =7 <i>Other grant</i> chaza: _____ <i>specify type</i> Olunye =8 <i>Other</i> Chaza: _____ <i>specify</i> Andazi = 9 <i>Don't know</i>

8.	Uhlala kwikhaya elinjani? <i>What kind of home do you live in?</i>	Ityotyombe/ uhlaliso olungahlelwanga = 1 <i>Shack/informal dwelling</i> Indlu yesitena = 2 <i>Formal house</i> Ifleti/ indlu kamaspala = 3 <i>Flat/council home</i> Enye = 4, chaza: _____ <i>Other, specify</i>	
9.	Ingaba indlu yakho inazo ezi zinto zilandelayo: <i>Does your house have the following: Read and answer for all</i>	a. Indlu yangasese <i>A toilet inside</i>	Hayi/No =0 Ewe/Yes =1
		b. Amanzi abalekayo empompo <i>Running water inside</i>	Hayi/No =0 Ewe/Yes =1
		c. Umbane <i>Electricity inside</i>	Hayi/No =0 Ewe/Yes =1
		d. Isikhenkcisi <i>A refrigerator</i>	Hayi/No =0 Ewe/Yes =1
		e. Umnxeba <i>A telephone</i>	Hayi/No =0 Ewe/Yes =1
		f. Umabona kude <i>A television</i>	Hayi/No =0 Ewe/Yes =1
10.	Bangaphi abantu abahlala kule ndlu bedibene nawe(abadala,abancinci)? <i>Including yourself, how many people (adults and children) live in your house?</i>	Inani labantu: _____ <i># of people:</i>	
11.	Bangaphi abadala (iminyaka-16 nangaphezulu)bedibene nawe abahlala kule ndlu? <i>How many adults (aged 16 or older), including you, live in your house?</i>	Inani labadala: _____ <i># of adults</i>	
12.	Bangaphi abantwana (iminyaka -15 nanganeno) abahlala nawe? <i>How many children (aged 15 and under) live in your house?</i>	Inani labantwana: _____ <i># of children</i>	
13.	Ukhulelwe kangaphi (kudibene nesi isisu)? <i>How many times have you been pregnant (including current pregnancy)?</i>	inani lokukhulelwa: _____ <i># of pregnancies:</i>	
14.	Ingaba ubuzama ukuba nosana ngelixesha ufumanisa ukuba ukhulelwe (Kwesi isisu)? <i>Were you trying to have a baby when you found out you were pregnant (in this pregnancy)?</i>	Hayi/No = 0 Ewe/Yes = 1 Andazi/I don't know = 9	
15.	Bangaphi abantwana obazeleyo? <i>How many children have you given birth to?</i>	Inani labantwana: _____ <i># of children</i> Ukuba = 0, Gqithela ku Q20 If 0, SKIP to Q20	
16.	Bangaphi kwaba bantwana abaphilayo? <i>How many of these children are living?</i>	Inani labantwana: _____ <i># of children</i>	
17.	Bangaphi kwaba bantwana abahlala nawe ngoku? <i>How many of these children currently live with you?</i>	Inani labantwana: _____ <i># of children</i>	
18.	Bangaphi kwaba bantwana ekufumaniseke bakho ukuba baphila nentsholongwane? <i>How many of your children have tested HIV-positive?</i>	Inani labantwana abaphila nentsholongwane: _____ <i># of HIV-positive children</i>	
19.	Bangaphi kwaba bantwana baphila nentsholongwane abasaphilayo? <i>How many of these children who have tested HIV- positive are currently living?</i>	Inani labantwana abaphila nentsholongwane abaphilayo ngoku: _____ <i># of HIV-positive children currently alive</i>	

20.	Uya thandana ngoku? <i>Are you currently in a relationship?</i>	Hayi/No = 0 → Gqithela ku Q25 SKIP to Q25 Ewe/Yes = 1
21.	Ungaluchaza njani uthando lwakho? <i>How would you describe your current relationship?</i>	Utshatile = 1 <i>Married</i> Anditshatanga ,ndiya hlalisana =2 <i>Not married, living together</i> Nditshatile, asihlali kunye = 3 <i>Married, not living together</i> Anditshatanga, asihlali kunye = 4 <i>Not married, not living together</i> Enye = 5, cacisa: _____ <i>Other, specify</i>
22.	Lileshe ellingakanani unobudlelwana nalomntu? <i>How long have you been in a relationship with this person?</i>	Ixesha Inyanga Months _____ Duration in: Iminyaka Years _____
23.	Ingaba eli qabane lakho ngutata womnye wabantwana bakho(kunye nalo umkhulelweyo)? <i>Is your current partner the parent of any of your children? (including current pregnancy)</i>	Hayi/No = 0 Ewe/Yes = 1
24.	Ulichazele na iqabane lakho ngesimo sakho sentsholongwane? <i>Have you disclosed your HIV status to your current partner?</i>	Hayi/No = 0 Ewe/Yes = 1
25.	Ubukhe wabelana ngesondo nabanye abantu ingenguye lomntu uthandana naye? <i>In the last 12 months have you had any sexual relationships/sexual partners? (if in a relationship then other than this partner)</i>	Hayi/No = 0 → Gqithela ku Q28 → SKIP to Q 28 Ewe/Yes = 1
26.	Bunjani ubudlelwanebakho namanye amaqabane ngaphandle kweqabane lakho langoku ukuba akhona? <i>What is the nature of your relationship(s)? (other than current partner if applicable)</i> Rhangqa konke okungqamene nawe. <i>Mark all that apply.</i>	a. Umlingane/nditshatile <i>Spouse/ married</i> b. Iqabane lam <i>Boyfriend</i> c. Iqabane lethutyana <i>Casual Partner/One Night Stands</i> d. Omnye ,cacisa: _____ <i>Other, specify</i>
27.	Ubaxelele aba bantu wabelana nabo ngesondo ukuba uphila nentsholongwane? <i>Have you disclosed your HIV status to any of these other sexual partners?</i>	Hayi/No = 0 Ewe/Yes = 1
28.	Ubuqala ukufumanisa ukuba unentsholongwa kagawulayo kolumitho okanye phambi kokuba ukhulelwe? <i>Did you first test HIV positive in this pregnancy or before this pregnancy?</i>	Koku ukukhulelwa =1 → Gqithela ku Q32 <i>In his pregnancy</i> SKIP to Q32 Phambi koku ukukhulelwa =2 <i>Before this pregnancy</i>
29.	Kwakunini ukuqala kwakho ukufumanisa ukuba unentsholongwane kagawulayo? <i>When did you 1st test HIV-positive?</i>	Umhla: ___ Inyanga: ___ Unyaka: ___ Day Month Year
30.	Kwakutheni ukuze oluhlolo lwenziwe? <i>Why was this test conducted?</i>	Ndivavanywe ngelishesha ndikhulelweyo = 1 <i>Tested during pregnancy</i> VCT/Ndandifuna ukuvavanywe =2 <i>VCT/Wanted to be tested</i> Ndafunyaniswa ndinesifo sephepha (TB) = 3 <i>Diagnosed with TB</i> Ndangeniswa esibhedlele = 4 <i>Admitted to the hospital</i> Enye = 5, cacisa: _____ <i>Other, specify</i>

31.	Ingaba wawukhulelwe ukuqala kwakho ukufumane ukuba unentsholongwane kagawulayo? <i>Were you pregnant when you first tested HIV-positive?</i>	Hayi/No = 0 Ewe/Yes = 1
32.	Wakhe wanazo iziphumo ezingena chaphaza kuvavanyo lwentsholongwane kagawulayo? <i>Have you ever tested negative on an HIV test?</i>	Hayi/No = 0 →Gqithela ku Q36 SKIP to Q36 Ewe/Yes = 1
33.	Ugqibele nini ukuba neziphumo ezingenachaphaza zovavanyo lwentsholongwane kagawulayo? <i>When did you last test HIV-negative?</i>	Umhla: ___ Inyanga: ___ Unyaka: ___ Day Month Year
34.	Kwakutheni ukuze uvavanywe ngelo xesha? What was the reason for you doing the HIV test? <i>Why did you test at that time?</i>	Ndivavanywe ngelishesha ndikhulelweyo = 1 <i>Tested during pregnancy</i> VCT/Ndandifuna ukuvavanywe =2 <i>VCT/Wanted to be tested</i> Ndafunyaniswa ndinesifo sephepha (TB) = 3 <i>Diagnosed with TB</i> Ndangeniswa esibhedlele = 4 <i>Admitted to the hospital</i> Enye = 5, cacisa: _____ <i>Other, specify</i>
35.	Wawukhulelwe ngeloxesha uvavanyelwa intsholongwane? <i>Were you pregnant at the time of that test?</i>	Hayi/No = 0 Ewe/Yes = 1
36.	Wakhe waxelela nabanina ukuba unentsholongwane kagawulayo? <i>Have you told anyone that you are HIV-positive?</i>	Hayi/No = 0 →Gqithela ku Q39 SKIP to Q39 Ewe/Yes = 1
37.	Ngawaphi amlungu osapho lwakho owaxeleleyo ngesimo sakho sentsholongwane? <i>Which of your family members have you told about your HIV status?</i> Nceda phendula lombuzo ngelungu ngalinye losapho oludweliswe ngezantsi. <i>Please answer this question for each of the family members listed below.</i> Wamxelele u_____ ukuba unentsholongwane kagawulayo? <i>Have you told your _____ that you are HIV positive?</i>	
a.	Umyeni/iqabane <i>Husband/partner/boyfriend</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
b.	Umama <i>Mother</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
c.	Utata <i>Father</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
d.	Udade <i>Sister</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
e.	Umtakwenu <i>Brother</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
f.	Intombi <i>Daughter</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
g.	Unyana <i>Son</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
h.	Umalume <i>Uncle</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
i.	U-anti <i>Aunt</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9

j.	Umza wesikhomo <i>Male cousin</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
k.	Umza wesikhomokazi <i>Female cousin</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
l.	Enye indoda yalapha <i>Other male family member</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
m.	Esinye isikhomokazi <i>Other female family member</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
38.	Ngaphandle kwabantu bakowenu aba badweliswe ngentla, ngubani omnye umntu owamxelelyo ukuba uphila nentsholongwane? (funda uphendule yonke imibuzo) <i>Aside from family members listed above, who else have you told about your HIV status? (read and answer for all)</i>	
a.	Amanesi/ogqira <i>Health professionals</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
b.	Iqumru lenxaso labantu abaphila nentsholongwane <i>Support group</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
c.	Umntu owabelana naye ngesondo ongahlali naye <i>A sexual partner who does not live with you</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
d.	Isihlobo <i>Friends</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
e.	Inkokheli ngokwa kwamoya <i>Spiritual leader</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
f.	Umntu okuqashileyo/wayekuqashile <i>Current or former employer</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
g.	Ukuchaza esidlangaleni <i>Public disclosure/ community</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
h.	Abanye, chaza: _____ <i>Other, specify</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
39.	Wakhe wakhulelwa phambi koku ukukhulelwa? <i>Have you ever been pregnant before this pregnancy?</i>	Hayi/No = 0 → Gqithela ku Q45 <i>SKIP to Q45</i> Ewe/Yes = 1
40.	Ngokuya ubukhulelwe ngaphambi koku ukukhulelwa wawuke wanikwa amayeza okhusela usana lungosuleleki yintsholongwane (ezeku khusela umntwana hayi amachiza okutho malalisa intsholongwane wobomi bonke) <i>When you were pregnant before this pregnancy have you ever been given medication at the clinic to keep your baby from getting HIV infected? (prophylaxis NOT lifelong ART)</i>	Hayi/No = 0 → Gqithela ku Q45 <i>SKIP to Q45</i> Ewe/Yes = 1
41.	Ukuba nguEwe, zingaphi izisu ufumane la machiza ngesisizathu? <i>If yes, during how many pregnancies have you received medication for this purpose?</i>	Inani lezisu: _____ <i># of pregnancies</i>

42.	Kwezi zisu siyi _____ ofumene kuzo amachiza, zingaphi izisu otye kuzo iipilisi ngelishesha ubelekayo qha? <i>For the _____ pregnancies that you received medication, For how many pregnancies did you take pills while you were pregnant and for how many pregnancies did you take pills only at delivery?</i>	Ngoku wawubeleka <i>Only at Delivery (Nevirapine) #:</i> _____ Ngelishesha ukhulelwe <i>While you were pregnant (AZT)? #:</i> _____
43.	Bekunini ukugqibela kwakho ukufumana la machiza ngesisizathu? <i>When was the last time that you received medication for this purpose?</i>	Umhla: _____ Inyanga: _____ Unyaka: _____ Day Month Year
44.	Uwafumene phi la machiza ukugqibela kwakho? <i>Where did you receive the medication the last time?</i>	Igama lekliniki: _____ <i>Name of clinic:</i>
45.	Wawuke wawathatha amachiza okuthomalalisa intsholongwane (awobomi bakho bonke) <i>Have you ever taken triple drug antiretroviral therapy (lifelong ART)?</i>	Hayi/No = 0 → Skip to Q51 Ewe/Yes = 1
46.	Ukuba nguEwe, ingaba wawafumana amachiza okuthomalalisa intsholongwane ukugqibela kakho? <i>If yes, where did you receive ART the last time?</i>	Igama lekliniki: _____ <i>Name of clinic:</i>
47.	Uqale nini ukutya la machiza okuthomalalisa intsholongwane kagawulayo? <i>When did you start taking ART?</i>	Umhla: _____ Inyanga: _____ Unyaka: _____ Day Month Year
48.	Usawatya amachiza okuthomalalisa intsholongwane kagawulayo? <i>Are you still on ART?</i>	Hayi/No = 0 Ewe/Yes = 1 → SKIP to Q51
49.	Ukuba nguHayi, uyeke nini ukuwatya amachiza okuthomalalisa intsholongwane kagawulayo? <i>If No, when did you stop taking ART?</i>	Umhla: _____ Inyanga: _____ Unyaka: _____ Day Month Year

50.	<p>Uyekele ntoni ukutya amachiza athomalalisa intsholongwane? Why did you stop taking ART? (rhagqa zonke ezibhekisa kuwe) Circle all that apply</p>	<p>a. Ndaphelelwa ngumchiza andaya ukuyakuwalanda <i>I ran out of medicine and didn't go for refills</i> b. Anencasa embi <i>The medicine tastes bad</i> c. Ndulibala <i>I just forgot</i> d. Bendikhathazwa yimiphumela yawo <i>I was worried about the side effects</i> e. Bendingafuni abanye bandiqaphele ukuba nditya amachiza <i>I did not want others to notice me taking the medicine</i> f. Ndandigula <i>I was ill</i> g. Ndacinga ukuba andisawafuni nganto <i>Didn't think I needed it anymore</i> h. Bendinginga ndingahlala ndiphilile ngaphandle kwawo <i>Can stay healthy without it</i> i. Bendinginga ukuba lamayeza anganobu ngozi kum. <i>I felt the medicine might be harmful to me</i> j. Ndizive ndinoxinizelelo <i>I felt depressed</i> k. Ndandiphilile <i>I was well</i> l. Ebemaninzi la machiza ekufuneka ndiwathathe <i>There was too much medicine to take</i> m. Bendingekho ekhaya <i>I was away from home</i> n. Bendixakekile zezinye izinto <i>I was busy with other things</i> o. Ndiye ndafunda ukuba zikho ezinye iindlela endinganyanga okanye ndiphilise intsholongwane kagawulayo <i>I learned that there are other ways to treat or cure HIV</i> p. Enye, cacisa: _____ <i>Other, Specify</i></p>
51.	<p>Ubukhe watshaya isigarethi kulenyanga iphelileyo? Did you smoke cigarettes in the last month?</p>	<p>Hayi No = 0 → END Ewe Yes = 1</p>
52.	<p>Utshaya isigarethi ezingaphi ngemini? How many cigarettes do you smoke in a day?</p>	<p># _____ cigarettes</p>

Date completed: __/__/____ Signed counsellor completing CRF: _____

Date of QC: __/__/____ Signed measurement nurse: _____

Appendix B: Phase 2 Demographic and Medical History Questionnaire

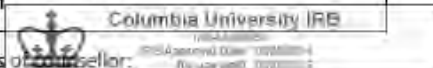
MCH-ART: Demographics & Medical History, Phase 2 1st visit
Xhosa-English Version 2.5.1, 04 Feb 2013

PID: 2 - _____

Visit Date: ____/____/____	
Phambi kokuba uphendule uyacelwa ugqibezele iinkcukacha apho unokufunyanwa khona xa ufunwa. <i>Before completing this questionnaire please remember to complete the locator information form.</i>	
Siza kubuza imibuzo embalwa <i>We are now going to ask you a few questions:</i>	
1. Uze njani ekloniki namhlanje? <i>How did you get to the clinic today?</i>	Uqeshe imoto = 1 <i>Hired car</i> Uze ngemoto yakho=2 <i>My own car</i> Uze ngetaxi=3 <i>Taxi</i> Ngebhasi=4 <i>Bus</i> Ngenyawo=5 <i>Walk</i> Olunye =6, cacisa: _____ <i>Other, specify</i>
2. Uthathe ixesha elingakanani ukuza ekloniki namhlanje? <i>How long did it take you to get to the clinic today?</i>	Imizuzu/Minutes: _____ Iyure/Hours: _____
3. Uhlawule malini ngesithuthi? <i>How much did you pay for transport?</i>	Rand: _____
4. Uthathe ixesha emsebenzini ukuza apha? <i>Did you take time off of work to come here?</i>	Hayi/No = 0 Ewe/Yes = 1
5. Kuye kwafuneka wenze isivumelwano nabantu bajonge umntwana/abantwana? <i>Did you have to make special arrangements for people to watch your child/children?</i>	Hayi No = 0 → Gqithela ku Q7 <i>SKIP to Q7</i> Ewe Yes = 1 Andinabantwana = 2 → Gqithela ku Q7 <i>Don't have any children SKIP to Q7</i>
6. Kuye kwafuneka uhlawule umntu oza kujonga usana ngelifxesha uze ekloniki? <i>Did you pay someone to watch your child so you could come to the clinic?</i>	Hayi/No = 0 Ewe/Yes = 1
7. Usakhulelwe? <i>Are you still pregnant?</i>	Hayi/No = 0 → END contact SC to complete termination <i>CRF</i> Ewe/Yes = 1
8. Uneveki ezingaphi ukhulelwe? <i>How many weeks pregnant are you?</i>	Iiveki/Weeks: _____ okanye/or Iinyanga/Months: _____
9. Kolu umitho ingaba, ugqira okanye unesi uthe une-TB? <i>During your current pregnancy, has a doctor or nurse told you that you have TB?</i>	Hayi No = 0 → Gqithela ku Q14 <i>SKIP to Q14</i> Ewe Yes = 1
10. Uxelelwe nini ngoku kugula? <i>When did you receive this diagnosis?</i>	Umhla: _____ Inyanga: _____ Unyaka: _____ Day Month Year
11. Uxelelwe phi ngoku kugula? <i>Where did you receive this diagnosis?</i>	Igama lekloniki : _____ <i>Name of clinic</i>
12. Iphi emzimbeni wakho le TB? <i>Where in your body was the TB (eg, lungs, other location)?</i>	Indawo emzimbeni : _____ <i>Place in body</i>
13. Uye wafumana unyango lwayo? <i>Did you receive treatment for TB?</i>	Hayi/No = 0 Ewe/Yes = 1
14. Ngaphandle koku kukhulelwa, ugqira okanye unesi bakhe bakuxelela ukuba une-TB? <i>Other than during this pregnancy has a doctor or nurse ever told you that you have TB?</i>	Hayi No = 0 → Gqithela ku Q20 <i>SKIP to Q20</i> Ewe Yes = 1

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Initials



15.	Waxeelwa nini ngoku kugula kuqala ingekuko ngoku ukhulelwe? <i>When did you receive this diagnosis the last time (not during this pregnancy)?</i>	Umhla: _____ Inyanga: _____ Unyaka: _____ Day Month Year		
16.	Waye walufumana unyango ngoko? <i>Did you receive treatment for TB the last time?</i>	Hayi/No = 0 Ewe/Yes = 1		
17.	Kungamaxesha amangaphi ewonke ufumana unyango lweTB? <i>How many times in total have you been treated for TB?</i>	Amaxesha: _____ # of times Ukuba ngu-0 Gqithela ku Q20/if 0, SKIP to Q20		
18.	Walufumana phi unyango lwe TB? <i>Where did you receive your TB treatment?</i>	Igama lekliniki : _____ Name of clinic		
19.	Lixesha elingakanani ufumana unyango lweTB ukugqibela kwakho ukunyangelwa yona? <i>How long did you receive treatment for TB the last time you were treated for TB?</i>	6 nyanga=1 6 months 8 nyanga=2 8 months 9 nyanga=3 9 months Iyaqhubekeka=4 On-going Amanye=5, cacisa: _____ Other, specify Andazi=9 Don't know		
20.	Wakhe whacitha ubusuku esibhedlele? <i>Have you ever spent the night in hospital?</i>	Hayi No = 0 → Gqithela ku Q22 SKIP to Q22 Ewe Yes = 1		
21.	Ukuba nguEwe, cacisa ngezantsi ulaliso ngalunye <i>If yes, list details for each admission below:</i>			
	a. Isizathu <i>Reason for admission</i>	b. Ulaliswe nini? <i>Date of Admission</i>	c. Isibhedlele/kliniiki <i>Hospital/ Clinic</i>	d. Wawukhulelwe <i>Were you pregnant at the time of this admission?</i>
i.		Umhla: _____ Inyanga: _____ Unyaka: _____ Day Month Year		Hayi/No = 0 Ewe/Yes = 1
ii.		Umhla: _____ Inyanga: _____ Unyaka: _____ Day Month Year		Hayi/No = 0 Ewe/Yes = 1
iii.		Umhla: _____ Inyanga: _____ Unyaka: _____ Day Month Year		Hayi/No = 0 Ewe/Yes = 1
iv.		Umhla: _____ Inyanga: _____ Unyaka: _____ Day Month Year		Hayi/No = 0 Ewe/Yes = 1
v.		Umhla: _____ Inyanga: _____ Unyaka: _____ Day Month Year		Hayi/No = 0 Ewe/Yes = 1

22.	Ukugqibela kwethu ukuthetha nawe, ukhe wathunyelwa kwesinye isibhedlele kuba uguliswa kukukhulelwa (Mowbray, okanye Groote Schuur) <i>Since we last spoke to you, have you been referred to any other health facility for pregnancy-related care (eg, Mowbray or Groote Schuur)?</i>	Hayi/No = 0 → Gqithela ku Q23 SKIP to Q23 Ewe/Yes = 1		
a.	Ubuthunyelwe phi? <i>Where were you referred?</i>	Igama lendawo: _____ <i>Location</i>		
b.	Wawusithini umhla wokuthunyelwa kwakho? <i>What was the date of the referral?</i>	Umhla: _____ Inyanga: _____ Unyaka: _____ <i>Day Month Year</i>		
c.	Yintoni isizathu sokuthunyelwa kwakho? <i>What was the reason for the referral?</i>	Isizathu: <i>Reason</i>		
d.	Ingaba wafumana unyango olutsha/ amayeza? <i>Did you receive any new treatment or medications as a result of this referral?</i>	Hayi/No = 0 Ewe/Yes = 1 Ukuba nguEwe, cacisa: _____ <i>If Yes, specify</i>		
23.	Ukugqibela kwethu ukuthethanawe uye wathunyelwa kwesinye isibhedlele ngenxayokugula (Jooste, Groote Schuur) <i>Since we last spoke to you, have you been referred to any other health facility for other medical care (eg, GF Jooste or Groote Schuur)?</i>	Hayi/No = 0 → Gqithela ku Q24 SKIP to Q24 Ewe/Yes = 1		
a.	Ubuthunyelwe phi? <i>Where were you referred?</i>	Igama lendawo: _____ <i>Location</i>		
b.	Wawusithini umhla wokuthunyelwa kwakho? <i>What was the date of the referral?</i>	Umhla: _____ Inyanga: _____ Unyaka: _____ <i>Day Month Year</i>		
c.	Yintoni isizathu sokuthunyelwa kwakho? <i>What was the reason for the referral?</i>	Isizathu: <i>Reason</i>		
d.	Ingaba wafumana unyango olutsha/ amayeza? <i>Did you receive any new treatment or medications as a result of this referral?</i>	Hayi/No = 0 Ewe/Yes = 1 Ukuba nguEwe, cacisa: _____ <i>If Yes, specify</i>		
24.	Wakhe waxelela nabanina ukuba unentsholongwane kagawulayo? <i>Have you told anyone that you are HIV-positive?</i>	Hayi/No = 0 Ewe/Yes = 1		
25.	Nceda phendula lombuzo ngelungu ngalinye losapho oludweliswe ngezantsi. <i>Please answer this question for each of the family members listed below.</i>	i. Bahlala nawe? <i>Do they live with you?</i> If NA, do not answer b and c for that person	ii. Bayayazi na ukuba uphila nentsholongwane? <i>Do they know you are HIV positive?</i>	iii. Bayayazi na ukuba utya iARVs? <i>Do they know if you are taking ARVs?</i>
a.	Umyeni/iqabane <i>Husband/partner/boyfriend</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9	Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
b.	Umama <i>Mother</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9	Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
c.	Utata <i>Father</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9	Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
d.	Udade <i>Sister</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9	Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1

e.	Umtakwenu <i>Brother</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9	Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
f.	Intombi <i>Daughter</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9	Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
g.	Unyana <i>Son</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9	Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
h.	Umalume <i>Uncle</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9	Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
i.	U-anti <i>Aunt</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9	Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
j.	Umza wesikhomo <i>Male cousin</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9	Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
k.	Umza wesikhomokazi <i>Female cousin</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9	Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
l.	Enye indoda yalapha efemelini <i>Other male family member</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9	Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
m.	Esinye isikhomokazi se femili <i>Other female family member</i>	Hayi/No = 0 Ewe/Yes = 1 N/A = 9	Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
26.	Ngaphandle kwabantu bakowenu aba badweliswe ngentla, ngubani omnye umntu owamxalelyo ukuba uphila nentsholongwane?(funda uphendule yonke imibuzo) <i>Aside from family members listed above, who else have you told about your HIV status? (read and answer for all)</i>		i. Bayayazi na ukuba uphila nentsholongwane ? <i>Do they know you are HIV positive?</i>	ii. Bayayazi na ukuba utya iARVs? <i>Do they know if you are taking ARVs?</i>
a.	Amanesi/ogqira <i>Health professionals</i>		Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
b.	Iqumru lenxaso labantu abaphila nentsholongwane <i>Support group</i>		Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
c.	Umntu owabelana naye ngesondo ongahlali naye <i>A sexual partner who does not live with you</i>		Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
d.	Isihlobo <i>Friends</i>		Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
e.	Inkokheli ngokwa kwamoya <i>Spiritual leader</i>		Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
f.	Umntu okuqashileyo/wayekuqashile <i>Current or former employer</i>		Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
g.	Ukuchaza esidlangaleni <i>Public disclosure/ community</i>		Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9
h.	Abanye, chaza: _____ <i>Other, specify</i>		Hayi/No = 0 Ewe/Yes = 1	Hayi/No = 0 Ewe/Yes = 1 N/A = 9

27.	Ukugqibela kwethu ukuthetha kuye kwakho utshintsho phakathi kwakho nomyeni/iqabane? <i>Since we last spoke to you, have there been any changes in your relationship with your husband or partner?</i>	Hayi/No = 0 → Gqithela ku Q33 SKIP to Q33 Ewe/Yes = 1
28.	Ukuba nguEwe, yintoni ethe yatshintsha kokuthandana <i>If Yes, what has changed in your relationship since we last spoke?</i>	
<i>If participant reports that there have been changes in relationship, complete the following questions (Q29-32) with updated information.</i>		
29.	Unomntu omtsha othandana naye? <i>Are you currently in a new relationship?</i>	Hayi/No = 0 → Gqithela ku Q33 SKIP to Q33 Ewe/Yes = 1
30.	Loo mntu umtsha uthandana naye uhlala nawe <i>Is your new partner living with you?</i>	Hayi/No = 0 Ewe/Yes = 1
31.	Uyathandana /wabelana ngesondo nabanye abantu ngaphandle kwalo mntu mtsha? <i>Do you have relationships/sexual partners with people other than this new partner?</i>	Hayi/No = 0 → Gqithela ku Q33 SKIP to Q33 Ewe/Yes = 1
32.	Sinjani isimo sobunye ubuhlobo bakho? <i>What is the nature of your other relationship(s)?</i> Rhangqa konke okungqamene nawe. <i>Mark all that apply.</i>	a. Umlingane/nditshatile <i>Spouse/ married</i> b. Iqabane lam <i>Boyfriend</i> c. Iqabane lethutyana <i>Casual Partner/One Night Stands</i> d. Omnye ,cacisa: _____ <i>Other, specify</i>
33.	Emva kokugqibela kwethu ukuthetha ,ukhe watya iAZT? <i>Since we last spoke to you, have you taken any AZT?</i>	Hayi/No = 0 → Gqithela ku Q34 SKIP to Q34 Ewe/Yes = 1
a.	Uyifumana phi i-AZT? <i>From where did you receive this AZT?</i>	Indawo: _____ <i>Location</i>
b.	Uqale nini ukuyifumana? <i>On what date did you start taking the AZT?</i>	Umhla: _____ Inyanga: _____ Unyaka: _____ <i>Day Month Year</i>
c.	Ugqibele nini ukuyitya? <i>When did you last take AZT?</i>	Umhla: _____ Inyanga: _____ Unyaka: _____ <i>Day Month Year</i>
34.	Ubukhe watya iART koku ukukhulelwa? <i>Have you taken ART at all during this pregnancy?</i>	Hayi/No = 0 Ewe/Yes = 1 → SKIP to Q36
35.	Ukuba hayi ,ukhe wabonana nogqira /unesi kwikliniki enikeza nge ART emva kokuba sithethile okukugqibela? <i>If No, have you seen a doctor or nurse at the ART clinic since we last spoke to you?</i>	Hayi/No = 0 Ewe/Yes = 1 → Gqithela ku Q35b SKIP to Q35b
a.	Ukuba hayi ,kutheni? <i>If No, why not?</i>	Isizathu: <i>Reason</i> Gqithela ku Q38 SKIP to Q38
b.	Ukuba ewe, uye kweyiphi ikliniki? <i>If Yes, where did you go?</i>	Igama lekliniki: _____ <i>Clinic name</i>
c.	Ugqibele nini ukuya? <i>When did you last go?</i>	Umhla: _____ Inyanga: _____ Unyaka: _____ <i>Day Month Year</i>
d.	Uye amaxesha amangaphi sagqibela ukuthetha? <i>How many times have you been since we last spoke to you?</i>	Amaxesha: _____ <i># of times</i> Gqithela ku Q38 SKIP to Q38

36.	Ukuba utya iART, uqale ukuwatya emva kokuba sigqibele ukuthetha? <i>If you have taken ART, did you start taking ART since the time that we last spoke to you?</i>	Hayi/No = 0 → Gqithela ku Q37 SKIP to Q37 Ewe/Yes = 1
a.	Ukuba ewe, uqale ngawuphi umhla? <i>If Yes, what day did you start?</i>	Umhla: _____ Inyanga: _____ Unyaka: _____ Day Month Year
b.	Uqale phi? <i>Where did you start?</i>	Igama lekliniki: _____ Clinic name
37.	Loluphi usuku ukugqibela kwakho ukutya iART? <i>When was the last day you took ART?</i>	Umhla: _____ Inyanga: _____ Unyaka: _____ Day Month Year
a.	Ukhe wawutya iART akho kwezi ntsuku zi-7 zidlulileyo? <i>Have you taken ART at all in the last 7 days?</i>	Hayi/No = 0 Ewe/Yes = 1 → Gqithela ku Q38 SKIP to Q38
b.	Ukuba hayi, kutheni? <i>If No, why not?</i>	Isizathu: Reason
38.	Ekugqibeleni kwethu ukuthetha, ubukhe wathetha nekhawunsela ekliniki ngokutya iART? <i>Regardless of whether or not you have taken ART: Since we last spoke to you have you spoken to a counsellor at the clinic/ hospital about taking ART?</i>	Hayi/No = 0 → Phela apha/END Ewe/Yes = 1
a.	Ukuba ewe, uye phi? <i>If Yes, where did you go?</i>	Igama lekliniki: _____ Clinic name
b.	Emva kokuba sithethile nawe, ukhawunselwe kangaphi? <i>Since we last spoke to you how many times have you been counselled?</i>	Amaxesha: _____ # of times
c.	Uye wathetha nabani ngoku ubukhawunselwa? <i>Who did you speak to during this counselling?</i>	
d.	Ngoku ubukhawunselwa niye nathetha ngantono? <i>What did you talk about during this counselling?</i>	



Date completed: ____ / ____ / ____

Signed counsellor completing CRF: _____

Date of QC: ____ / ____ / ____

Signed measurement nurse: _____

Appendix C: University of Cape Town 2015/2016 Protocol Approval (MCH-ART)

 <p>UNIVERSITY OF CAPE TOWN UNIVERSITEIT VAN KAPSTAD</p>	<p>HUMAN RESEARCH FACULTY OF HEALTH SCIENCES Human Research Ethics Committee</p> <p style="font-size: 1.2em; font-weight: bold;">6 OCT 2015</p> 	
FHS016: Annual Progress Report / Renewal		
<p>HREC office use only (FWA00001637; IRB00001938)</p> <p>This serves as notification of annual approval, including any documentation described below.</p>		
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until/next renewal date 20.10.2016
<input type="checkbox"/> Not approved	See attached comments	
Signature Chairperson of the HREC	Signed	Date Signed 7/11/2015
Comments to PI from the HREC		
<p>Principal Investigator to complete the following:</p> <p>1. Protocol information</p>		
Date (when submitting this form)	23 SEP 2015	
HREC REF Number	451/2012	Current Ethics Approval was granted until 30 OCT 2014
Protocol title	Strategies to optimize antiretroviral therapy services for maternal & child health: the MCH-ART study	
Protocol number (if applicable)	N/A	
Are there any sub-studies linked to this study?	<input checked="" type="checkbox"/> YES	
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.	<p>HREC REF 194/2013 Estimation of delivery dates using obstetric ultrasound in the MCH-ART study</p> <p>HREC REF 550/2015 Childbearing, family planning and relationships among women living with HIV in Gugulethu, Cape Town.</p>	
Principal Investigator	Prof Landon Myer	
Department / Office Internal Mail Address	CIDER, School of Public Health and Family Medicine, Faculty of Health Sciences	
1.1 Does this protocol receive US Federal funding?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
<p>23 July 2014 Page 1 of 9 FHS016</p> <p>(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)</p>		

Appendix D: University of Columbia 2015/2016 Protocol Approval (MCH-ART study)

-----Original Message-----

From: Rascal IRB Notice [mailto:no-reply-rascal@columbia.edu]

Sent: Tuesday, May 19, 2015 10:32 PM

To: Allison Buba

Subject: Rascal IRB-AAAK8059 Status Notification From: Rascal IRB Notice
[mailto:rascal@columbia.edu] Sent: 05/19/2015 at 22:31 To:

Title: Strategies to optimize antiretroviral therapy services for maternal & child health:
the MCH-ART study

PI: Elaine Abrams

This is a courtesy email from RASCAL.

Your IRB-IRB-AAAK8059 has been approved by the IRB. DO NOT START any human subjects research until you have received and reviewed the correspondence in RASCAL or the IRB approval letter indicating that the study has been approved. It is important that any conditions or restrictions on the approval are addressed prior to starting research with human subjects.

You will receive detailed information from the IRB about this action in the next several (average 3) business days, via the RASCAL Correspondence function.

YOU ARE RESPONSIBLE for accessing the correspondence when it arrives and abiding by the terms stated therein.

Please do not 'reply' to this email. Communication related to your protocol must be done within Rascal, via the Correspondence function (specifically, through the "add correspondence" link).

If you have any technical questions please call the RASCAL Help Line.

If you have any other questions, please call your IRB office.

RASCAL Help Line [212.851.0213](tel:212.851.0213)
Research Administration System
Columbia University

Appendix E: Phase 1 Informed Consent Form (MCH-ART study)

Informed Consent #1 (Phase 1 study participation)

Phase 1 Informed Consent Form

TITLE OF RESEARCH: Strategies to optimize antiretroviral therapy services for maternal & child health: the MCH-ART study

WHAT IS THE PURPOSE OF THIS STUDY?

We are from the University of Cape Town and ICAP at Columbia University. You are being asked to take part in a study that is being conducted at the Gugulethu Midwife Obstetric Unit (MOU). The purpose of this study is to understand how to improve health care services for HIV-positive women during their pregnancy and after they deliver the baby.

We know that it is important for their own health as well as the health of their baby, that HIV-positive women receive the HIV care and treatment that they need both during and after delivery. Information learned in this study will help us to improve HIV services for pregnant women.

You are being asked to take part in this study because you are a pregnant woman who is HIV-positive and you are getting your pregnancy care here at the Gugulethu MOU. The purpose of this consent is to give you information to help you decide if you want to take part in this study.

WHAT DO I HAVE TO DO IF I AGREE TO TAKE PART?

If you agree to take part, you will do the following at today's visit:

- Answer questions about your household, medical history, partnership status, HIV testing history and disclosure status, family planning and previous use of HIV drugs
 - If you are currently taking HIV drugs, we will ask you additional questions about HIV and HIV drugs (including side effects and adherence).
- Have 5mLs (1 teaspoon) of blood drawn from your arm)

NOTE: The blood that is drawn today will be stored and used to check your viral load (this is the amount of HIV in your blood) at a later time. Results from these tests will **not** be available to you, the clinic, or the study staff. When the health care providers at the clinic need to check your viral load, they will take a separate blood specimen. When it is stored, your blood and test results will not have your name or any other way of identifying you attached to it.

Review of medical records

As part of this study, we will also be looking at and taking information from your antenatal, obstetric, ART clinic, laboratory and pharmacy records. From these records, we are interested in learning about the pregnancy care you received as well as information about your delivery. We also want to learn about the HIV care and treatment that you received during your pregnancy and after you delivered. Finally, we want to learn about your baby's health status after delivery as well.

All data that we review and abstract is confidential and no participant names are recorded on study documents.

Contact for future study

After the completion of this visit, it is possible that we will contact you again at your next clinic visit or at another time in the future to take part in additional research studies. At that time, you would be asked to review and sign another consent form. You can choose to not take part in any future studies if you are asked. You will be asked to provide contact information so that we may get in touch with you regarding additional research studies. Study staff will talk with you about the best way to contact you.

WHAT ARE THE POTENTIAL RISKS?

If you decide to participate, you may feel uncomfortable about some of the personal questions you are asked about your health or your pregnancy. You may refuse to answer any question that you do not want to answer. There is some risk in sharing personal and medical information. We will be careful to keep all your information as private as possible.

Drawing blood is normally done as part of routine medical care and presents a slight risk of discomfort. Experienced staff will draw blood under sterile conditions in order to protect you against these risks.

WHAT ARE THE POTENTIAL BENEFITS?

There is no direct benefit to you if you take part in this study but if we identify any health care problem during the course of the study, we will make sure you are referred to the appropriate health care services. The information gained in this study may help to improve ART services for HIV-infected pregnant women in Cape Town, the Western Cape Province, and across South Africa.

WHAT ARE THE ALTERNATIVES TO TAKING PART?

The alternative to taking part in this study is to continue with your usual care at the MOU.

WHAT ABOUT CONFIDENTIALITY?

If you agree to take part, all information collected during the study will be kept strictly confidential. Your name will not be written on the study forms and will not be used in connection with any information or lab specimens that are collected as part of the study.

All study materials will be stored in locked filing cabinets. Only study staff and personnel involved in routine audits will have access to these materials. All staff involved in data collection and management will get specific training in confidentiality.

Even with these procedures in place, if the study staff learns that you are a risk to yourself or someone else or of possible child abuse and/or neglect, study staff will tell the proper authorities.

WILL I BE GIVEN ANYTHING FOR TAKING PART?

No, there is no compensation for taking part in the study today.

ARE THERE ANY COSTS?

There is no cost for being in this study.

CAN I LEAVE THE STUDY?

You have the right to decide not to take part in the study, to refuse to answer any questions, or to withdraw from the study at any time without any penalty. It will have no effect on the care that you receive at the Gugulethu MOU or any other health facility.

FUTURE USE OF SPECIMENS:

Phase 1 Informed Consent Form

If you agree, any leftover blood from the sample you have provided for this research project may be used for future HIV related research. It is possible that these stored samples may be tested to see if the HIV in your blood is resistant to any types of HIV medications or to look at other questions related to HIV.

At this time, we cannot provide details of when this testing may be conducted. However, additional testing will not be done using these stored samples without the approval of the appropriate ethics committees involved in this research.

If you agree to let us keep your stored samples for future research, they may be kept in a locked freezer for up to 5 years. If we do use your samples in the future, your name or other identifiers will not be included with this information (as with the rest of the information we collect for this study).

Please initial below to indicate whether or not you give permission for your specimens to be used for future research. You may still remain in the study, no matter which you choose.

_____ (initial) I agree to have my blood stored for future research.

_____ (initial) I agree to have my blood stored for future research related to this study ONLY.

_____ (initial) I do NOT agree to the storage of my blood for future research.

DO YOU HAVE ANY QUESTIONS?

If there is anything that is unclear or if you need further information, please ask us and we will provide it.

Do you have any questions?

FOR ADDITIONAL INFORMATION:

If you have any questions or have any problems while taking part in this research study, you should contact:

Dr Landon Myer
School of Public Health and Family Medicine
Faculty of Health Sciences, University of
Cape Town
Tel: 021 406 6661
Email: Landon.Myer@uct.ac.za

Dr Elaine Abrams
ICAP, Columbia University
Mailman School of Public Health
College of Physicians and Surgeons
Tel: +1 212 342 0543
Email: ejal@columbia.edu

If you have any questions about your rights as a research participant, you may contact the following member of the ethics committee:

Prof Marc Blockman
Chair, Human Research Ethics Committee
Faculty of Health Sciences, University of Cape

Columbia University Medical Center IRB
Tel: +1 212 305 5883

Phase 1 Informed Consent Form

Town
Tel: 021 406 6338

CONSENT STATEMENT:

I have read this form, or someone has read it to me. I have been offered a copy of this consent form. I was encouraged and given time to ask questions. I agree to be in this study. I know that after choosing to be in this study, I may withdraw at any time. My being in the study is voluntary. I understand that whether or not I participate will not affect my health care services received today, or at any time in the future.

Please indicate your consent with your signature.

Volunteer's name _____

Signature of Volunteer e Date

Staff member's name _____

Signature of study staff Date

If the volunteer is unable to read or write the entire counselling process must be observed by an independent witness who can then confirm the procedure once the she has given consent.

Fingerprint of volunteer:

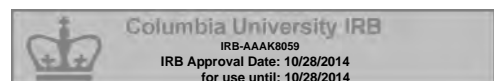
Witness:

I confirm that I am independent of the study and that I witnessed the entire informed consent counselling process in the home language of the volunteer

Witness's name _____

Signature of witness Date

Thank you.



Appendix F: Phase 2 Informed Consent Form (MCH-ART study)

Informed Consent #2 (Phase 2 study participation)

Phase 2 Informed Consent Form

TITLE OF RESEARCH: Strategies to optimize antiretroviral therapy services for maternal & child health: the MCH-ART study

WHAT IS THE PURPOSE OF THIS STUDY?

We are from the University of Cape Town and ICAP at Columbia University. You are being asked to take part in a study that is being conducted at the Gugulethu Midwife Obstetric Unit (MOU). The purpose of this study is to understand how to improve health care services for HIV-positive women during their pregnancy and after they deliver the baby.

We know that it is important for their own health as well as the health of their baby, that HIV-positive women receive the HIV care and treatment that they need both during and after delivery. Information learned in this study will help us to improve HIV services for pregnant women.

You are being asked to take part in this study because you are a pregnant woman with known HIV infection who is about to start taking HIV drugs (antiretroviral therapy) and you took part in the first phase of the study. The purpose of this consent form is to give you information to help you decide if you want to take part in the next phase of this study.

WHAT DO I HAVE TO DO IF I AGREE TO TAKE PART?

If you agree to take part, you will come in for up to 3 visits. These visits will take place today while you are in the clinic, when you are getting close to delivering your baby and within one week of delivering your baby. These study visits are separate from the usual clinic visits that you will have for your pregnancy and HIV care. Study visits will be timed so that they take place on the same days that you come in for your usual pregnancy and/or HIV care. Each visit will take about 30-45 minutes.

At the two visits that are conducted *while you are pregnant*, you will do the following:

- Answer questions about your recent pregnancy- and HIV-related health care, HIV disclosure, and use of HIV drugs (including side effects and adherence).
 - At different visits, we will ask you additional questions about HIV, stigma, social support, infant feeding practices, family planning, experiences of partner violence, and mental health (including drug and alcohol use).
- Have 5mLs (1 teaspoon) of blood drawn from your arm each time

One-week after delivery

One week after you give birth to your baby, you will come to the clinic for a visit that will include the following:

- Answer questions about your recent pregnancy- and HIV-related health care, HIV disclosure, and use of HIV drugs (including side effects and adherence).
 - At this visit, we will ask you additional questions about family planning after delivery, how you felt about the HIV care that you received, infant feeding practices and infant health and health care.
- Have 5mLs (1 teaspoon) of blood drawn from your arm

Phase 2 Informed Consent Form

NOTE: The blood that is drawn today will be stored and used to check your viral load (this is the amount of HIV in your blood) at a later time. Results from these tests will not be available to you, the clinic, or the study staff. When the health care providers at the clinic need to check your viral load, they will take a separate blood specimen. When it is stored, your blood and test results will not have your name or any other way of identifying you attached to it.

Follow-up of missed visits

You will be asked to provide contact information so that we may get in touch with you during the study. Study staff will talk with you about the best way to contact you. In the event that you miss one of the scheduled study visits, a member of the study staff will contact you in order to find another day and time to complete your visit. If you repeatedly miss study visits or the staff is unable to contact you using the information that you provide, it may be necessary to visit you at home in order to reschedule the missed study visit.

Contact for future study

After the completion of the visit one week after delivery, *it is possible that we will contact you again at your next clinic visit or at another time in the future to take part in additional research studies. At that time, you would be asked to review and sign another consent form. You can choose to not take part in any future studies if you are asked.* You will be asked to provide contact information so that we may get in touch with you regarding additional research studies. Study staff will talk with you about the best way to contact you.

WHAT ARE THE POTENTIAL RISKS?

You may feel uncomfortable about some of the personal questions you are asked. You may refuse to answer any question that you do not want to answer. There is some risk in sharing personal and medical information. We will be careful to keep all your information as private as possible.

Drawing blood is normally done as part of routine medical care and presents a slight risk of discomfort. Experienced staff will draw blood under sterile conditions in order to protect you against these risks.

WHAT ARE THE POTENTIAL BENEFITS?

There is no direct benefit to you if you take part in this study. The information gained in this study may help to improve ART services for HIV-infected pregnant women in Cape Town, the Western Cape Province, and across South Africa.

WHAT ARE THE ALTERNATIVES TO TAKING PART?

The alternative to taking part in this study is to continue with your usual care at the MOU.

WHAT ABOUT CONFIDENTIALITY?

If you agree to take part, all information collected during the study will be kept strictly confidential. Your name will not be written on the study forms and will not be used in connection with any information or lab specimens that are collected as part of the study.

All study materials will be stored in locked filing cabinets. Only study staff and personnel involved in routine audits will have access to these materials. All staff involved in data collection and management will get specific training in confidentiality.

Even with these procedures in place, if the study staff learns that you are a risk to yourself or someone else or of possible child abuse and/or neglect, study staff will tell the proper authorities.

WILL I BE GIVEN ANYTHING FOR TAKING PART?

At the end of each visit, you will be given R20 in cash to cover the transport cost to your next scheduled study visit, and an R80 grocery voucher. You will also receive a small gift for the first visit after birth and refreshments will be provided at all visits.

ARE THERE ANY COSTS?

There is no cost for being in this study.

CAN I LEAVE THE STUDY?

You have the right to decide not to take part in the study, to refuse to answer any questions, or to withdraw from the study at any time without any penalty. It will have no effect on the care that you receive at the Gugulethu MOU or any other health facility.

FUTURE USE OF SPECIMENS:

If you agree, any leftover blood from the samples you have provided for this research project may be used for future HIV related research. It is possible that these stored samples may be tested to see if the HIV in your blood is resistant to any types of HIV medications or to look at other questions related to HIV.

At this time, we cannot provide details of when this testing may be conducted. However, additional testing will not be done using these stored samples without the approval of the appropriate ethics committees involved in this research.

If you agree to let us keep your stored samples for future research, they may be kept in a locked freezer for up to 5 years. If we do use your samples in the future, your name or other identifiers will not be included with this information (as with the rest of the information we collect for this study).

Phase 2 Informed Consent Form

Please initial below to indicate whether or not you give permission for your specimens to be used for future research. You may still remain in the study, no matter which you choose.

_____ (initial) I agree to have my blood stored for future research.

_____ (initial) I agree to have my blood stored for future research related to this study ONLY.

_____ (initial) I do NOT agree to the storage of my blood for future use.

DO YOU HAVE ANY QUESTIONS?

If there is anything that is unclear or if you need further information, please ask us and we will provide it.

Do you have any questions?

FOR ADDITIONAL INFORMATION:

If you have any questions or have any problems while taking part in this research study, you should contact:

Dr Landon Myer
School of Public Health and Family Medicine
Faculty of Health Sciences, University of
Cape Town
Tel: 021 406 6661
Email: Landon.Myer@uct.ac.za

Dr Elaine Abrams
ICAP, Columbia University
Mailman School of Public Health
College of Physicians and Surgeons
Tel: +1 212 342 0543
Email: ejal@columbia.edu

If you have any questions about your rights as a research participant, you may contact the following member of the ethics committee:

Prof Marc Blockman
Chair, Human Research Ethics Committee
Faculty of Health Sciences, University of Cape
Town
Tel: 021 406 6338

Columbia University Medical Center IRB
Tel: +1 212 305 5883

Phase 2 Informed Consent Form

CONSENT STATEMENT:

I have read this form, or someone has read it to me. I have been offered a copy of this consent form. I was encouraged and given time to ask questions. I agree to be in this study. I know that after choosing to be in this study, I may withdraw at any time. My being in the study is voluntary. I understand that whether or not I participate will not affect my health care services received today, or at any time in the future.

Please indicate your consent with your signature.

Volunteer's name _____

Signature of Volunteer Date

Staff member's name _____

Signature of study staff Date

If the volunteer is unable to read or write the entire counselling process must be observed by an independent witness who can then confirm the procedure once the she has given consent.

Fingerprint of volunteer:

Witness:

I confirm that I am independent of the study and that I witnessed the entire informed consent counselling process in the home language of the volunteer

Name: _____

Signature: _____

Date: _____

Thank you.



Appendix G: Data Sharing Agreement, MCH-ART Study

Strategies to optimize antiretroviral therapy services for maternal & child health: the MCH-ART study

Data Access, Confidentiality and Use Agreement

I, _____ (print name), agree to abide by the following rules and restrictions when using any dataset from the study entitled '*Strategies to optimize antiretroviral therapy services for maternal & child health: the MCH-ART study*'.

1. I **WILL** protect the MCH-ART study dataset by using and storing it on a password protected computer which only I have access to.
2. I **WILL** treat the dataset confidentially.
3. I **WILL NOT** produce a back-up data copy of the study datasets except as required for the maintenance of the dataset.
4. I **WILL** ensure that the back-up datasets are also stored according to the full confidentiality guidelines mentioned above.
5. I **WILL NOT** use the dataset without explicit approval from the study PI's and an approved concept note.
6. I **WILL NOT** use data obtained for the purposes of a specific concept note for other purposes.
7. I **WILL NOT** share the dataset with other individuals outside the co-investigator list without explicit approval from the study PI.

I have read and understood this document on the use of data from the MCH-ART study and agree to abide by these rules and restrictions.

Signed: _____ Date: _____

Organization _____

Approved: _____ Date: _____

Principal Investigator/s

Appendix H: Ethics Approval for Secondary analysis of MACH-ART data



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



Room E52-24 Old Main Building
Groote Schuur Hospital
OBSERVATORY 7925

Telephone [021] 406 6338 • Facsimile [021] 406 6411

Email: shuretta.thomas@uct.ac.za

Website: www.health.uct.ac.za/fhs/research/humanethics/forms

22 December 2015

HREC REF: 923/2015

Prof L Myer
Public Health & Family Medicine
Falmouth Building

Dear Prof Myer

**PROJECT TITLE: ADHERENCE TO ANTIRETROVIRAL TREATMENT (ART) AMONG HIV-
INFECTED PREGNANT WOMEN STARTING TREATMENT IMMEDIATELY VS DELAYED; A
COHORT STUDY (Sub-study linked to 451/2012) Masters Candidate - Ms N Langwenya**

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

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

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

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

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Ms Nontokozi Langwenya will also be involved in this study.

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

Yours sincerely

Signed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

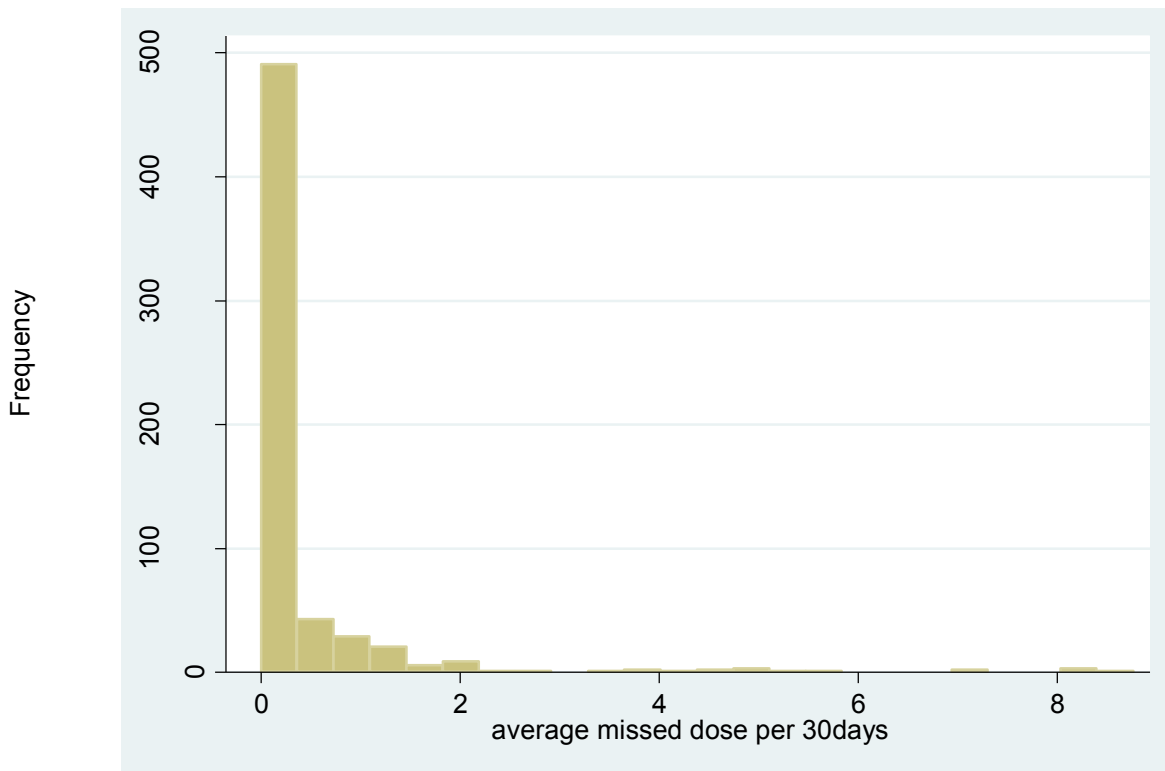
Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

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

HREC 923/2015.

Appendix I: Histogram of Self-reported missed ART doses during pregnancy



The distribution of the average missed ART doses during pregnancy is unimodal and skewed towards the right, with a majority of women reporting no missed ART doses during pregnancy. There does not appear to be any outliers, and the largest reported average missed ART dose was 8.761.

The median number of missed ART doses assessments was 3 (IQR: 2 -3). Women who delayed ART initiation following first antenatal visit had a lower median number of adherence assessment compared to those who initiated ART immediately (2 vs 3; $p < 0.01$).

Appendix J: Sub-analysis

Table D-1: Unadjusted and Adjusted logistic regression models of association between timing of ART initiation and any missed ART dose in pregnancy and (Timing of ART initiation grouped into 4 categories)

	CD4 \leq 350 cells/uL(n=312)			Overall		
	aOR	95 % CI	P value	aOR	95% CI	P value
Age in years	0.95	0.90 -1.00	0.067	0.96	0.93-0.98	0.031
Scholar /employed	0.85	0.49-1.83	0.576	0.91	0.62 - 1.34	0.638
Informal housing	1.56	0.93 – 2.63	0.094	1.56	1.08 - 2.27	0.017
Diagnosed HIV+ before current pregnancy	1.54	0.91-2.62	0.105	1.28	0.87-1.88	0.196
Gestation (weeks)	0.99	0.94-1.04	0.673	1.00	0.96 - 1.01	0.064
CD4 (cell/ μ L) 0 -250	1	(ref)		1	(ref)	
251-350	1.19	0.68 – 2.06	0.541	1.21	0.70 – 2.08	0.492
351-500				0.86	0.33 – 2.23	0.753
>500				0.88	0.33 – 2.33	0.797
PMTCT Option A	1	(ref)		1	(ref)	
Option B+	0.92	0.38 – 2.26	0.862	1.90	0.99-6.31	0.052
Median days on ART	1.00	0.99-1.01	0.524	1.00	0.99 - 1.01	0.354
Delay to ART initiation						
0-2 days	1	(ref)		1	(ref)	
3-14 days	0.48	0.19 – 1.22	0.126	0.93	0.48 – 1.78	0.825
15- 28 days	0.65	1.86 – 2.31	0.510	0.86	0.33 – 2.23	0.753
29 and above	0.67	1.78 – 2.54	0.558	0.88	0.33 – 2.33	0.797

Table D-2: Restricted to women initiating ART under Option B+ - Unadjusted and adjusted logistic regression models of association between timing of ART initiation and any missed ART dose in pregnancy (n=484)

	Unadjusted			Adjusted		
	OR	95 % CI	P value	aOR	95% CI	P value
Age in years	0.97	0.92 - 0.99	0.200	0.97	0.93 – 1.00	0.078
Scholar /employed	0.84	0.56 - 1.26	0.392	0.83	0.54 – 1.26	0.167
Informal housing	1.53	1.04 – 2.3	0.30	1.39	0.94 – 2.08	0.102
Diagnosed HIV+ before current pregnancy	0.96	0.65 – 1.41	0.850	1.04	0.96 – 1.58	0.167
Gestation (weeks)	1.00	0.98 – 1.028	0.798	1.03	0.99 -1.07	0.167
CD4 (cell/ μ L) 0 -250	1	(ref)		1	(ref)	
251-350	1.27	0.71 – 2.30	0.423	1.24	0.68 – 2.30	0.472
351-500	1.24	0.66 – 2.31	0.504	1.14	0.60 – 2.18	0.689
>500	1.51	0.633 – 2.10	0.643	1.03	0.56 – 1.91	0.914
Median days on ART	1.00	1.00 – 1.00	0.740	1.01	1.00 – 1.01	0.523
Delay to ART initiation						
Delayed (>2 days)	1	(ref)		1	(ref)	
Same-day (0-2 days)	1.40	0.80 – 2.45		1.14	0.61 – 2.14	0.681

Table D-3: Restricted to women initiating ART under Option A - Unadjusted and adjusted logistic regression models of association between timing of ART initiation and any missed ART dose in pregnancy (n=101)

	Unadjusted			Adjusted		
	OR	95 % CI	P value	aOR	95% CI	P value
Age in years	0.96	0.87 – 1.01	0.379	0.88	0.78 – 0.98	0.030
Scholar /employed	1.24	0.49 – 3.16	0.654	1.41	0.45 – 4.39	0.550
Informal housing	3.05	1.31 – 8.18	0.027	2.59	0.87 – 7.67	0.086
Diagnosed HIV+ before current pregnancy	4.83	1.64 – 14.22	0.004	6.85	1.90 – 24.67	0.003
Gestation (weeks)	0.99	0.91 – 1.06	0.679	0.94	0.79 – 1.11	0.461
CD4 (cell/μL) 0 -250	1	(ref)		1	(ref)	
251-350	0.98	0.32 – 2.97	0.972	1.14	0.30 – 4.22	0.850
>350	0.53	0.11 – 2.43	0.413	0.39	0.059 – 2.57	0.329
Median days on ART	1.00	0.99 – 1.01	0.904	0.99	0.96 – 1.01	0.220
Delay to ART initiation						
Delayed (>2 days)	1	(ref)		1	(ref)	
Same-day (0-2 days)	0.70	0.18 – 2.62	0.593	1.92	0.31 – 9.96	0.486

Appendix K: Journal Submission Guidelines

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](#).

Information prior to submission

- [Aims and Scope](#)
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Manuscript preparation

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Data deposition and release

Data deposition and release

Protein and nucleotide sequences
Mass spectrometry
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.

Ethical policies

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MANUSCRIPT PREPARATION

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Article categories

Research - full reports of data from original research studies

Headings: Introduction, Methods, Results, Discussion, Conclusions

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