HIV viral load monitoring in HIV-infected pregnant women established on antiretroviral therapy in Cape Town, South Africa

by

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RVMPRI001

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Master of Public Health (Epidemiology)

Faculty of Health Sciences
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University of Cape Town
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Declaration

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Date: 15 August 2016
Abstract

Background: Antiretroviral therapy (ART) services have expanded over the past decade, providing treatment to over 15 million people globally. It is imperative that this scale-up of ART provision be accompanied by optimal treatment response monitoring strategies to timely and accurately detect treatment failure. Routine viral load (VL) monitoring is the preferred ART response monitoring tool and its use has been increasing across Africa; however, there are few insights into VL monitoring practices during pregnancy. This thesis describes public sector VL testing practices in a cohort of HIV-infected pregnant women who initiated ART before pregnancy in Cape Town, South Africa.

Methods: This study was conceived in 2015 as a sub-analysis of the first phase of an on-going prospective trial: the Strategies to optimize antiretroviral therapy services for maternal and child health (MCH-ART) Study, being conducted in Gugulethu, Cape Town, South Africa. Consecutive HIV-infected pregnant women on ART before pregnancy and making their first visit to a primary care antenatal clinic between March 2013 and June 2014 were enrolled into the study. Pre-existing demographic, obstetric and ART history data collected during enrolment into the MCH-ART study were used. In addition, HIV VL results were obtained from the National Health Laboratory Service (NHLS) system from 15 months prior to the estimated date of conception to delivery. VL testing and VL results were described for the two periods: (i) before conception (from estimated date of conception to 15 months prior) and (ii) during pregnancy (from estimated date of conception to delivery).

Results: Among 520 women the median age was 31 years [Interquartile range (IQR), 28-35 years] and the median duration of ART use was 2.7 years [IQR, 1.5-5.1 years]. Before conception, 66% (n=311) of women had at least one VL test done in routine adult ART services, and 9% of these results (n=29) were >1000 copies/mL. During the pregnancy, 80% (n=415) of women had at least one VL test done and 12% (n=49) of these results were >1000 copies/mL. Pregnant women with elevated VL >1000 copies/mL were more likely to have been on ART for longer (p=0.049), report at least 2 missed ART doses in the preceding 30 days (p=0.043) and be on a protease inhibitor-based regimen (p=0.016). Among women with VL >1000 copies/mL during pregnancy, 59% (n=29) had a repeat VL done at a median of 3.5 months after the initial test (IQR, 2.1-4.4 months) with 52% (n=15) of these women having a VL >1000 copies/mL on this second test.

Conclusion: While coverage of VL monitoring appears high in this setting, a substantial fraction of women with elevated VL in pregnancy were never retested. With increasing numbers of HIV positive women using ART, greater attention is needed to design and implement effective strategies for VL monitoring in pregnancy.
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I would like to thank my supervisor, Professor Landon Myer, who suggested the topic for this dissertation and has offered me his guidance and support through the writing process.

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Landon Myer
Division of Epidemiology & Biostatistics and Centre for Infectious Diseases Epidemiology & Research, University of Cape Town, South Africa.
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ANC</td>
<td>Antenatal Care</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral Therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>MCH-ART</td>
<td>Strategies to optimize antiretroviral therapy services for maternal and child health</td>
</tr>
<tr>
<td>MOU</td>
<td>Midwife-Obstetric Unit</td>
</tr>
<tr>
<td>MTCT</td>
<td>Mother-to-child transmission</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Non-Nucleoside Reverse Transcriptase Inhibitors</td>
</tr>
<tr>
<td>NHLS</td>
<td>National Health Laboratory Services</td>
</tr>
<tr>
<td>NVP</td>
<td>Nevirapine</td>
</tr>
<tr>
<td>PI</td>
<td>Protease Inhibitor</td>
</tr>
<tr>
<td>PMTCT</td>
<td>Prevention of mother-to-child transmission</td>
</tr>
<tr>
<td>UCT</td>
<td>University of Cape Town</td>
</tr>
<tr>
<td>UCT-HREC</td>
<td>University of Cape Town Human Research Ethics Committee</td>
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<tr>
<td>VL</td>
<td>Viral load</td>
</tr>
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<td>World Health Organization</td>
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Part I: Protocol

HIV viral load monitoring in HIV-infected pregnant women established on antiretroviral therapy in Cape Town, South Africa

Synopsis

Background and Rationale: Mother-to-child transmission (MTCT) accounts for the majority of new HIV transmissions among children below the age of 15 years. The main predictor of risk of vertical transmission of HIV is maternal plasma HIV viral load (VL), with low maternal VL levels associated with the lowest risk of transmission. With more countries adopting the new World Health Organization (WHO) guidelines of initiating lifelong antiretroviral therapy (ART) to all pregnant and breastfeeding women, there will be an increase in the number of HIV-infected women conceiving on ART. It is thus imperative that this scale up of ART provision be accompanied by optimal treatment response monitoring strategies to timely and accurately detect treatment failure. The WHO has recommended routine VL monitoring as the preferred ART response monitoring tool, however its use in low-income settings has been restricted by the costs and limited laboratory capacity. In recent years, use of VL monitoring has been increasing across Africa; however, there are few insights into VL monitoring practices during pregnancy.

Aim and objectives: The overall aim of the proposed research is to describe public sector VL monitoring practices among HIV-infected pregnant women who initiated ART before pregnancy. The study’s primary objective is to describe the distribution of HIV VL testing in routine care services among HIV-infected pregnant women who initiated ART before pregnancy. The primary outcomes are (i) frequency of maternal VL testing and (ii) maternal VL levels before conception and during pregnancy. Additional objectives include describing clinical and demographic characteristics of HIV-infected pregnant women on ART before pregnancy, evaluating the pattern of HIV VL testing among those women that had at least one raised VL during pregnancy and identifying the predictors of (i) having a VL test performed and (ii) having a raised VL>1000 copies/mL during pregnancy.

Study design, population and sampling: This will be a sub-study of the first phase of a prospective on-going trial – the Strategies to optimize antiretroviral therapy services for maternal and child health (MCH-ART) Study, being conducted in Gugulethu, Cape Town, South Africa. The MCH-ART study, which aims to compare a mother-and-child health-focused ART service to the general adult ART services during the postpartum period, is comprised of 3 phases; phase 1 being a cross-sectional evaluation of consecutive HIV-infected pregnant women seeking ANC, phase 2 an observational cohort of all women from phase 1 eligible for initiation of ART and phase 3 a randomized trial of strategies for delivering ART to breastfeeding women from phase 2 during
the postpartum period. This study enrolled consecutive HIV-infected pregnant women making their first visit to a primary care antenatal clinic (ANC) between March 2013 and June 2014. The proposed study will be a retrospective cohort analysis of women enrolled in the MCH-ART study who initiated ART before pregnancy. Pre-existing demographic, obstetric and ART history data collected during MCH-ART enrollment will be used. In addition, routine HIV VL results will be abstracted from the National Health Laboratory Service (NHLS) system from 15 months before the estimated date of conception to delivery.

Given the importance of maternal VL levels on the risk of MTCT, the proposed study has the potential to make a significant contribution towards informing policy makers and service providers of how well the health care system is performing at assessing ART response among HIV-infected pregnant women on ART.

**Background**

In 2014, over 35 million people were living with HIV globally with a significant proportion of these people (over two-thirds) residing in sub-Saharan Africa [1]. Provision of ART has significantly improved the lives of people living with HIV by reducing the number of HIV-related illness, AIDS-related deaths and preventing new HIV infections. Among the people living with HIV globally, approximately 15 million are on HIV treatment [1], with South Africa having one of the largest treatment programs [2].

Plasma HIV VL is the main predictor of both heterosexual [3] and perinatal HIV transmission [4,5] and most antiretroviral (ARV) drugs work by inhibiting HIV replication, reducing plasma VL levels. Reducing the maternal VL levels has been shown to decrease HIV-related maternal mortality and the risk of MTCT of HIV [6-9] while improving maternal health and reducing the risk of onward horizontal transmission to their partners. There is no VL level above or below which transmission always or never occurs [4,10,11] as vertical HIV transmission has been known to occur even in the presence of low maternal viremia [12] and not all infants born to mothers with elevated VL levels will be infected. However, the risk of perinatal transmission is high at higher maternal VL levels [4] and low at lower maternal HIV VL levels [13,14] with Mandelbrot et al. reporting no HIV transmission events among infants born to women who initiated ART before conception and were virally suppressed at delivery [14].

In September 2015, new guidelines were released by WHO recommending lifelong ARV treatment for all HIV-infected pregnant and breastfeeding women regardless of CD4 cell count or WHO clinical stage (Option B+) [15]. As more countries adopt Option B+, there will be an increase in the number of HIV-infected women conceiving on ART. It is therefore imperative that this scale up of ART provision be accompanied by optimal strategies for treatment response monitoring in order to timely detect treatment failure. ART response can be monitored clinically (by clinical
evaluation), immunologically (by measurement of CD4+ T cells), virologically (by measurement of HIV VL levels) or by a combination of these. Relying solely on clinical and immunological monitoring can lead to delayed detection of virologic failure as well as the accumulation of drug resistant strains [16,17]. Routine laboratory monitoring is associated with improved health and survival outcomes when compared with clinical monitoring alone [18].

WHO currently recommends routine virologic monitoring as the preferred ART response monitoring tool with a VL test at 6 and 12 months after ART initiation, then 12 monthly thereafter [19]. For pregnant women on ART for \( \geq 3 \) months, the 2015 South African guidelines further recommend a VL test at confirmation of pregnancy and 6 monthly thereafter throughout the pregnancy and breastfeeding period. For those HIV positive pregnant women not on ART, a VL test is recommended 3 and 6 months after ART initiation, then 6 monthly till the end of breastfeeding [20].

The main advantages of VL monitoring are that it can be used as a tool to identify patients in need of adherence support [21,22], allows more accurate and timely identification of treatment failure [16,23,24] and prevents unnecessary changing of 1st line regimens to 2nd line drugs in individuals with blunted CD4 cell count response to ART but undetectable HIV VL levels [25]. The impact of VL monitoring on mortality still remains unclear with inconsistent findings. A study reported lower mortality rates among patients on ART managed in centers with VL monitoring when compared to those managed in sites that did not have VL monitoring [26]. This was not consistently shown in a systematic review of optimal strategies for ART response monitoring with one study showing a beneficial effect and another showing no beneficial effect [27]. On the other hand there is evidence of viral suppression having an HIV mortality benefit with patients on ART who achieved viral suppression and a CD4 count \( \geq 350 \) cells/µL having a reduced mortality and normal life expectancy [28].

VL monitoring has been the standard of care in most high-income countries for some years but its use in resource limited settings has been restricted by the high costs and inadequate laboratory capacity [29]. In addition to late presentation for ANC and inadequate antenatal prevention of mother-to-child transmission (PMTCT) prophylaxis, the absence of VL monitoring among pregnant and breastfeeding women has been shown to be a risk factor for MTCT [30].

In 2014 UNAIDS announced new global treatment targets in-order to improve HIV response in low and middle income countries to end the HIV epidemic by 2030 [31]. The 90-90-90 goal aims to have 90% of people living with HIV tested, 90% of HIV-infected people on ART and 90% of those on treatment virally suppressed by 2020. In-order to achieve the third target, ongoing virologic monitoring is required. The use of VL monitoring is increasing across Africa however there is little insight into VL monitoring practices during pregnancy. Our study proposes to
describe public sector VL monitoring practices in a cohort of HIV-infected pregnant women on ART at conception in Cape Town, South Africa.

**Justification**

HIV infection in young children is acquired primarily through vertical transmission and maternal HIV VL level is the most important determinant of the risk of MTCT, with high maternal VL levels associated with the greatest risk of HIV transmission. It is presumed that women who conceive on ART have the lowest HIV transmission rates as these women have the highest potential of being virally suppressed throughout pregnancy and breastfeeding. With the initiation of lifelong ART in all pregnant and breastfeeding HIV-infected women, there will be an increase in the number of women conceiving on ART. It is of concern that there are limited data on VL monitoring practices in the public sector among this population with most VL data coming from clinical trials. It is important to understand maternal VL testing practices and maternal viral suppression within the public sector where most of these women are followed up.

**Aim and Objectives**

**Aim**

The overall aim of the proposed project is to describe public sector VL monitoring practices among HIV-infected pregnant women who initiated ART before pregnancy.

**Objectives**

1. To describe HIV VL testing in routine care among HIV-infected pregnant women who initiated ART before pregnancy. The primary outcomes are (i) frequency of maternal VL testing and (ii) maternal VL levels before conception and during pregnancy.

2. To describe clinical and demographic characteristics of HIV-infected pregnant women who initiated ART before pregnancy.

3. To evaluate the pattern of VL testing during pregnancy among HIV-infected pregnant women who initiated ART before pregnancy that have at least one raised VL during pregnancy. Outcomes include (i) frequency of re-testing after an initial raised VL result, (ii) timing between the two consecutive VL tests and (iii) maternal viral re-suppression.

4. To identify the predictors of (i) having a VL test and (ii) having a raised VL>1000 copies/mL during pregnancy among HIV-infected pregnant women who initiated ART before pregnancy.
Hypothesis

We hypothesize that public sector VL testing among HIV-infected pregnant women who initiated ART before pregnancy occurs frequently, however subsequent VL testing for those with a raised VL is not consistent.

Methods

The proposed study will be a sub-study of the prospective Strategies to optimize antiretroviral therapy services for maternal and child health (MCH-ART) trial (ClinicalTrials.gov NCT01933477) being conducted at the Gugulethu Midwife Obstetric Unit (MOU) in Gugulethu, Cape Town, South Africa. The MCH-ART study has been described in detail elsewhere [32] but in brief, its main objective is to compare a mother-and-child health-focused ART service to the general adult ART services during the postpartum period. It is comprised of 3 phases; phase 1 being a cross-sectional evaluation of consecutive HIV-infected pregnant women seeking ANC, phase 2 an observational cohort of all women from phase 1 eligible for initiation of ART and phase 3 a randomized trial of strategies for delivering ART to breastfeeding women from phase 2 during the postpartum period. The proposed study will be a sub-study of the phase 1 component.

The Gugulethu MOU is a large primary care ANC clinic situated in the peri-urban area of Gugulethu in Cape Town, South Africa. It provides basic antenatal, obstetric and postpartum services. HIV prevalence among women attending the Gugulethu MOU clinic in 2011 was 28%. Over 5500 women sought antenatal care at the MOU between March 2013 and June 2014, of whom 1839 (33%) were HIV positive [33]. PMTCT services have been offered at the Gugulethu MOU since 2001 and annual VL monitoring has been routine in this setting since 2010.

Study design

Retrospective cohort study design

Population and sampling

Consecutive HIV-infected pregnant women making their first visit to Gugulethu MOU ANC clinic between March 2013 and June 2014, enrolled in the MCH-ART study and who had been on ART at the estimated date of conception will be included.

Inclusion criteria

- Age 18 years or older
- Enrolled into the MCH-ART study
- On triple-drug ART at the estimated date of conception
Exclusion criteria

- Initiated ART during the current pregnancy
- Determined to have not been pregnant at first ANC presentation or suffered a pregnancy loss

Measurements

Clinical and demographic characteristics
Pre-existing demographic, obstetric and ART history data collected during MCH-ART enrolment will be used for this study (Appendix 6 and 7). All enrolled participants received a research ultrasound to determine gestational age (GA) at the first ANC visit which was used to calculate the estimated date of conception. Data on obstetric outcomes was abstracted from patient folders and delivery registers at health institutions of delivery. Where no delivery data was available, estimated gestation at delivery was used to estimate a delivery date assuming delivery occurred at 40 weeks gestation.

Laboratory measurements
At enrolment into MCH-ART, women completed an informed consent form (Appendix 5) including consent for abstraction of their routine clinic data. CD4 cell count and hemoglobin levels at first ANC presentation will be abstracted from the patient clinic folders. Public sector VL results will be abstracted from the National Health Laboratory Services (NHLS) system from 15 months before the estimated date of conception to delivery.

Measurement of adherence
Adherence was measured at the first ANC visit by the self-reported number of missed ART doses in the preceding 30 days.

Definitions of outcome variables
VL testing and VL results will be reported for the 2 time periods (i) before conception and (ii) during pregnancy as shown in Figure 1 below.

(i) HIV VL testing before conception – Only women who have been on ART for at least 6 months at the estimated time of conception will be included in the ‘before conception’ analysis as the first VL test is performed 6 months after ART initiation. The ‘before conception’ period will extend from the estimated date of conception to 15 months prior. For women with more than one VL result during this period, the ‘before conception’ VL will be defined as the VL result closest to the estimated date of conception.
Figuré 1. Eligibility criteria and VL window periods for the time periods; before conception and during pregnancy.

(ii) HIV VL testing during pregnancy – The ‘during pregnancy’ VL window will extend from the estimated date of conception to delivery. For women with more than one VL result during their pregnancy, ‘during pregnancy’ VL will be defined as the VL result closest to the estimated date of conception.

VL results will be categorised into ≤50, 51-1000 and >1000 copies/mL. Viremia will be defined at >1000 copies/mL following recommended definitions of virologic failure (19).

Table 1 below shows a list of all variables to be used in this analysis.
Table 1. Variables to be used in this analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Continuous (years)</td>
</tr>
<tr>
<td>Completion of high school</td>
<td>Binary (Yes / No)</td>
</tr>
<tr>
<td>Employment status</td>
<td>Binary (Yes / No)</td>
</tr>
<tr>
<td>Marital status</td>
<td>Binary (Married or cohabiting /single or in relationship but not cohabiting)</td>
</tr>
<tr>
<td>HIV status disclosure</td>
<td>Binary (Yes / No)</td>
</tr>
<tr>
<td>Gravidity</td>
<td>Count</td>
</tr>
<tr>
<td>Parity</td>
<td>Count</td>
</tr>
<tr>
<td>Gestation at first ANC visit</td>
<td>Continuous (weeks)</td>
</tr>
<tr>
<td>Gestation at delivery</td>
<td>Continuous (weeks)</td>
</tr>
<tr>
<td>Currently on ART</td>
<td>Binary (Yes / No)</td>
</tr>
<tr>
<td>ART regimen</td>
<td>Categorical (TDF-3TC-EFV or NVP / Other NNRTI-based regimen / PI-based regimen / not sure)</td>
</tr>
<tr>
<td>Duration on ART</td>
<td>Continuous (years)</td>
</tr>
<tr>
<td>Missed at least 2 ART doses</td>
<td>Binary (Yes / No)</td>
</tr>
<tr>
<td>in the past 30 days</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>Continuous (cells/µL)</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Continuous (g/dL)</td>
</tr>
<tr>
<td>Viral load test done</td>
<td>Binary (Yes / No)</td>
</tr>
<tr>
<td>Viral load test result</td>
<td>Numerical (copies/mL)</td>
</tr>
</tbody>
</table>

NNRTI - non-nucleoside reverse transcriptase inhibitor; TDF - tenofovir; 3TC - lamivudine; EFV - efavirenz; NVP - nevirapine; PI - protease inhibitor

Data management

Information regarding the demographic characteristics, obstetric and ART history and delivery outcomes is stored in a password protected Microsoft Access database. Laboratory measurements will be abstracted from the NHLS system directly into a Microsoft Access database. All study records will contain anonymous participant identification numbers and all Microsoft Access databases will be password protected and maintained in a firewall-protected UCT server with nightly backups. Only key members of the study team will have access to the study databases.

Data analysis

All statistical analysis will be done using Stata (Version 13.0) (Stata Corporation, College Station, Texas, USA). Continuous variables will be summarized using means and confidence intervals (CI) or medians and interquartile ranges (IQR) for normally and non-normally distributed variables respectively. Categorical variables will be described using proportions.

Frequency tables will be used to compare proportions of women who received a VL test to those who did not. Among women that received a VL test, proportions of women with a VL result in the
categories ≤50, 51-1000 and >1000 copies/mL will be compared. Associations between the demographic, obstetric and ART history variables and the VL levels will be examined using ANOVA and Kruskal Wallis test for normally and non-normally distributed numerical variables respectively and chi-squared or Fisher’s exact tests for categorical variables according to the expected number of observations within each cell. Logistic regression will be used to identify the predictors of having a VL test during pregnancy and predictors of having a raised VL >1000 copies/mL during pregnancy.

Ethics

Ethical review

The MCH-ART study was approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (UCT-HREC) (REC REF: 451/2012) (Appendix 1 and 2), the Institutional Review Board of the Columbia University Medical Centre (Appendix 3) as well as the Provincial Government of the Western Cape Department of Health (Appendix 4). This study will seek approval from the UCT-HREC.

Informed consent

At enrolment into the primary study, participants gave consent for the abstraction of their routine clinic data on obstetric and HIV-related care (Appendix 5). In addition, the data for this study will come from retrospective review of routinely collected service data and there will be no direct contact with participants. For these reasons, we will not obtain informed consent from individual patients.

Confidentiality

The following steps will be taken to minimize the risk of any loss of confidentiality throughout the study design and conduct.

- All personnel involved in data collection and management will undergo training on their ethical obligations to ensure participant confidentiality and sign confidentiality documents.
- Participants will be identified by an anonymous identification number and no paper based forms will contain participant names. All paper forms will be kept in a locked cabinet in a locked office.
- All databases will be password-protected and will be maintained in a firewall-protected UCT server.
- The results of the study will not report on individual patients ensuring confidentiality.
Risks

We consider this study to be of low risk to participants with the potential risks including loss of confidentiality in the process of data collection and data management. The study team has put in place measures to minimize the possibility of these risks as noted above.

Benefits

Direct benefit

There will be no direct benefit to patients in this study as it is a retrospective analysis of routinely collected data. Patients may benefit from the findings of this study based on the improved VL monitoring strategies that could be implemented ensuring viral suppression during pregnancy with improved maternal and child outcomes.

Indirect benefit

All HIV-infected pregnant women on ART could benefit from this study as the proposed study has the potential to identify gaps in the virologic monitoring of patients on ART which could advise policy makers of the areas that need intervention. Given the anticipated increase in the number of HIV-infected women who will be receiving ART before becoming pregnant, advancing our knowledge among this population will be of benefit to both health service providers and maternal and child health. As the women in the study group are representative of those for whom the research outcomes are intended, justice is maintained.

Reporting and Implementation

The results of this study will be submitted to a peer-reviewed journal for publication and presented at appropriate HIV/AIDS conferences and meetings so that they can be maximally accessed by those involved in providing ART to pregnant women. The nurses involved in the management of pregnant women at the Gugulethu MOU will be informed of the results.

Logistics

Table 2 below shows the timetable in which the researcher anticipates this study will be conducted within.
Table 2: Timetable

<table>
<thead>
<tr>
<th>Task</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Merge, clean and check datasets</td>
<td>February 2016</td>
</tr>
<tr>
<td>Analysis</td>
<td>March 2016</td>
</tr>
<tr>
<td>Prepare draft manuscript</td>
<td>March 2016</td>
</tr>
<tr>
<td>Prepare final manuscript and submit for publication</td>
<td>June 2016</td>
</tr>
</tbody>
</table>

Budget

Priscilla Tsondai will be responsible for data management and analysis of the merged database as part of her MPH studies and does not require any payment.

References


Part II: Literature review

Introduction

The South African national HIV prevalence among women attending antenatal care (ANC) aged 15-49 years was approximately 30% in 2012 [1]. Rates of mother-to-child transmission (MTCT) have been declining over the past few years and studies have shown that they decline to less than 5% and can be as low as 2%, with high coverage of effective antiretroviral therapy (ART) drugs and complete cessation of breastfeeding [2]. Approximately 80% of new childhood HIV transmissions occur during the intrapartum period and of all the factors associated with MTCT of HIV, plasma maternal VL has been found to be the main determinant [3,4]. Reducing maternal VL levels by use of ART during the pregnancy and breastfeeding phases has led to large decreases in the MTCT rates [5]. The past decade had seen a huge scale up of ART provision services. It is critical that this scale up be accompanied by effective treatment monitoring to timely and accurately detect treatment failure, especially among HIV-infected pregnant women in order to prevent maternal AIDS-related deaths as well as prevent HIV transmission to the children.

Objectives

This literature review investigates HIV VL monitoring among HIV-infected pregnant women on ART. The objectives of the literature review are:

- To identify the role of VL in vertical transmission of HIV
- To determine the role of ART in prevention of mother-to-child-transmission of HIV
- To compare existing ART treatment monitoring strategies
- To describe management of viremia among HIV-infected adults on ART in resource-limited settings
- To describe VL monitoring among HIV-infected pregnant women on ART in resource-limited settings

Literature search strategy

A search of the Medline bibliographic database using the PubMed interface was performed using the following search terms:

1. HIV OR AIDS OR Human immunodeficiency virus
   AND
2. Antiretroviral OR ARV OR ART OR HAART OR anti-retroviral
   AND
3. Pregnant OR pregnancy OR maternal OR maternity
AND
4. Viral load OR monitoring OR viremia

**Inclusion criteria**

- Population studied included HIV-infected pregnant women on triple therapy ART in resource-limited settings
- Studies reporting on factors influencing MTCT of HIV in resource-limited settings
- Studies describing outcomes of clinical, immunological and/or virological ART monitoring strategies in resource-limited settings

**Exclusion criteria**

- Population of interest mainly children, adolescents and/or ART-naive adults
- Studies focusing on retention in care, therapeutic drug monitoring, pharmacokinetics and pharmacodynamics of ARVs, efficacy and safety of ARVs
- Cost-effectiveness studies

The search was restricted to those studies published in English between 2006 and April 2016 and yielded 784 studies. Titles and abstracts were screened for relevance, after which 45 articles which met the inclusion criteria were reviewed. Additional studies were identified through searching bibliographies of included articles.

**Summary and interpretation of literature**

**Role of VL in vertical transmission of HIV**

Transmission of HIV from a mother to her child occurs either during pregnancy, labour and delivery or after delivery through any-one of the following ways:

(i) During pregnancy (in-utero) – when infection spreads either hematogenously, by crossing the placenta or by ascending from the genital tracts into the amniotic fluids,

(ii) During labour and delivery (intrapartum) – through the fetus having contact with maternal blood or fluids mucocutaneously or when there is mixing of maternal and fetal blood during contractions,

(iii) After delivery (postpartum) - through breastfeeding [6].

Several factors have been implicated in the risk of MTCT of HIV. These include; advanced maternal AIDS-related illness, low CD4 cell count during pregnancy, route of delivery, breastfeeding [7,8], prematurity [9], co-infections with genital herpes, syphilis and hepatitis C [10-12], low birth weight,
intra-uterine growth restriction, maternal and fetal anemia and failure of the newborn to complete postnatal oral ARV drugs [13]. Plasma HIV VL is well recognized as the strongest predictor of both horizontal [14] and vertical HIV transmission [3,4,9,15-18]. A study reported a nearly threefold increase in the risk of perinatal HIV transmission for each additional log_{10} increase in VL [19] and these findings have been echoed in other studies. All studies have shown higher transmission events among mothers with higher VL levels [20-22] with one reporting no HIV transmission events among infants born to women on ART at conception and virally suppressed at delivery [23]. The levels of HIV VL in the community have also been found to have an impact on MTCT as they have an effect on HIV incidence in the population [24], thereby influencing the rate by which women of reproductive age acquire HIV.

Maternal VL may be the main determinant of vertical HIV transmission, however there is no VL level above or below which transmission always or never occurs [3,25,26]. Transmission has been known to occur even in the presence of low maternal VL [27] while on the other hand, not all infants born to mothers with elevated VL levels get infected. The risk of perinatal transmission is proportional to the maternal VL levels, being low at lower maternal VL levels and high at higher maternal VL levels [3,16,17,23]. One of the keys to reducing MTCT rates is controlling viral replication which in turn reduces maternal plasma and genitourinary HIV VL levels [3,28].

**Role of ART in prevention of mother-to-child-transmission (PMTCT) of HIV**

Without any intervention, approximately 20 – 40% of infants born to HIV-infected mothers will be infected with HIV [29]. The role of ARVs in PMTCT of HIV was first defined over two decades ago when the PACTG 076 study demonstrated that the risk of HIV transmission from a mother to her child could be reduced by as much as 67.5% (95% CI: 40.7-82.1) with the use of a single drug - zidovudine - when given to the mother during pregnancy and delivery, and to their infant postnatally [30]. This could arguably be the finding that significantly altered the management of HIV-infected pregnant women.

Another landmark moment in the use of ART for PMTCT came in 2011 when Malawi implemented a new approach of lifelong ART for all pregnant and breastfeeding women with HIV regardless of CD4 count or clinical stage (Option B+). The rationale behind this included: limited access to CD4 cell count analysis, high fertility rate, the fact that most mothers became pregnant again soon after stopping breastfeeding and presented to ANC late which delayed their re-starting of ARV prophylaxis, concerns over development of resistance with the stopping and re-starting of prophylaxis regimens, regular attendance of HIV care by mothers being on lifelong ART and the benefits of improved maternal health and decreased HIV-related mortality and prevention of HIV transmission to non-infected partners by early ART start [31]. This policy was supported by studies showing that three drug
regimens were the most effective at reducing MTCT [13,32-34] and by the fact that adoption of this policy meant that subsequent pregnancies were protected from conception.

Delivery by caesarean section before labour and rupture of membranes, reducing the time membranes are ruptured before a child is born, avoidance of breastfeeding in settings where formula feeds are easily accessible or encouraging exclusive breastfeeding in settings where formula feeds are less affordable and cannot be safely offered are all factors which can reduce the risk of MTCT [35-39]. These measures, effective as they may be, are not always feasible to adopt in many settings. This therefore leaves ARV drugs as the cornerstone of PMTCT.

Risk of MTCT decreases with an increase in the duration that a mother has been on ART. Use of ART prior to conception and its initiation early in pregnancy guarantees the mother to be on ART for longer before labour and delivery, which is associated with lower rates of HIV transmission [16,40]. Fitzgerald et al. [41] has reported reductions in HIV transmission by as much as 20% for each additional week a mother was on ART and has recorded no transmission events among women on ART for at least 8 weeks by the time of delivery. The earlier ART is started, the higher the probability of being virally suppressed at delivery and the lower the rate of perinatal transmission [23,42]. Women conceiving on ART have substantial improvements in virological control over time [43].

In South Africa, single dose nevirapine for the mother during labour and to the baby after delivery was introduced into the national PMTCT programme in 2002 [44]. This was modified to the initiation of triple drug ART to HIV-infected pregnant or breastfeeding women with a CD4 ≤200 cells/uL in 2005 before the threshold was increased to a CD4 cell count ≤350 cells/uL in 2010 [45]. In keeping with WHO guidelines, these guidelines were later revised to ART initiation in all HIV-infected pregnant or breastfeeding women regardless of CD4 cell count or WHO clinical stage throughout the pregnancy and breastfeeding periods in 2013 [46].

In September 2015, new guidelines were released by WHO recommending lifelong ARV treatment for all HIV-infected persons regardless of CD4 cell count or WHO clinical stage [47]. ARV drugs not only limit transmission of HIV by reducing viral replication hence lowering maternal VL [48] but also provide infant pre- and post-exposure prophylaxis as well as reducing the influence of other perinatal risk factors (low CD4 cell count, prolonged rupture of membranes, invasive procedures and low birth weight) on vertical HIV transmission [32]. ART is a safe and effective means of attaining maternal virologic suppression [34] and prevents MTCT of HIV while also improving maternal wellbeing [49].

**ART treatment response monitoring strategies**

Over 15 million people are receiving ART worldwide [50] which has been made possible by the rapid scale up of systems to initiate ART to all HIV positive persons in need of it. This progress has made it critical to put in place measures that will timely identify non-adherent patients and in the case of
treatment failure, determine whether ART regimens need to be switched or not. Response to ART can be monitored clinically (by clinical evaluation), immunologically (by measurement of CD4+ T cells) or virologically (by measurement of HIV RNA levels).

Strategies of monitoring individuals on ART have changed over the years. Clinical monitoring with or without immunological monitoring was the main strategy recommended by the WHO in the 2006 and 2010 WHO guidelines [51,52] and was mainly used in low income settings with virologic monitoring being the standard of care in high income countries [53]. WHO encouraged countries to start phasing in virologic monitoring and in 2013, recommended routine virologic monitoring (VL measurements 6 and 12 months after ART initiation, then 12 monthly thereafter) as the preferred monitoring approach to diagnose and confirm ARV treatment failure [46]. In settings where VL testing was not routinely available, targeted virologic monitoring based on immunological or clinical criteria was to be used to diagnose treatment failure [46]. Each of these different monitoring strategies has advantages and disadvantages which are explored below.

Clinical monitoring versus Immunological monitoring.

The most common clinical monitoring system used in resource-limited settings is the WHO Clinical Staging and Disease Classification System. This system categorises HIV disease on the basis of clinical manifestations from Stage I to IV, progressing from primary infection to advanced HIV/AIDS following clinical evaluation of a patient for specific symptoms, signs or clinical conditions. WHO clinical stages do not always correlate with CD4 cell counts as patients with low CD4 cell counts may still be clinically well, not displaying any signs or symptoms of ill-health. Clinical failure is a very late development and therefore, relying on clinical grounds alone to define treatment failure is suboptimal as it would entail only intervening once people start displaying features of advanced disease.

Mortality and morbidity comparisons among populations monitored clinically versus those monitored immunological have shown increased mortality among populations monitored clinically and better health and survival outcomes when CD4 cell count testing was added [54,55]. This could be due to earlier switching to second line regimens among patients with access to immunologic monitoring. When evaluating the ability to detection adverse drug effects among patients on ART, having CD4 cell counts along clinical monitoring had no additional benefits [54]. Few countries have solely relied on clinical monitoring with most having some CD4 cell count assessments alongside clinical monitoring.

Immunologic monitoring versus Virologic monitoring.

Immunological monitoring has been the main predictor of HIV disease progression [56] and death [57], ART eligibility assessment and ART treatment response monitoring [51,52]. Due to different individual variations in immunological responses to ART, changes in CD4 cell counts are difficult to interpret. Absolute CD4 cell counts during pregnancy are affected by hemodilution, decreasing during
pregnancy. These therefore need to be interpreted with care and may not be appropriate to diagnose treatment failure during pregnancy. CD4 cell count percentage is a better marker during pregnancy but its use is limited in that it is a measure not routinely done for adults and there will be no previous readings to which comparisons can be made.

Relying on immunologic monitoring to detect treatment failure is also limited due to the poor sensitivity and low positive predictive value immunologic monitoring has on detecting patients not virally suppressed after ART initiation [58-60]. Virologic monitoring provides an early and more accurate indication of treatment failure and the need to switch to second-line drugs usually before clinical or immunological deterioration occurs. Addition of VL monitoring leads to higher switch rates [61], reducing the time patients are on a failing regimen [62]. Relying on CD4 cell count to identify patients failing virologically could lead to delays in intervening where necessary as immunologic monitoring is not always reliable at identifying women with an elevated VL at risk of transmitting HIV to their child [63].

Addition of VL testing decreases the probability of switching to second line regimens unnecessarily. The immunologic response to ART lags behind virologic response as some virally suppressed patients have stagnant CD4 cell counts after months on treatment [64]. By identifying those that are virally suppressed even in the presence of low CD4 cell counts, virologic monitoring prevents them being unnecessarily switched to second line drugs, saving the health care system money. Virologic monitoring can also be used as a tool to monitor adherence and to discriminate between treatment failure and non-adherence, allowing patients in-need of adherence support to be identified and assisted [65,66]. By intervening in patients flagged by VL testing, patients remain on the first line regimens for longer, decreasing costs of providing second line to a larger proportion of individuals. The impact of virologic monitoring on mortality still remains unclear with some studies reporting no additional effect on mortality of adding VL testing to immunological monitoring [55,67] while one study reported a beneficial effect [61].

Use of VL monitoring is increasing, raising questions on the necessity of immunological monitoring among virally suppressed individuals with access to VL testing [68]. CD4 cell count testing has played a major role in assessing patients eligible for ART, however as more countries adopt the new WHO guidelines of initiating ART to all HIV-infected persons, there may be a need to either decrease the frequency of CD4 cell count monitoring [69] or stop it as a cost saving measure.

Management of viremia among HIV-infected adults on ART in resource-limited settings

Intermittent episodes of low level viremia also known as viral blips (VL between 50-1000 copies/mL) occur frequently, are associated with higher levels of viral replication but do not predict virologic failure [70,71]. They are more likely to occur in patients in whom the peripheral blood mononuclear cells with replication-competent HIV-1 decay at a slow pace [71]. Episodes of viral blips are not
associated with greater rates of virologic failure [70] and are thought to be a result of specimen variation, processing errors and the inability of current ART regimens to completely stop HIV replication [71].

Raised VL was defined as VL above 5000 copies/mL in an adherent person with no other reasons for an elevated VL in 2010 [52]. In 2013 this threshold was lowered to 1000 copies/mL [46] as the risk of HIV transmission at VL levels less than 1000 copies/ml is low making it unnecessary to switch ART regimens in patients with a VL level below this threshold [46]. In the 2013 South African guidelines, to detect and confirm treatment failure, a plasma VL above 1000 copies/mL must be obtained on two consecutive VL measurements 3-6 months apart with adherence support in between [46]. As viral resistance checking is not routinely performed in this setting due to the costs, a diagnosis of treatment failure is done based on receipt of a second VL result above 1000 copies/mL, necessitating the switching of ART regimens.

**VL monitoring among HIV-infected pregnant women on ART in resource-limited settings**

The WHO guidelines have always made a clear distinction between HIV-infected adults and HIV-infected pregnant and breastfeeding women with regards to when to start ART and which drugs to use. HIV-infected pregnant and breastfeeding women are given special mention with often different recommendations due to the fact that health related issues among this population affect not only the mother but also her child. These women have historically started ART at higher CD4 cell counts when compared to other adults receiving ART and were the second group (after infants less than the age of 5 years) to be initiated on ART regardless of CD4 cell count or WHO clinical staging [46].

This has, however not been the case with regards to VL monitoring strategies. Until recently, recommendations as to the timing and frequency of VL monitoring among pregnant and breastfeeding women on ART have been the same as those of HIV-infected adults on ART. In 2013, the South African antiretroviral treatment guidelines made the distinction by recommending VL testing for all pregnant women on ART at their first ANC presentation regardless of when the last VL test had been performed [72]. Results were to be reviewed within 2 weeks and for women with VL ≤1000 copies/mL, repeat tests were to be performed every 6 months throughout the pregnancy and breastfeeding periods. For women with VL >1000 copies/mL, adherence was to be reviewed and re-enforced with a repeat VL test done after one month instead of the recommended 3 months used for adults on ART. These recommendations increased the frequency of VL monitoring among pregnant and breastfeeding women receiving ART as VL testing for the rest of the adults on ART was being routinely done at month 6, 12 then annually thereafter.

Given the importance of viremia in HIV transmission risk, there is a clear need for close ART treatment monitoring during the pregnancy and breastfeeding periods. More frequent VL monitoring during this time is necessary in order to timely intervene either by offering adherence support or by
switching failing ART regimens where necessary. This is to ensure sustained viral suppression throughout pregnancy, labour and delivery and postpartum during breastfeeding to decrease the risk of HIV transmission from a mother to her child. The value of more frequent VL monitoring among HIV-infected pregnant and breastfeeding women is well recognised, however there is not enough evidence as to the best timing intervals and the frequency of VL testing during pregnancy and breastfeeding.

Needs for future research

The role of ART in reducing the risk of HIV transmission is well established, however the role of VL monitoring in resource limited settings still needs to be evaluated. VL monitoring is essential for individual health as being virally suppressed reduces mortality and onward transmission of HIV which would ultimately reduce HIV incidence at a population level. With the rapid scale up of lifelong ART provision to all HIV-infected pregnant and breastfeeding women, there will be an increase in the number of woman living with HIV on ART. It is therefore critical to put up measures that can timely identify treatment failure, preventing development of resistant strains. Also, an increase in the number of healthy women initiating ART will generate different adherence issues. Hans et al. in a study comparing long term retention of women initiated ART under Option B+ to those initiated ART due to ill-health in Malawi reported that after 3 years, only approximately 70% of all women started ART under option B+ were still in care. He also reported that women initiated ART during pregnancy under Option B+ were 5 times more likely to have no follow up visit and those who attended their first follow up visit, were 1.6 times more likely to be lost to follow-up within the first year [73]. These adherence issues being raised from Malawi which was the first site to implement Option B+, need to be explored as they could have an impact on how ART treatment monitoring can be tailored for this population and on the frequency and optimal timing of VL monitoring among pregnant women on ART.

The cost of VL testing is the major barrier to routine VL monitoring in resource-limited settings, where the majority of HIV-infected people reside. More cost-effective strategies for VL monitoring like point-of-care VL tests need further research. These new strategies eliminate the need for specimen storage and transportation to central processing sites, reducing the turn-over time before a patient receives their result. These strategies would be cost-saving for patients as they would eliminate the need for patients to make second clinic appointments for result collection as well as having health benefits as they would enable clinicians to timely intervene when necessary.

References


HIV viral load monitoring in HIV-infected pregnant women established on antiretroviral therapy in Cape Town, South Africa

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Keywords: HIV, mother-to-child transmission, pregnancy, antiretroviral therapy, viral load, South Africa.

1This manuscript is written according to the requirements in the Authors guidelines for the Journal of the International AIDS Society (JIAS). An extract of these guidelines is appended in Part IV of this mini-dissertation (Appendix 8).
Abstract

Introduction: Use of HIV viral load (VL) monitoring is increasing across Africa however there are few insights into VL monitoring strategies during pregnancy. We describe public sector VL monitoring practices in a cohort of HIV-infected pregnant women established on antiretroviral therapy (ART) in Cape Town, South Africa. Annual VL monitoring has been routine in this setting since 2010, with two consecutive VL results >1000 copies/mL used to diagnose virologic failure.

Methods: We enrolled consecutive HIV-infected pregnant women making their first visit to a primary care antenatal clinic between March 2013 and June 2014 who initiated ART before pregnancy. All women received a research ultrasound to determine gestation at booking from which an estimated date of conception was calculated. Laboratory systems were then used to follow-up routine VL testing practices from 15 months before the estimated date of conception to delivery.

Results: Among 520 women the median age was 31 years [Interquartile range (IQR), 28-35 years] and the median duration of ART use was 2.7 years [IQR, 1.5-5.1 years]. In the 15 months before the estimated date of conception, 66% (n=311) of women had at least one VL test done and 9% of these results (n=29) were >1000 copies/mL. During the pregnancy, 80% (n=415) of women had at least one VL test done and 12% (n=49) of these results were >1000 copies/mL. Pregnant women with elevated VL >1000 copies/mL were more likely to have been on ART for longer (p=0.049), report at least 2 missed ART doses in the preceding 30 days (p=0.043) and be on a protease-inhibitor-based regimen (p=0.016). Among women with VL >1000 copies/mL during pregnancy, 59% (n=29) had a repeat VL test done at a median of 3.5 months after the initial test (IQR 2.1-4.4 months) and 52% of women (n=15) had a VL >1000 copies/mL on this second test.

Conclusions: While coverage of VL monitoring appears high in this setting, a substantial fraction of women with elevated VL in pregnancy are never retested. With increasing numbers of HIV positive women using ART, greater attention is needed to design and implement effective strategies for VL monitoring in pregnancy.
Introduction

An estimated 150,000 children below the age of 15 were newly infected with HIV in 2015 [1], predominantly through mother-to-child transmission (MTCT). Plasma HIV viral load (VL) is known to be the main predictor of perinatal HIV transmission [2,3] with most antiretroviral (ARV) drugs reducing the risk of MTCT of HIV by reducing the level of maternal HIV VL [4]. This is evident in studies showing that infants born to mothers who are virally suppressed at delivery had either no transmission events or very low transmission rates dependent on the maternal VL levels [5-8].

The new World Health Organization (WHO) guidelines recommend the initiation of lifelong ART to all people living with HIV regardless of CD4 cell count or clinical stage of the disease [9]. This will result in an increase in the number of women receiving ART which in turn will result in an increase in the proportion of women conceiving on ART. It is assumed that women who conceive on ART have the greatest potential of being virally suppressed throughout pregnancy and delivery. To assess if this is true, we need to identify and implement effective monitoring strategies. VL monitoring has been the standard of care in most high-income settings for decades but due to the high costs and inadequate laboratory facilities, CD4 cell count and clinical monitoring have been the main monitoring tool in resource-limited settings [10]. However, in recent times there has been an increase in the use of VL monitoring across Africa. In South Africa, HIV VL monitoring has been provided in the public sector since 2004 for all HIV positive adults on ART yet there are little data on routine public sector VL monitoring practices during pregnancy, with most data among this key population coming from trial settings.

Given the important role HIV VL plays in MTCT of HIV, understanding maternal VL testing practices and maternal viral suppression within the public sector of a high burden setting, where the majority of HIV positive women are followed up is of great importance in-order for timely interventions to be put in place, not only to prevent new mother-to-child transmissions but also for the health of the mother [11]. This study aimed to describe public sector HIV VL monitoring practices, describing the following outcomes (i) frequency of maternal VL testing and maternal VL levels before and during pregnancy, (ii) patterns of VL re-testing among those with at least one raised VL during pregnancy and (iii) predictors of having a VL test and having a raised VL>1000 copies/mL during pregnancy, in a cohort of HIV-infected pregnant women initiated on ART before pregnancy in Cape Town, South Africa. We hypothesize that public sector VL testing among HIV-infected pregnant women who initiated ART before pregnancy occurs frequently, however subsequent VL testing for those with a raised VL is not consistent.
Methods

We conducted a retrospective cohort study nested within the first phase of the Strategies to optimize antiretroviral therapy services for maternal and child health (MCH-ART) trial (ClinicalTrials.gov NCT01933477) which has been described in detail elsewhere [12]. In summary, the MCH-ART trial was conducted at the Gugulethu Midwife-Obstetric Unit (MOU) in Cape Town, South Africa with enrolment between March 2013 and June 2014. Its primary objective was to compare a mother-and-child health-focused ART service to the general adult ART services during the postpartum period with phase 1 being a cross-sectional evaluation of consecutive HIV-infected pregnant women seeking antenatal care. Between March 2013 and June 2014, 5551 women booked for ANC at the Gugulethu MOU, of whom 1840 (33%) were HIV positive. Among these, 1554 women were enrolled into the MCH-ART study with reasons for exclusion including: ineligible (93%), missed (7%) and refused (0.3%).

The Gugulethu MOU is a large primary care antenatal care (ANC) clinic situated in the peri-urban area of Gugulethu in Cape Town, South Africa. It provides basic antenatal, obstetric and postpartum services to over 4000 women per year, with complicated cases referred to a hospital. Uptake of ANC services in this community is high with over 95% of pregnant women attending ANC before delivery. HIV-infected women on ART receive their ARV drugs within the routine adult HIV clinics. When pregnant, they are referred to the MOU for their ANC but their ART management remains within the HIV clinics. When pregnant, they are referred to the MOU for their ANC but their ART management remains within the HIV clinics. VL monitoring has been routine in this setting since 2010, with local guidelines specifying VL testing at 6 and 12 months after ART initiation then annually thereafter [13]. Adherence counselling and a repeat VL 3-6 months later are indicated for all with raised VL >1000 copies/mL, with two consecutive VL results >1000 copies/mL used to diagnose virologic failure.

Consecutive HIV-infected pregnant women making their first visit to the Gugulethu MOU between March 2013 and June 2014, aged ≥18 years, enrolled into the MCH-ART study and who had been on ART at the estimated time of conception, were eligible for this analysis. Women who had initiated ART during the current pregnancy, who were then determined not to be pregnant at the first ANC visit or had suffered a pregnancy loss were excluded. Of the 1554 women enrolled into the MCH-ART study, 575 women had been on ART at the time of booking and of these, 520 women fulfilled the eligibility criteria and were included in this analysis. Reasons for exclusion included not pregnant (1%), initiated ART after conception but before presentation to Gugulethu MOU (8%) and birth outcomes unknown (1%).

At enrolment into the parent study, the women filled in a questionnaire giving details of their demographic characteristics (age, schooling history, employment status and marital status), obstetric history (parity and gravidity) and ART history (ART initiation dates, disclosure, current
regimen and adherence). Adherence was assessed at booking through self-reported number of missed doses in the past 30 days. As part of the study, all women underwent an ultrasound to determine gestational age (GA). This GA was then used to estimate the date of conception. Data on haemoglobin and CD4 cell count at the first ANC visit, and on the delivery details were abstracted from the patient clinic folders. In addition, HIV VL testing (Abbott RealTime HIV-1, level of detection 50 copies/mL), including date of VL test and associated VL results were abstracted from the South African National Health Laboratory Service (NHLS) system from 15 months before the estimated date of conception to delivery.

Data were analysed using Stata Version 13.0 (Stata Corporation, College Station, TX, USA). Maternal characteristics at the first ANC presentation were summarised using medians and IQRs for continuous variables and using proportions for categorical variables. Chi-squared and Fishers exact tests were used to compare proportions between groups according to the expected number of observations within each cell and Kruskal Wallis tests were used to compare medians between groups. Viremia was defined at VL >1000 copies/mL following recommended definitions of virologic failure [14].

The proportion of women with a VL result and the associated VL levels were described for the two time periods (i) before conception and (ii) during pregnancy as shown in Figure 1 below.

(i) HIV VL testing before conception - Only women who had been on ART for at least 6 months at the estimated time of conception were included in the ‘before conception’ analysis as the first VL test is only performed 6 months after ART initiation [13]. The ‘before conception’ period extended from the estimated date of conception to 15 months prior. For women with more than one VL result during this period, the ‘before conception’ VL was defined as the VL result closest to the estimated date of conception.

![Figure 1](image_url)

**Figure 1.** Eligibility criteria and VL window periods for the time periods; before conception and during pregnancy.
(ii) HIV VL testing during pregnancy – VL tests were included in the ‘during pregnancy’ period if they were done between the estimated date of conception and delivery. For women with more than one VL result during their pregnancy, the ‘during pregnancy’ VL was defined as the VL result closest to the estimated date of conception.

Women receiving VL monitoring and proportions with VL results in the categories VL ≤50, 51-1000 and >1000 copies/mL were described using proportions with 95% confidence intervals (CIs). Logistic regression, using complete case analysis, was used to identify the predictors of having a VL result and of having a raised VL >1000 copies/mL during pregnancy with results presented as odds ratios (OR) with 95% CI.

The parent study was approved by the Human Research Ethics Committee of the University Of Cape Town Faculty Of Health Sciences (HREC-UCT), the Institutional Review Board of the Columbia University Medical Centre as well as the Provincial Government of the Western Cape Department of Health. Ethical approval for this analysis was obtained from the HREC-UCT (HREC REF: 097/2016).

**Results**

*Maternal characteristics at start of ANC*

Maternal characteristics at the first ANC visit are shown in Table 1. The median age at the start of ANC was 31 years [Interquartile range (IQR), 28-35 years]. 23% (n=117) had completed high school, 38% (n=200) were currently employed and 49% (n=254) were either married or staying with their partners. Median gestation was 21 weeks [IQR, 15-28 weeks]; median duration of ART use was 2.7 years [IQR, 1.5-5.1 years] and 16% (n=75) reported having missed at least 2 ART doses in the preceding 30 days. Information on ART regimen was available for 85% (n=442) of women and 35% (n=153) of them did not know which regime they were on. Of those who knew their ART regimens, the majority were on a tenofovir based regimen with either efavirenz or nevirapine. The median CD4 cell count was 402 cells/µL [IQR, 282-535] and 19% (n=86) had a haemoglobin level less ≤10g/dL. 82% (n=398) of the women delivered at term.

*Viral load testing before conception*

470 women who had been on ART for at least 6 months at the estimated time of conception were included in the analysis for before conception VL testing. Of these women, 66% (95% CI: 62-70) had at least one VL result in adult HIV services before conception. Women who had a VL before conception did not differ significantly from those who did not with respect to age, completing high school, marital status or ART regimen. Of those with a VL result, VL of ≤50, 51-1000 and >1000 copies/mL were found in 85% (95% CI: 80-89), 6% (95% CI: 3-9) and 9% (95% CI: 6-13) of women respectively.
Table 1. Description of HIV-infected pregnant women on ART at conception at the start of antenatal care

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of non-missing (%)</th>
<th>Pregnant women on ART at conception (n = 520)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (IQR), years</td>
<td>520 (100)</td>
<td>31 (28 - 35)</td>
</tr>
<tr>
<td>&lt; 25, n (%)</td>
<td>40 (8)</td>
<td></td>
</tr>
<tr>
<td>25 – 29</td>
<td>151 (29)</td>
<td></td>
</tr>
<tr>
<td>30 – 34</td>
<td>197 (38)</td>
<td></td>
</tr>
<tr>
<td>≥ 35</td>
<td>132 (25)</td>
<td></td>
</tr>
<tr>
<td>Completed high school</td>
<td>520 (100)</td>
<td>117 (23)</td>
</tr>
<tr>
<td>Currently employed</td>
<td>520 (100)</td>
<td>200 (38)</td>
</tr>
<tr>
<td>Married/Cohabiting</td>
<td>520 (100)</td>
<td>254 (49)</td>
</tr>
<tr>
<td>Disclosure to anybody</td>
<td>520 (100)</td>
<td>515 (99)</td>
</tr>
<tr>
<td>Median gravidity (IQR)</td>
<td>520 (100)</td>
<td>3 (2 - 3)</td>
</tr>
<tr>
<td>Primagravida</td>
<td>520 (100)</td>
<td>50 (10)</td>
</tr>
<tr>
<td>Median gestation at booking (IQR), weeks</td>
<td>503 (97)</td>
<td>21 (15 - 28)</td>
</tr>
<tr>
<td>≤ 14, n (%)</td>
<td>102 (20)</td>
<td></td>
</tr>
<tr>
<td>14 - 28</td>
<td>277 (55)</td>
<td></td>
</tr>
<tr>
<td>&gt; 28</td>
<td>124 (25)</td>
<td></td>
</tr>
<tr>
<td>Median gestation at delivery (IQR), weeks</td>
<td>488 (94)</td>
<td>39 (37 - 40)</td>
</tr>
<tr>
<td>&lt; 37</td>
<td>90 (18)</td>
<td></td>
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<tr>
<td>≥ 37</td>
<td>398 (82)</td>
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<tr>
<td>Currently on ART</td>
<td>520 (100)</td>
<td>520 (100)</td>
</tr>
<tr>
<td>ART regimen</td>
<td>442 (85)</td>
<td></td>
</tr>
<tr>
<td>TDF-3TC-EFV/NVP</td>
<td>194 (44)</td>
<td></td>
</tr>
<tr>
<td>other NNRTI-based regimen</td>
<td>60 (14)</td>
<td></td>
</tr>
<tr>
<td>PI-based regimen</td>
<td>35 (8)</td>
<td></td>
</tr>
<tr>
<td>Participant doesn’t know</td>
<td>153 (35)</td>
<td></td>
</tr>
<tr>
<td>Median duration on ART (IQR), years</td>
<td>520 (100)</td>
<td>2.7 (1.5 - 5.1)</td>
</tr>
<tr>
<td>&lt;2</td>
<td>184 (35)</td>
<td></td>
</tr>
<tr>
<td>2 – 4</td>
<td>164 (32)</td>
<td></td>
</tr>
<tr>
<td>≥ 4</td>
<td>172 (33)</td>
<td></td>
</tr>
<tr>
<td>Number of missed ART doses in past 30 days</td>
<td>479 (92)</td>
<td></td>
</tr>
<tr>
<td>1+</td>
<td>106 (22)</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>75 (16)</td>
<td></td>
</tr>
<tr>
<td>Median CD4 cell count (IQR), cells/µL</td>
<td>510 (98)</td>
<td>402 (282 - 535)</td>
</tr>
<tr>
<td>≤ 200,</td>
<td>54 (11)</td>
<td></td>
</tr>
<tr>
<td>201 - 350</td>
<td>150 (29)</td>
<td></td>
</tr>
<tr>
<td>351 - 500</td>
<td>144 (28)</td>
<td></td>
</tr>
<tr>
<td>&gt; 500</td>
<td>162 (32)</td>
<td></td>
</tr>
<tr>
<td>Median haemoglobin (IQR), g/dl</td>
<td>520 (100)</td>
<td>11.4 (10.5 - 12.2)</td>
</tr>
<tr>
<td>≤ 10, n (%)</td>
<td>86 (19)</td>
<td></td>
</tr>
</tbody>
</table>

ART – antiretroviral therapy; IQR – interquartile range; NNRTI – non-nucleoside reverse transcriptase inhibitor; TDF – tenofovir; 3TC – lamivudine; EFV – efavirenz; NVP – nevirapine; PI – protease inhibitor (lopinavir/ritonavir)

In a multivariable logistic regression model including age, marital status and years of ART use, having a VL before conception was associated with time on ART (aOR for a one-year increase in ART use 0.90; 95% CI: 0.83-0.99). Having a raised VL >1000 copies/mL before conception was associated with being married or cohabiting (aOR 2.48; 95% CI: 1.05-5.87) and with time on ART.
(aOR for a one-year increase in ART use 1.23; 95% CI: 1.05-1.45). In same model, having a lower VL ≤1000 copies/mL was associated with older age (aOR for a one-year increase in age, 0.91; 95% CI: 0.82-1.00).

**Viral load testing during pregnancy**

80% (95% CI: 76-83) of women had at least one VL during pregnancy (Figure 2). 21% (n=87) of these tests were done at ANC facilities while 79% (n=328) were done at routine adult HIV clinics. 19% (n=101) of these tests were done within 7 days of booking. Of those with a VL during pregnancy, VL of <50, 51-1000 an >1000 copies/mL were found in 80% (95% CI: 75-83), 9% (95% CI: 6-12) and 12% (95% CI: 9-15) of women respectively.

![Flow diagram of HIV viral load testing during pregnancy among HIV-infected pregnant women on ART.](image)

Women who had a VL test during pregnancy did not differ significantly from those who did not with respect to age, completing high school, employment status, marital status, disclosure to current partner, gravidity, ART regimen, gestational age at first ANC visit, gestational age at delivery or number of missed doses in the past 30 days (Table 2). However, women who had been on ART for longer were less likely to have a VL test done during pregnancy ($P=0.005$).
Table 2. Description of HIV-infected pregnant women on ART according to whether an HIV viral load test was done during pregnancy or not (N=520)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of non-missing (%)</th>
<th>VL test not done (n = 105)</th>
<th>VL test done (n = 415)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (IQR), years</td>
<td>520 (100)</td>
<td>32 (28 - 34)</td>
<td>31 (28 - 35)</td>
<td>0.960</td>
</tr>
<tr>
<td>&lt; 25, n (%)</td>
<td></td>
<td>4 (4)</td>
<td>36 (9)</td>
<td>0.104</td>
</tr>
<tr>
<td>≥ 25</td>
<td></td>
<td>101 (96)</td>
<td>379 (91)</td>
<td></td>
</tr>
<tr>
<td>Completed high school</td>
<td>520 (100)</td>
<td>21 (20)</td>
<td>96 (23)</td>
<td>0.492</td>
</tr>
<tr>
<td>Currently employed</td>
<td>520 (100)</td>
<td>41 (39)</td>
<td>159 (38)</td>
<td>0.890</td>
</tr>
<tr>
<td>Married/Cohabitling</td>
<td>520 (100)</td>
<td>50 (48)</td>
<td>204 (49)</td>
<td>0.778</td>
</tr>
<tr>
<td>Disclosure to current partner</td>
<td>514 (99)</td>
<td>85 (81)</td>
<td>346 (85)</td>
<td>0.365</td>
</tr>
<tr>
<td>Multigravida</td>
<td>520 (100)</td>
<td>96 (91)</td>
<td>374 (90)</td>
<td>0.685</td>
</tr>
<tr>
<td>Median gestation at booking (IQR), weeks</td>
<td>503 (98)</td>
<td>20 (15 - 25)</td>
<td>21 (16 - 28)</td>
<td>0.211</td>
</tr>
<tr>
<td>≤ 14, n (%)</td>
<td></td>
<td>22 (22)</td>
<td>80 (20)</td>
<td></td>
</tr>
<tr>
<td>14 - 28</td>
<td></td>
<td>58 (58)</td>
<td>219 (54)</td>
<td>0.479</td>
</tr>
<tr>
<td>&gt; 28</td>
<td></td>
<td>20 (20)</td>
<td>104 (26)</td>
<td></td>
</tr>
<tr>
<td>ART regimen, n (%)</td>
<td>442 (85)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF-3TC-EFV/NVP</td>
<td></td>
<td>46 (51)</td>
<td>148 (42)</td>
<td>0.384</td>
</tr>
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<td>other NNRTI-based regimen</td>
<td></td>
<td>10 (11)</td>
<td>50 (14)</td>
<td></td>
</tr>
<tr>
<td>PI-based regimen</td>
<td></td>
<td>8 (9)</td>
<td>27 (8)</td>
<td></td>
</tr>
<tr>
<td>Participant doesn’t know</td>
<td></td>
<td>26 (29)</td>
<td>127 (36)</td>
<td></td>
</tr>
<tr>
<td>Median duration on ART (IQR), years</td>
<td>520 (100)</td>
<td>3.3 (1.8 - 5.8)</td>
<td>2.5 (1.5 - 4.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>&lt;2, n (%)</td>
<td></td>
<td>28 (27)</td>
<td>156 (38)</td>
<td>0.035</td>
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<tr>
<td>2 - 4</td>
<td></td>
<td>32 (30)</td>
<td>132 (32)</td>
<td></td>
</tr>
<tr>
<td>≥ 4</td>
<td></td>
<td>45 (43)</td>
<td>127 (31)</td>
<td></td>
</tr>
<tr>
<td>Number of missed ART doses in past 30 days</td>
<td>479 (92)</td>
<td></td>
<td>25 (26)</td>
<td></td>
</tr>
<tr>
<td>1+, n (%)</td>
<td></td>
<td>25 (26)</td>
<td>81 (21)</td>
<td>0.302</td>
</tr>
<tr>
<td>2+</td>
<td></td>
<td>21 (22)</td>
<td>54 (14)</td>
<td>0.061</td>
</tr>
</tbody>
</table>

ART – antiretroviral therapy; IQR – interquartile range; NNRTI – non-nucleoside reverse transcriptase inhibitor; TDF – tenofovir; 3TC – lamivudine; EFV – efavirenz; NVP – nevirapine; PI – protease inhibitor (lopinavir/ritonavir)

Pregnant women that had been on ART for longer (P=0.049), were on a protease-inhibitor (PI) based regimen (P=0.016) and those reporting having missed at least 2 ART doses in the preceding 30 days (P=0.043) were more likely to have raised VL >1000 copies/mL (Table 3).

In simple logistic regression models (Table 4), raised VL >1000 copies/mL during pregnancy was associated with reporting two or more missed ART doses in the past 30 days (OR 2.32; 95% CI: 1.12-4.82). In a multivariable model including age, marital status, years of ART use, reporting 2 or more missed ART doses in the past 30 days was strongly associated with having a raised VL >1000 copies/mL (aOR 2.19; 95% CI: 1.04-4.60).
Table 3. Description of HIV-infected pregnant women on ART by viral load levels during pregnancy.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VL ≤ 50 copies/mL</th>
<th>VL 51-1000 copies/mL</th>
<th>VL &gt; 1000 copies/mL</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (IQR), years</td>
<td>31 (28 - 35)</td>
<td>30 (28 - 34)</td>
<td>32 (28 - 34)</td>
<td>0.473</td>
</tr>
<tr>
<td>&lt; 25, n (%)</td>
<td>26 (8)</td>
<td>5 (14)</td>
<td>5 (10)</td>
<td>0.440</td>
</tr>
<tr>
<td>≥ 25, n (%)</td>
<td>304 (92)</td>
<td>31 (86)</td>
<td>44 (90)</td>
<td></td>
</tr>
<tr>
<td>Completed high school</td>
<td>82 (25)</td>
<td>6 (17)</td>
<td>8 (16)</td>
<td>0.263</td>
</tr>
<tr>
<td>Currently employed</td>
<td>132 (40)</td>
<td>10 (28)</td>
<td>17 (35)</td>
<td>0.307</td>
</tr>
<tr>
<td>Married/Cohabiting</td>
<td>164 (50)</td>
<td>19 (53)</td>
<td>21 (43)</td>
<td>0.605</td>
</tr>
<tr>
<td>Disclosure to partner</td>
<td>277 (85)</td>
<td>32 (91)</td>
<td>37 (79)</td>
<td>0.286</td>
</tr>
<tr>
<td>Multigravida</td>
<td>295 (89)</td>
<td>33 (92)</td>
<td>46 (94)</td>
<td>0.688</td>
</tr>
<tr>
<td>Median gestation at booking (IQR), weeks</td>
<td>21 (15 - 28)</td>
<td>26 (18 - 32)</td>
<td>21 (15 - 28)</td>
<td>0.120</td>
</tr>
<tr>
<td>≤ 14, n (%)</td>
<td>68 (21)</td>
<td>3 (9)</td>
<td>9 (18)</td>
<td>0.324</td>
</tr>
<tr>
<td>14 - 28, n (%)</td>
<td>173 (54)</td>
<td>19 (54)</td>
<td>27 (55)</td>
<td></td>
</tr>
<tr>
<td>&gt; 28, n (%)</td>
<td>78 (24)</td>
<td>13 (37)</td>
<td>13 (27)</td>
<td></td>
</tr>
<tr>
<td>ART regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF-3TC-EFV/NVP</td>
<td>124 (45)</td>
<td>12 (38)</td>
<td>12 (29)</td>
<td>0.016</td>
</tr>
<tr>
<td>other NNRTI-based regimen</td>
<td>40 (14)</td>
<td>5 (16)</td>
<td>5 (12)</td>
<td></td>
</tr>
<tr>
<td>PI-based regimen</td>
<td>16 (6)</td>
<td>1 (3)</td>
<td>10 (24)</td>
<td></td>
</tr>
<tr>
<td>Participant doesn’t know</td>
<td>98 (35)</td>
<td>14 (44)</td>
<td>15 (36)</td>
<td></td>
</tr>
<tr>
<td>Median time on ART (IQR), years</td>
<td>2.4 (1.3 - 4.6)</td>
<td>2.9 (2.2 - 5.9)</td>
<td>3.1 (1.9 - 4.9)</td>
<td>0.049</td>
</tr>
<tr>
<td>&lt;2, n (%)</td>
<td>134 (41)</td>
<td>8 (22)</td>
<td>14 (29)</td>
<td>0.139</td>
</tr>
<tr>
<td>2 – 4, n (%)</td>
<td>98 (30)</td>
<td>15 (42)</td>
<td>19 (39)</td>
<td></td>
</tr>
<tr>
<td>≥ 4, n (%)</td>
<td>98 (30)</td>
<td>13 (36)</td>
<td>16 (33)</td>
<td></td>
</tr>
<tr>
<td>Number of missed ART doses in past 30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1+, n (%)</td>
<td>63 (21)</td>
<td>4 (12)</td>
<td>14 (29)</td>
<td>0.194</td>
</tr>
<tr>
<td>2+, n (%)</td>
<td>40 (13)</td>
<td>2 (6)</td>
<td>12 (25)</td>
<td>0.043</td>
</tr>
</tbody>
</table>

ART – antiretroviral therapy; IQR – interquartile range; NNRTI – non-nucleoside reverse transcriptase inhibitor; TDF-tenofovir; 3TC – lamivudine; EFV – efavirenz; NVP – nevirapine; PI – protease inhibitor (lopinavir/ritonavir)

Table 4. Relative odds of having a raised VL >1000 copies/mL during pregnancy among HIV-infected pregnant women on ART

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate OR (95% CI)</th>
<th>p-value</th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0.96 (0.91 - 1.02)</td>
<td>0.233</td>
<td>0.95 (0.89 - 1.02)</td>
<td>0.167</td>
</tr>
<tr>
<td>Married/Cohabiting</td>
<td>1.33 (0.73 - 2.43)</td>
<td>0.347</td>
<td>1.13 (0.60 - 2.12)</td>
<td>0.715</td>
</tr>
<tr>
<td>Time on ART, years</td>
<td>1.08 (0.96 - 1.21)</td>
<td>0.194</td>
<td>1.12 (0.99 - 1.26)</td>
<td>0.083</td>
</tr>
<tr>
<td>Missed at least 2 ART doses in past 30 days</td>
<td>2.32 (1.12 - 4.82)</td>
<td>0.023</td>
<td>2.19 (1.04 - 4.60)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Among the women with a raised VL >1000 copies/mL, 59% (95% CI: 44-73) had a 2nd VL during pregnancy. The median duration between the two tests was 3.5 months (IQR, 2.1-4.4 months). Women were more likely to have a 2nd test if the initial test was conducted in the first trimester as compared to having it in the 2nd or 3rd trimesters (62% vs 38%, P=0.011). There were no
significant differences with respect to age, completing high school, marital status or ART regimen between women who had a repeat test and those who did not. Of those that had a second test, VL of ≤1000 and >1000 copies/mL were observed in 48% (95% CI: 29-67) and 52% (95% CI: 33-71) of women respectively.

Discussion

Approximately two-thirds of women in our study had at least one VL result in the 15 months before conception while over three-quarters had at least one VL result during pregnancy. Of those with a VL before conception, 9% had a raised VL>1000 copies/mL, while 91% had VL≤1000 copies/mL. Of those with at least one VL result during pregnancy, 12% of women had a raised VL>1000 copies/mL and 88% had VL≤1000 copies/mL. Only 59% of the women with at least one raised VL during pregnancy had a repeat test and 52% of those with a repeat test still had a raised VL>1000 copies/mL on the subsequent test.

It is of major concern that not all women received a VL test before conception or during pregnancy and because of this, some women with raised VL during these periods may not have been detected. Not being able to timely detect these women presents opportunities for missed interventions in these women before labor and delivery, a time when the highest risk of transmitting the virus from a mother to their child lies.

A relatively large proportion of women that had a VL test before conception had VL levels ≤1000 copies/mL which is in keeping with results reported by Matthews et al. [15]. Of those that had a VL test during pregnancy, approximately 88% had VL ≤1000 copies/mL. An analysis done on the same cohort reviewing study VL results at booking showed that 87% of women had VL ≤1000 copies/mL at the time of first presentation for ANC [16]. Other cohorts have also described similar results of a relatively large proportion of women on ART at the time of conception being virally suppressed during pregnancy [2,8,15,17]. These results of 88% suppression among HIV-infected pregnant women on ART are good and very close to the 90% UNAIDS target. The associations we found between having a raised VL during pregnancy and ART adherence are expected and have been shown in previous studies [18-20]. The association between having a raised VL and being on a PI-based regimen could however, be an effect rather than the cause as these women could have been switched to that regimen because they were failing. On the other hand, this could also mean that they are failing on their second line regimen and may be in need of 3rd line drugs.

The WHO recommends an adherence intervention and a repeat VL test within 3-6 months for all patients with a raised VL >1000 copies/mL [14]. In our study, just under 60% of women with an initial raised VL during pregnancy had a repeat VL done during pregnancy with none of the women that had a first raised VL in their 3rd trimester having a repeat VL result before delivery. The repeat VL test was done 3.5 months, on average, after the initial elevated VL. This shows that a
substantial proportion (41%) of women with elevated VL during pregnancy were never re-tested before the critical window of intrapartum transmission risk. Of the women that had a subsequent VL test, just under 50% had a raised VL on the second test denoting treatment failure according to WHO guidelines. With South African infant feeding guidelines encouraging women to exclusively breastfeed for the first six months after delivery then introducing appropriate complementary foods from six months, having no VL test or intervention during pregnancy for those women with a raised VL during pregnancy could increase the risk of MTCT of HIV during the breastfeeding period. Of note, our study could not explore further the reasons for this viremia during pregnancy or the reasons for the viremia on the repeat tests and future studies are needed to explore these factors.

In this setting, HIV-infected women on ART are routinely followed up in adult HIV chronic care clinics. Once they become pregnant, they are referred to the MOU for ANC but they continue to receive their ARVs from the adult HIV clinic. In our study, one-fifth of the VL results available during pregnancy were done within ANC services. This could mean ANC clinics are beginning to take on some responsibility in the management of these women as part of the integrated management of HIV-positive pregnant women. WHO recommends integration of ANC and ART services to offer HIV positive pregnant women a comprehensive care package from a single set of health care providers. By offering this service, the need to que in different clinics is eliminated, saving them time and money which could all improve retention in care. However, the low proportion of women with repeat tests could also be due to this breakdown in the continuity of care for these women as the service providers at the ANC may not follow up on previous VL results done at the HIV chronic care facilities and if viremia occurs towards delivery, the service provider at the chronic HIV care clinics may not follow up results from the ANC clinic. Better monitoring strategies need to be put in place to adequately follow up women as they transition from routine HIV care services to ANC services and back. It however, remains unclear as to whether shifting ART treatment services to the ANC for pregnant women on ART during the periods of pregnancy and breastfeeding would result in better VL follow up.

There are several limitations to this study. We did not have data on HIV transmission rates which could have brought valuable insight into transmission risks among this population. Furthermore, we only had access to routine data conducted within the Western Cape Province. Considering the high rate of migration among this population, together with the fact that VL data was only abstracted up to the time of delivery and there was lack of postpartum VLs, this raises the possibility that some women had VL results which might not have been captured, accounting for the low rate of repeat VL tests detected for women with raised VLs during pregnancy. Also, adherence was self-reported and was not available for the before conception period. In addition, we did not have any information on the interventions that may have been implemented between the two VL tests. This
analysis enrolled women that were part of a trial therefore, interpretation of these findings to routine clinical care practice should be done with caution as patients that consent to being in a trial could be systematically different from those that do not. Use of routine public sector VL data was the main strength of this study as it enabled us to assess VL monitoring in routine clinical settings outside of research support where the majority of patients are followed up.

As national programs adopt the new “treat all” WHO guidelines, recommending ART for all HIV-infected people, there will be an increase in the number of HIV positive women conceiving on ART. Lack of VL monitoring for these women during pregnancy and breastfeeding would result in those with viremia not being timely identified. Lowering maternal plasma VL is one of the key factors for preventing MTCT [21] therefore, vigilance in VL monitoring among pregnant and breastfeeding women on ART is essential if we are to eliminate MTCT of HIV.

Conclusion

In conclusion, this study demonstrates that not all women on ART receive VL testing before conception and during pregnancy and that a substantial proportion of women with an elevated VL during pregnancy were never retested. Vigilance in VL monitoring of HIV-infected pregnant women is crucial and better VL monitoring strategies need to be implemented to enable women with increased VL to be timely identified and interventions implemented speedily.

Potential conflicts of interest

The author has no competing interests to declare.

Acknowledgements and funding

The author would like to thank all the Gugulethu MOU and MCH-ART staff members and all the women who participated in this research. The author would also like to thank the funders of the MCH-ART study – the National Institute of Child Health and Human Development (NICHD). This analysis did not receive any external funding.

Author’s contribution

The author was responsible for data collection and data management. She was also responsible for the data analysis, drafting of the manuscript and finalising the final version.

References


24 October 2012

HREC REF: 451/2012

A/Prof L Myer
CIDER
School of Public Health & Family Medicine
FHS

Dear A/Prof Myer

PROJECT TITLE: STRATEGIES TO OPTIMIZE ANTIRETROVIRAL THERAPY SERVICES FOR MATERNAL & CHILD HEALTH: THE MCH-ART STUDY.

Thank you for addressing the issues raised by the Human Research Ethics Committee.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study including the following documentation:-

- Study protocol MCH-ART study: Version 1.2 (FINAL DRAFT, dated 08 Oct 2012)
- Phase 1 Informed Consent form: Version 2.0, 18 October 2012
- Phase 2 Informed Consent Form: Version 2.0 18 October 2012
- Phase 3 Informed Consent Form: Version 2.0 18 Oct 2012

Approval is granted for one year till the 28 October 2013.

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

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

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

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.
## Appendix 2: MCH-ART ethics renewal

**UNIVERSITY OF CAPE TOWN**

**FHS016: Annual Progress Report / Renewal**

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| [ ] Approved | Annual progress report | Approved until/next renewal date | 30.10.2016 |
| [ ] Not approved | See attached comments |

**Signature Chairperson of the HREC**

**Date Signed**

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### 1. Protocol information

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<th>Strategies to optimize antiretroviral therapy services for maternal &amp; child health: the MCH-ART study</th>
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<thead>
<tr>
<th>Protocol number (if applicable)</th>
<th>N/A</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Are there any sub-studies linked to this study?</th>
<th>YES</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>If yes, could you please provide the HREC Refs for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Prof Landon Myer</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Department / Office Internal Mail Address</th>
<th>CIDER, School of Public Health and Family Medicine, Faculty of Health Sciences</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>1.1 Does this protocol receive US Federal funding?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>1.2 If the study receives US Federal Funding, does the annual report require full committee approval?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

23 July 2014

(Note: Please complete the Closure form (FHS019) if the study is completed within the approval period)
Appendix 3: MCH-ART Columbia University ethics renewal

November 1, 2015

Elaine Abrams
ICP ICAP · 823100X
Mailman School of Public Health/ICAP
722 West 168th Street
MSPH

Protocol Number: IRB-AAA8059
Title: Strategies to optimize antiretroviral therapy services for maternal & child health: the MCH-ART study
Approval Date: 10/06/2015  Expiration Date: 10/05/2016

Grant #: 1R01HD074558-01

Dear Dr. Abrams,

On October 6, 2015, the renewal for the above-mentioned study was reviewed and approved by expedited review, category #9, by the Chair of the Columbia University Medical Center Institutional Review Board #3. It is noted that study enrollment is permanently closed.

Important Reminder: A request for continuation or completion of a research protocol is due at least 60 days before this research protocol’s expiration date, unless otherwise requested by the Board. This renewal was submitted on 09/24/2015 with an expiration of 10/28/2015.

The following study-related materials were approved:
- MCH-ART MICS indicators Version 1_23April 2015_tp, attached 5/12/2015
- CBCL_pid- English, attached 5/12/2015
- CBCL Xhosa final sent ASEBA May 2008_pid, attached 5/12/2015
- Infant Dem and MH - Phase 3_18 months pp_V1.0 X-E_clean, attached 5/12/2015
- Qualitative Interview guide, 01October2014- Xhosa, attached 10/16/2014
- Qualitative Interview guide, 01October2014- English, attached 10/16/2014
- In-depth interview ICF, 16May2014- Xhosa, attached 9/9/2014
- In-depth interview ICF, 16May2014- English, attached 9/9/2014
- Neurodevelopmental feedback form, 02July2014- Xhosa, attached 9/9/2014
- Neurodevelopmental ICF, 18July2014- Xhosa, attached 9/9/2014
- Infant Adherence, Phase 3 6-12 mo, Xhosa, attached 5/1/2014
- Infant Adherence, Phase 3 6wk&3mo, Xhosa- clean, attached 5/1/2014
- Infant Adherence, Phase 2 <7dayspp, Xhosa-clean, attached 5/1/2014
- Infant Demo & Med Hx, Phase 3 6wks, Xhosa- clean, attached 5/1/2014
- Infant Feeding, Phase 3 3mo-12mo, Xhosa- clean, attached 5/1/2014
- Infant Feeding, Phase 3 6wk, Xhosa-clean, attached 5/1/2014
- Infant Feeding, Phase 2 <7dayspp, Xhosa- clean, attached 5/1/2014
- Infant Demo & Med Hx, Phase 3 12mo, Xhosa- clean, attached 5/1/2014
- Infant Demo & Med Hx, Phase 3 9mo, Xhosa- clean, attached 5/1/2014
- Infant Demo & Med Hx, Phase 3 6mo, Xhosa- clean, attached 5/1/2014
- Infant Demo & Med Hx, Phase 3 3mo, Xhosa- clean, attached 5/1/2014
- Infant Demo & Med Hx, Phase 2 <7dayspp, Xhosa- clean, attached 5/1/2014
- Verbal Autopsy Tool, attached 5/1/2014
- Telephone Follow-up CRF, 09April2014, attached 5/1/2014
- Home Visit CRF, 24 April2014, attached 5/1/2014
- Food Security questionnaire- Xhosa, 25April2014, attached 5/1/2014
- Food Security questionnaire- English, 02April2014, attached 5/1/2014
- Resource Interview questionnaire- Xhosa, 25April2014, attached 5/1/2014
- Resource Interview questionnaire- English, 14April2014, attached 5/1/2014
The following changes included with the renewal were also approved:
- MCH-ART Unanticipated Problems September 2015.pdf

Any proposed changes in the protocol must be immediately submitted to the IRB for review and approval prior to implementation, unless such a change is necessary to avoid immediate harm to the participants. Additionally, any unanticipated problems that involve risks to subjects must be reported to the IRB in accordance with the CUMC Unanticipated Problems: Reporting to the IRB of Unanticipated Problems Involving Risks policy. All submissions for modifications and unanticipated problems must be submitted through RASCAL.

Renewal applications should be submitted 60 days before the expiration date of this study through RASCAL. Failure to obtain renewal of your study prior to the expiration date will require discontinuance of all research activities for this study, including data analysis. You must inform the IRB when your study has been completed via a Closure report in Rascal.

If you have any questions regarding this approval, please call Diana Lesmes at (212) 342-3182 or Yaritza Collazo at (212) 305-1007. Columbia University appreciates your commitment towards the ethical conduct of human research.

Sincerely,

Yaritza Collazo, CIP
Manager, IRB #3
School of Public Health & Family Medicine  
University of Cape Town  
Faculty of Health Sciences  
Falmouth Building  
Anzio Road  
Observatory  

For attention: Prof Landon Myer  

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

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.  

Please contact the following people to assist you with any further enquiries in accessing the following sites:  

Gugulethu CHC  
Dr Katy Murie  
Contact No. 021-633 0020  

Kindly ensure that the following are adhered to:  

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.  
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final report within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).  
3. The reference number above should be quoted in all future correspondence.  

Yours sincerely  

Signed  

DR T Naledi  
DIRECTOR: HEALTH IMPACT ASSESSMENT  
DATE: 20/5/2013  
CC MS P OLCKERS  

DIRECTOR: KLIPFONTEIN / MITCHELLS PLAIN
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 not 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 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                      Dr Elaine Abrams
School of Public Health and Family Medicine ICAP, Columbia University
Faculty of Health Sciences, University of Mailman School of Public Health
Cape Town                           College of Physicians and Surgeons
Tel: 021 406 6661                    Tel: +1 212 342 0543
Email: Landon.Myer@uct.ac.za         Email: eja1@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                   Columbia University Medical Center IRB
Chair, Human Research Ethics Committee Tel: +1 212 305 5883
Faculty of Health Sciences, University of Cape
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

Witness’s name__________________________

__________________________________________
Signature of witness                  Date

Thank you.
<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
</table>
| 1. Mingaphi iminyaka yakho  
*What is your age?*                                                            | UmAfrika = 1  
Indiya Indian = 2  
Umntu webala Coloured = 3  
Umlungu White = 4  
Olunye = 5, cacisa: __________ | Age: __________/Iminyaka/years |
| 2. Uloluphi uhlanga  
*What population group do you belong to?*  
UmAfrika African = 1  
Indiya Indian = 2  
Umntu webala Coloured = 3  
Umlungu White = 4  
Olunye = 5, cacisa: __________ | Other specify |
| 3. Uthetha oluphi ulwimi ekhayai?  
*What language do you speak at home?*  
isiXhosa = 1  
isiZulu = 2  
isiBhulu Afrikaans = 3  
isiNgesi English = 4  
Olunye = 5, cacisa: __________ | Other specify |
| 4. Lelephi elona bangla liphezulu oliphumeleleyo?  
*What is the highest level of schooling/education that you have completed?*  
Umgangatho/Grade:________ Okanye/or  
Ibanga/ Standard:________ | Imfundno enomsila/ Postsecondary:________ |
| 5. Ngoku uyasebenza okanye uyafunda  
*Are you currently working and/or studying?*  
Hayi No = 0 → Gqithela ku Q7 SKIP to Q7  
Ewe Yes = 1 | |
| 6. Ukuba nguEwe, yeyephi kwezi zilandelayo echaza, bhetele ukuba wenza ntoni?  
*If yes, which of one the following best describes what you do?*  
Khetha ibenyé /Choose one only | |
| 7. Ngowuphi owona mthombo wemali kwikhaya lakho?  
*What is the MAJOR source of income for your household?*  
Khetha ibenyé /Choose one only | |

Appendix 6: MCH-ART Demographics & Medical history questionnaire
MCH-ART: Demographics & Medical History, Phase 1
Xhosa-English of Version 3.0, 15 October 2013
8. **Uhlala kwikhaya elinjani?**  
*What kind of home do you live in?*

| Indlu yesitena | 1: Shack/informal dwelling  
|----------------|----------------------------------|
|                | 2: Formal house  
|                | 3: Flat/council home  

*Enye = 4, chaza:________*

**Other, specify**

9. **Ingaba indlu yakho inazo ezi zinto zilandelayo:**  
*Does your house have the following: Read and answer for all*

<table>
<thead>
<tr>
<th>Element</th>
<th>Hayi/No</th>
<th>Ewe/Yes</th>
</tr>
</thead>
</table>
| A. Indlu yangasese  
| (A toilet inside) |         |         |
| B. Amanzi abalekayo empompo  
| (Running water inside) |         |         |
| C. Umbane  
| (Electricity inside) |         |         |
| D. Isikhenkcisi  
| (A refrigerator) |         |         |
| E. Umnxeba  
| (A telephone) |         |         |
| F. Umabona kude  
| (A television) |         |         |

10. **Bangaphi abantu abahlala kule ndlu bedibene nawe(abadala,abancinci)?**  
*Including yourself, how many people (adults and children) live in your house?*

Inani labantu: __________  
# of people:

11. **Bangaphi abadala (iminyaka-16 nangaphezulu)bedibene abahlala kule ndlu?**  
*How many adults (aged 16 or older), including you, live in your house?*

Inani labadala: __________  
# of adults:

12. **Bangaphi abantwana (iminyaka -15 nanganeno ) abahlala nawe?**  
*How many children (aged 15 and under) live in your house?*

Inani labantwana:____________  
# of children:

13. **Ukholelwé kangaphi (kudibene nesi isisu)?**  
*How many times have you been pregnant (including current pregnancy)?*

Inani lokukhelulelwa: __________  
# of pregnancies:

14. **Ingaba ubuzama ukuba nosana ngelixesha ufumisa usuka ukuholelwé (Kwesi isisu)?**  
*Were you trying to have a baby when you found out you were pregnant (in this pregnancy)?*

Hayi/No = 0  
Ewe/Yes = 1  
Andazi/I don't know = 9

15. **Bangaphi abantwana obazeleyo?**  
*How many children have you given birth to?*

Inani labantwana:__________  
# of children:

16. **Bangaphi kwaba bantwana abaphilayo?**  
*How many of these children are living?*

Inani labantwana:__________  
# of children:

17. **Bangaphi kwaba bantwana abahlaya ngoku?**  
*How many of these children currently live with you?*

Inani labantwana:__________  
# of children:

18. **Bangaphi kwaba bantwana ekufumaniseke bakho ukuba baphila nentsholongwane?**  
*How many of your children have tested HIV-positive?*

Inani labantwana abaphila nentsholongwane:__________  
# of HIV-positive children:

19. **Bangaphi kwaba bantwana baphila nentsholongwane abasaphilayo?**  
*How many of these children who have tested HIV-positive are currently living?*

Inani labantwana abaphila nentsholongwane abaphilayo ngoku: __________  
# of HIV-positive children currently alive:
### MCH-ART: Demographics & Medical History, Phase 1

**PID: 1 - __ __ __ __ - __ __**

**Xhosa-English of Version 3.0, 15 October 2013**

**20. Uya thandana ngoku?**
*Are you currently in a relationship?*

<table>
<thead>
<tr>
<th>Hayi/No</th>
<th>Gqithela ku Q25</th>
<th>Ewe/Yes = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayi/No</td>
<td><em>SKIP to Q25</em></td>
<td>Ewe/Yes = 1</td>
</tr>
</tbody>
</table>

**21. Ungaluchaza njani uthando lwakho?**
*How would you describe your current relationship?*

<table>
<thead>
<tr>
<th>Utshatile = 1</th>
<th>Married</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nditshatile, asihlali kunye = 2</td>
<td><em>Not married, living together</em></td>
</tr>
<tr>
<td>Nditshatile, asihlali kunye = 3</td>
<td><em>Married, not living together</em></td>
</tr>
<tr>
<td>Nditshatile, asihlali kunye = 4</td>
<td><em>Not married, not living together</em></td>
</tr>
<tr>
<td>Enye = 5, cacisa:____________</td>
<td><em>Other, specify</em></td>
</tr>
</tbody>
</table>

**22. Lileshe ellengakanani unobudlelwana nalomntu?**
*How long have you been in a relationship with this person?*

<table>
<thead>
<tr>
<th>Ixesha</th>
<th>Inyanga Months________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration in:</td>
<td>Iminyaka Years________</td>
</tr>
</tbody>
</table>

**23. Ingaba eli qabane lakho ngutata womnye wabantwana bakho(kunye nalo umkhulelwyo)?**
*Is your current partner the parent of any of your children? (including current pregnancy)*

<table>
<thead>
<tr>
<th>Hayi/No = 0</th>
<th>Ewe/Yes = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>SKIP to Q 28</em></td>
<td><em>SKIP to Q 28</em></td>
</tr>
</tbody>
</table>

**24. Ullichazele na iqabane lakho ngesimo sakho sentsholongwane?**
*Have you disclosed your HIV status to your current partner?*

<table>
<thead>
<tr>
<th>Hayi/No = 0</th>
<th>Ewe/Yes = 1</th>
</tr>
</thead>
</table>

**25. Ubukhe wabelana ngesondo nabanye abantu ingenguye lomntu uthandana naye?**
*In the last 12 months have you had any sexual relationships/sexual partners? (if in a relationship then other than this partner)*

<table>
<thead>
<tr>
<th>Hayi/No = 0</th>
<th><em>Gqithela ku Q28</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>SKIP to Q 28</em></td>
<td><em>SKIP to Q 28</em></td>
</tr>
</tbody>
</table>

**26. Bunjani ubudlelwanebakho namanye amaqabane ngaphandle kweqabane lakho langoku ukuba akhona?**
*What is the nature of your relationship(s)? (other than current partner if applicable)*

<table>
<thead>
<tr>
<th>Rhangqa konke okungqamene nave.</th>
<th>Mark all that apply.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Umlingane/nditshatile</td>
<td><em>Spouse/ married</em></td>
</tr>
<tr>
<td>b. Iqabane lam</td>
<td><em>Boyfriend</em></td>
</tr>
<tr>
<td>c. Iqabane lethutyana</td>
<td><em>Casual Partner/One Night Stands</em></td>
</tr>
<tr>
<td>d. Omnye ,cacisa:____________</td>
<td><em>Other, specify</em></td>
</tr>
</tbody>
</table>

**27. Ubaxelele aba bantu wabelana nabo ngesondo ukuba uphila nentsholongwane?**
*Have you disclosed your HIV status to any of these other sexual partners?*

<table>
<thead>
<tr>
<th>Hayi/No = 0</th>
<th>Ewe/Yes = 1</th>
</tr>
</thead>
</table>

**28. Ubuqala ukufumanisa ukuba unentsholongwa kagawulayo kolumitho okanye phambi kokuba ukhulelwwe?**
*Did you first test HIV positive in this pregnancy or before this pregnancy?*

<table>
<thead>
<tr>
<th>Koku ukukhulelwa =1</th>
<th>Gqithela ku Q32</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>SKIP to Q32</em></td>
<td><em>SKIP to Q32</em></td>
</tr>
</tbody>
</table>

**29. Kwakunini ukuqala kwakho ukufumanisa ukuba unentsholongwane kagawulayo?**
*When did you 1st test HIV-positive?*

<table>
<thead>
<tr>
<th>Umhla:___</th>
<th>Inyanga:____</th>
<th>Unyaka:____</th>
</tr>
</thead>
</table>

**30. Kwakutheni ukuze oluhololo lwensiwe?**
*Why was this test conducted?*

<table>
<thead>
<tr>
<th>Ndvipavanywe ngelixeshxe ndikhulelwyo = 1</th>
<th><em>Tested during pregnancy</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ndafunyaniswa ndinesifo sephema (TB) = 3</td>
<td><em>Diagnosed with TB</em></td>
</tr>
<tr>
<td>Ndangeniswa esibhelelele = 4</td>
<td><em>Admitted to the hospital</em></td>
</tr>
</tbody>
</table>

| Enye = 5, cacisa:____________ | *Other, specify* |

**Columbia University IRB**

IRB Approval Date: 10/29/2014

For use until: 10/28/2015
### Demographics & Medical History, Phase 1

**PID:** 1 - __ __ __ __ - __ __

**Xhosa-English of Version 3.0, 15 October 2013**

**31.** Ingaba wawukhulele ukuqala kwakho ukufumane ukuba unentsholongwane kagawulayo?  
*Were you pregnant when you first tested HIV-positive?*
- **Hayi/No** = 0
- **Ewe/Yes** = 1

**32.** Wakhe wanazoe iziphumo ezingena chaphaza kuvavanyo lwentsholongwane kagawulayo?  
*Have you ever tested negative on an HIV test?*
- **Hayi/No** = 0 → Gqithela ku Q36  
  *SKIP to Q36*
- **Ewe/Yes** = 1

**33.** Uggibe ne niki ukuqala neziphumo ezingenachaphaza zovavanyo lwentsholongwane kagawulayo?  
*When did you last test HIV-negative?*
- Umhla: ___  
  Inyanga: _____  
  Unyaka: ______

**34.** Kwakutheni ukuze uvavanywe ngelo xesha?  
*What was the reason for you doing the HIV test?*
- Ndivavanywe ngelixesha ndikhulelweyo = 1  
  *Tested during pregnancy*
- VCT/Ndandifuna ukuvavanywe = 2  
  *VCT/Wanted to be tested*
- Ndagenyiswe esibhedlele = 4  
  *Diagnosed with TB*
- Ndangeniswa esibhedlele = 4  
  *Admitted to the hospital*
- Enye = 5, cacisa: __________  
  *Other, specify*

**35.** Wawukhulele ukuze ukuqala kwakho kwavulayo?  
*Were you pregnant at the time of that test?*
- **Hayi/No** = 0  
  *SKIP to Q39*
- **Ewe/Yes** = 1

**36.** Wakhe waxelela nabanina ukuba unentsholongwane kagawulayo?  
*Have you told anyone that you are HIV-positive?*
- **Hayi/No** = 0 → Gqithela ku Q39  
  *SKIP to Q39*
- **Ewe/Yes** = 1

**37.** Ngawaphi amlungu osapho lwakho owaxeleleyo ngesimo sakho sentsholonwane?  
*Which of your family members have you told about your HIV status?*
- Nceda phendula lombuzo ngalinye losapho oludweliswe ngezantsi.  
  Please answer this question for each of the family members listed below.
- Wawukhulele u_ _ _ _ _ _ _ ukuba unentsholongwane kagawulayo?  
*Have you told your ___ that you are HIV positive?*

<table>
<thead>
<tr>
<th>a.</th>
<th>Umyeni/iqabane</th>
<th>Husband/partner/boyfriend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayi/No = 0</td>
<td>Ewe/Yes = 1</td>
<td>N/A = 9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>b.</th>
<th>Umama</th>
<th>Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayi/No = 0</td>
<td>Ewe/Yes = 1</td>
<td>N/A = 9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>c.</th>
<th>Utata</th>
<th>Father</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayi/No = 0</td>
<td>Ewe/Yes = 1</td>
<td>N/A = 9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>d.</th>
<th>Udade</th>
<th>Sister</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayi/No = 0</td>
<td>Ewe/Yes = 1</td>
<td>N/A = 9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>e.</th>
<th>Umtakwenu</th>
<th>Brother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayi/No = 0</td>
<td>Ewe/Yes = 1</td>
<td>N/A = 9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>f.</th>
<th>Intombi</th>
<th>Daughter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayi/No = 0</td>
<td>Ewe/Yes = 1</td>
<td>N/A = 9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>g.</th>
<th>Unyana</th>
<th>Son</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayi/No = 0</td>
<td>Ewe/Yes = 1</td>
<td>N/A = 9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>h.</th>
<th>Umalume</th>
<th>Uncle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayi/No = 0</td>
<td>Ewe/Yes = 1</td>
<td>N/A = 9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>i.</th>
<th>U-anti</th>
<th>Aunt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayi/No = 0</td>
<td>Ewe/Yes = 1</td>
<td>N/A = 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
| **38.** Ngaphandle kwabantu bakowenu aba badweliswe ngentla, ngubani omnye umntu owamxelelyo ukuba uphila nentsholongwane? *(funda uphendule yonke imibuzo)*  
Aside from family members listed above, who else have you told about your HIV status? *(read and answer for all)* | **a.** Amanesi/ogqira  
*Health professionals* | Hayi/No = 0  
Ewe/Yes = 1  
N/A = 9 |
|  | **b.** Iqumru lenxaso labantu abaphila nentsholongwane  
*Support group* | Hayi/No = 0  
Ewe/Yes = 1  
N/A = 9 |
|  | **c.** Umntu owabelana naye ngesondo ongahlali naye  
*A sexual partner who does not live with you* | Hayi/No = 0  
Ewe/Yes = 1  
N/A = 9 |
|  | **d.** Isihlobo  
*Friends* | Hayi/No = 0  
Ewe/Yes = 1  
N/A = 9 |
|  | **e.** Inkokheli ngokwa kwamoya  
*Spiritual leader* | Hayi/No = 0  
Ewe/Yes = 1  
N/A = 9 |
|  | **f.** Umntu okuqashileyo/wayekuqashile  
*Current or former employer* | Hayi/No = 0  
Ewe/Yes = 1  
N/A = 9 |
|  | **g.** Ukuchaza esidlangalaleni  
*Public disclosure/community* | Hayi/No = 0  
Ewe/Yes = 1  
N/A = 9 |
|  | **h.** Abanye, chaza: ______________  
*Other, specify* | Hayi/No = 0  
Ewe/Yes = 1  
N/A = 9 |
| **39.** Wakhwe wakhulelwaphambi koku ukukhulelw?  
*Have you ever been pregnant before this pregnancy?* | Hayi/No = 0  
Gqithela ku Q45  
Ewe/Yes = 1  
*SKIP to Q45* |
| **40.** Ngokuya ubukhulelwengaphambikoku ukukhulelwawawuke waniwka amayezakhusela usana lungosulelekinyisholongwane (*ezekukhusela umntwana hayi amachiza okuthomalalisa nentsholongwane wobomibonke)*  
*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)* | Hayi/No = 0  
Gqithela ku Q45  
Ewe/Yes = 1  
*SKIP to Q45* |
| **41.** UkuBangaEwe, zingaphi izisu ufumane la machiza ngesisizathu?  
*If yes, during how many pregnancies have you received medication for this purpose?* | Inani lezisu: ______  
*# of pregnancies* |
<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
</table>
| 42. Kwezi zisu siyi____ ofumene kuzo amachiza, zingaphi izisu otye kuzo iipili ngelixeshu ubelekayo qha? | Ngoku wawubeleka  
Only at Delivery (Nevirapine) #:________  
Ngelixeshu ukhulelwe  
While you were pregnant (AZT)? #: ______  
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? |
| 43. Bekunini ukugqibela kwakho ukufumana la machiza ngesisizathu?        | Umhla:___ Inyanga:_____ Unyaka:______  
When was the last time that you received medication for this purpose? |
| 44. Uwafumene phi la machiza ukugqibela kwakho?                         | Igama lekliniki:_______________  
Where did you receive the medication the last time? |
| 45. Wawuke wawathatha amachiza okuthomalalisa intsholongwane (awobomi bakho bonke) | Hayi/No = 0  
Ewe/Yes = 1  
Have you ever taken triple drug antiretroviral therapy (lifelong ART)? |
| 46. Ukuba nguEwe, ingaba wawafumana amachiza okuthomalalisa intsholongwane ukugqibela kakho? | Igama lekliniki:_______________  
When was the last time you received medication for this purpose? |
| 47. Uqale nini ukutya la machiza okuthomalalisa intsholongwane kagawulayo? | Umhla:___ Inyanga:_____ Unyaka:______  
When did you start taking ART? |
| 48. Usawatya amachiza okuthomalalisa intsholongwane kagawulayo?         | Hayi/No = 0  
Ewe/Yes = 1  
Are you still on ART? |
| 49. Ukuba nguHayi, uyeke nini ukuwatya amachiza okuthomalalisa intsholongwane kagawulayo? | Umhla:___ Inyanga:_____ Unyaka:______  
If No, when did you stop taking ART? |
## 50. Uyekele ntoni ukutya amachiza athonalalisa intsholongwane?
*Why did you stop taking ART?*
(rhagqa zonke ezibhekisa kuwe)
Circle all that apply

<table>
<thead>
<tr>
<th>Option</th>
<th>Xhosa</th>
<th>English</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>Ndaphelelwana ngumchiza andaya ukuuyakuwalanda</td>
<td>I ran out of medicine and didn't go for refills</td>
</tr>
<tr>
<td>b.</td>
<td>Anencasa embi</td>
<td>The medicine tastes bad</td>
</tr>
<tr>
<td>c.</td>
<td>Ndulibala</td>
<td>I just forgot</td>
</tr>
<tr>
<td>d.</td>
<td>Bendikhathazwa yimiphumela yawo</td>
<td>I was worried about the side effects</td>
</tr>
<tr>
<td>e.</td>
<td>Bendingafuni abanye bandiqaphele ukuba nditya amachiza</td>
<td>I did not want others to notice me taking the medicine</td>
</tr>
<tr>
<td>f.</td>
<td>Ndandigula</td>
<td>I was ill</td>
</tr>
<tr>
<td>g.</td>
<td>Ndacinga ukuba andisawufuni nganto</td>
<td>Didn't think I needed it anymore</td>
</tr>
<tr>
<td>h.</td>
<td>Bendicinga ndingahlala ndiphilile ngaphandle kwawo</td>
<td>Can stay healthy without it</td>
</tr>
<tr>
<td>i.</td>
<td>Bendicinga ukuba lamayezu anganobu ngozi kum.</td>
<td>I felt the medicine might be harmful to me</td>
</tr>
<tr>
<td>j.</td>
<td>Ndizive ndinoxinizelelo</td>
<td>I felt depressed</td>
</tr>
<tr>
<td>k.</td>
<td>Ndandiphilile</td>
<td>I was well</td>
</tr>
<tr>
<td>l.</td>
<td>Ebemaninzi la machiza ekufuneka ndiwathathe</td>
<td>There was too much medicine to take</td>
</tr>
<tr>
<td>m.</td>
<td>Bendingekho ekhaya</td>
<td>I was away from home</td>
</tr>
<tr>
<td>n.</td>
<td>Bendixakekile zezinye izinto</td>
<td>I was busy with other things</td>
</tr>
<tr>
<td>o.</td>
<td>Ndiiye ndafunda ukuba zikho ezine iyindlela endinganyanya okanye ndiphilise intsholongwane kagawulayi</td>
<td>I learned that there are other ways to treat or cure HIV</td>
</tr>
<tr>
<td>p.</td>
<td>Enye, cacisa: ___________________________________________</td>
<td>Other, Specify</td>
</tr>
</tbody>
</table>

## 51. Ubukhe watshaya isagarethi kulenyanga iphelileyo?
*Did you smoke cigarettes in the last month?*

<table>
<thead>
<tr>
<th>Option</th>
<th>Xhosa</th>
<th>English</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayi No</td>
<td>0</td>
<td>END</td>
</tr>
<tr>
<td>Ewe Yes</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

## 52. Utshaya isigarethi ezingaphi ngemini?
*How many cigarettes do you smoke in a day?*

# ___________ cigarettes

---

**Date completed:** __/__/__
**Signed counsellor completing CRF:** ___________

**Date of QC:** __/__/__
**Signed measurement nurse:** ___________
This CRF is to be completed by women on ART only

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Yintoni igama lamachiza owatyayo?</td>
<td>Visit Date: __ __/ __ __/ __ __ __</td>
</tr>
<tr>
<td>What are the names of the ARVs you are taking?</td>
<td></td>
</tr>
<tr>
<td>2. Ukususela ukuqala kwakho ukutya amachiza, wawuke wawayeka na?</td>
<td>Hayi No --&gt; SKIP to Q5</td>
</tr>
<tr>
<td>Since you first started taking ART, have you ever stopped?</td>
<td>Ewe Yes</td>
</tr>
<tr>
<td>3. Mangaphi amaxesha uyeka uphinde uqalele ukutya amachiza?</td>
<td>Amaxesha: ____________ # times</td>
</tr>
<tr>
<td>How many times have you stopped and restarted ART?</td>
<td></td>
</tr>
<tr>
<td>When did you restart ART the last time?</td>
<td>Unyaka: ______________ Day Month Year</td>
</tr>
<tr>
<td>5. iART uzithatha kangaphi ngemini?</td>
<td>Amaxesha: ____________ # of times</td>
</tr>
<tr>
<td>How many times a day do you take your ART pills?</td>
<td></td>
</tr>
<tr>
<td>How many pills do you take each time?</td>
<td># of pills</td>
</tr>
<tr>
<td>7. Mangaphi amachiza entsholongwane ohlukeneyo owatyayo?</td>
<td># amchiza: ____________</td>
</tr>
<tr>
<td>How many different HIV medicines do you take?</td>
<td></td>
</tr>
<tr>
<td>8. Oko waqala ukuwatya, ungazibeka kweliphi inqanaba lokuty a ngendlela owawuyiboniswe yokutya amachiza akho?</td>
<td>Kakubi kakhulu=1 Very poor</td>
</tr>
<tr>
<td>Since you started taking them, how would you rate how well you usually do taking your HIV medicines in the way you are supposed to?</td>
<td>Kakubi=2 Poor</td>
</tr>
<tr>
<td></td>
<td>Ndiphakathi=3 Fair</td>
</tr>
<tr>
<td></td>
<td>Kakhule=4 Good</td>
</tr>
<tr>
<td></td>
<td>Kakhule kakhulu=5 Very good</td>
</tr>
<tr>
<td></td>
<td>Kakhule okugqithisileyo=6 Excellent</td>
</tr>
<tr>
<td>9. Ngoku cinga ngentsuku ezi-30 ezidlulileyo, yeypi phi kwezi zilandelayo echaza eyona ndlela otya ngayo amachiza akho?</td>
<td>Kakubi kunakuqala=1 Worse than usual</td>
</tr>
<tr>
<td>Now think about the last 30 days. How would you rate how well you did taking your HIV medicines?</td>
<td>Kakubi kunakuqala=2 Better than usual</td>
</tr>
<tr>
<td></td>
<td>Kuyafana njengesiqhelo=3 About the same as usual</td>
</tr>
<tr>
<td>10. Kwintsuku ezi-30 ezidlulileyo, zimini ezingaphi okhe wallabala ukutya amchiza akho entsholongwana?</td>
<td>Intsuku: ______________ (0-30) # of days</td>
</tr>
<tr>
<td>In the last 30 days, on how many days did you miss at least one dose of any of your HIV medicines?</td>
<td></td>
</tr>
<tr>
<td>11. Kwezi ntsuku zi-30 zidlulileyo owaty e kakhule kanjani amachiza akho entsholongwane njengohlobo omele ukuwatya ngalo?</td>
<td>Kakubi kakhulu=1 Very poor</td>
</tr>
<tr>
<td>In the last 30 days, how good a job did you do at taking your HIV medicines in the way that you were supposed to?</td>
<td>Kakubi=2 Poor</td>
</tr>
<tr>
<td></td>
<td>Ndiphakathi=3 Fair</td>
</tr>
<tr>
<td></td>
<td>Kakhule=4 Good</td>
</tr>
<tr>
<td></td>
<td>Kakhule kakhulu=5 Very good</td>
</tr>
<tr>
<td></td>
<td>Kakhule okugqithisileyo=6 Excellent</td>
</tr>
</tbody>
</table>
12. **Kwezi ntsuku zi-30 zidlulileyo, kukangaphi usitya amachiza akho entsholongwane ngendlela omele kuwatyanga ngayo?**  
*In the last 30 days how often did you take your HIV medicines in the way that you were supposed to?*

<table>
<thead>
<tr>
<th>Zange</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumbalwa</td>
<td>Rarely</td>
</tr>
<tr>
<td>Ngamanye amaxesha</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Ngesiqhelo</td>
<td>Usually</td>
</tr>
<tr>
<td>Malunga lonke ixesha</td>
<td>Almost always</td>
</tr>
<tr>
<td>Lonke ixesha</td>
<td>Always</td>
</tr>
</tbody>
</table>

13. **Kunzima kangakanani ukutyamachiza akho entsholongwana ngendlela omele kuwatyanga ngayo?**  
*How hard is it for you to take your HIV medicines in a way you are supposed to?*

<table>
<thead>
<tr>
<th>Kunzima kakhulu kakhulu</th>
<th>Extremely hard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kunzima kakhulu</td>
<td>Very hard</td>
</tr>
<tr>
<td>Kunzima nje</td>
<td>Somewhat hard</td>
</tr>
<tr>
<td>Akunzimanga</td>
<td>Not very hard</td>
</tr>
<tr>
<td>Akunzimanga kwaphela</td>
<td>Not hard at all</td>
</tr>
</tbody>
</table>

14. **Kwintsuku ezi-30 ezidlulileyo, zeziphi izinto ezibangele ulibale, okanye ezenze kubenzima ukutyamachiza akho?**  
*In the past 30 days which of the following things made you miss a pill or made it hard for you to take your pills?*

<table>
<thead>
<tr>
<th>Read all. Circle as many as apply.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Bendingekho ekhaya</td>
</tr>
<tr>
<td>Was away from home?</td>
</tr>
<tr>
<td>b. Zilahlekile</td>
</tr>
<tr>
<td>Lost your pills?</td>
</tr>
<tr>
<td>c. Bendixakekile ndisenza omnye umsebenzi</td>
</tr>
<tr>
<td>Was busy with other things?</td>
</tr>
<tr>
<td>d. Ndilibele</td>
</tr>
<tr>
<td>Simply forgot?</td>
</tr>
<tr>
<td>e. Bezinizni ipilisi ebekufuneka ndiziyi</td>
</tr>
<tr>
<td>Had too many pills to take?</td>
</tr>
<tr>
<td>f. Bendifumana imiphumela</td>
</tr>
<tr>
<td>Was getting side effects?</td>
</tr>
<tr>
<td>g. Bendibaleka imiphumela okanye ndingaziva mnandi</td>
</tr>
<tr>
<td>Wanted to avoid side effects or were feeling bad?</td>
</tr>
<tr>
<td>h. Bendizinika ikhefu kwipilisi</td>
</tr>
<tr>
<td>Wanted to take a break from the pills?</td>
</tr>
<tr>
<td>i. Bendingafuni abanye bazi ukuba ndiya ipilisi</td>
</tr>
<tr>
<td>Did not want others to notice you taking medication?</td>
</tr>
<tr>
<td>j. Kuye kwabakho utshintsho kwindlela endisebenza ngayo okanye ngendlela endiqhele</td>
</tr>
<tr>
<td>Had a change in daily routine or work schedule?</td>
</tr>
<tr>
<td>k. Bendingicinakukuba ipilisi ziyasebenza noba ezinye andizityanga</td>
</tr>
<tr>
<td>Thought that the pills would still work even if</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>l.</td>
</tr>
<tr>
<td>m.</td>
</tr>
<tr>
<td>n.</td>
</tr>
<tr>
<td>o.</td>
</tr>
<tr>
<td>p.</td>
</tr>
</tbody>
</table>

Date completed: _ _ / _ _ _ / _ _ _ _  Signed counsellor completing CRF: ___________

Date of QC: _ _ / _ _ _ / _ _ _ _  Signed Measurement Nurse: _____________
Appendix 8: Study ethics approval letter

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

07 April 2016

HREC REF: 097/2016

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

Dear Prof Myer

PROJECT TITLE: HIV VIRAL LOAD MONITORING IN HIV-INFECTED PREGNANT WOMEN ESTABLISHED ON ANTIRETROVIRAL THERAPY IN CAPE TOWN, SOUTH AFRICA—(Masters of Public Health candidate-MS P Tsondai) SUB-STUDY LINKED TO 451/2012

Thank you for your response letter to the Faculty of Health Sciences Human Research Ethics Committee dated 06 April 2016.

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

Approval is granted for one year until 30 April 2017.

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

Please quote the HREC REF in all your correspondence.

We acknowledge that the student Priscilla Tsondai will also be involved in this study

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

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

Yours sincerely

Signed

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

HREC 097/2016
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.
Appendix 9: Author guidelines for the Journal of the International AIDS Society (JIAS)

Author Guidelines

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

Manuscript preparation
Standards of reporting
File formats
Style and language
Cover letter
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Additional sections for manuscript
Competing interests
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Manuscript submission
Submission system
Copyright
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Publication fees

MANUSCRIPT PREPARATION
Standards of reporting
The JIAS endorses international standards of reporting. Please see the Uniform Requirements for Manuscripts Submitted to Biomedical Journals guidelines produced by ICMJE as a reference standard of reporting. Authors are also referred to the EQUATOR network website for further information on the available reporting guidelines for health research, and the MIBBI Portal for prescriptive checklists for reporting biological and biomedical research where applicable. A number of checklists are available for various study designs, including randomized controlled trials (CONSORT), systematic reviews (PRISMA), observational studies (STROBE), meta-analyses of observational studies (MOOSE) and diagnostic accuracy studies (STARD). For systematic reviews, an additional file should be provided by the authors listing all details concerning the search strategy. Please refer to the Cochrane Reviewers’ Handbook for an example of how a search strategy should be presented.

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

Contributions from pharmaceutical companies or other commercial organizations should follow the Good Publication Practice guidelines for pharmaceutical companies, which also apply to any companies or individuals that work on industry-sponsored publications, such as freelance writers, contract research organizations and communications companies.

The JIAS supports international standards of reporting of trials, in particular, prospective registering and numbering of clinical trials. Clinical trials are defined by the World Health Organization as all phase I to IV trials, which are research studies that prospectively assign human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Trials need to be registered prior to submission in a suitable, publicly available registry. Links to existing registries can be found through ICMJE here or through the primary registers that participate in the WHO International Clinical Trials Registry Platform. The trial registration number should be included as the last line of the manuscript Abstract.

File formats
Accepted file formats are OpenOffice, Microsoft Word, RTF or WordPerfect; in addition, a PDF copy of the manuscript needs to be prepared. Tables and figures should be inserted in the main text. Additional files, such as supporting information or large datasets, can be submitted in any file format and should be uploaded as a separate file. Footnotes are not allowed.

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

Cover letter
In the cover letter, please explain why your manuscript should be published in the journal. If necessary, address any issues relating to our editorial policies (see About JIAS) and declare any competing interests (see Competing interest).

You can also suggest potential peer reviewers for your manuscript: they should be experts in the field and be able to provide an objective assessment of the manuscript. Any suggested peer reviewers should not have published with any
of the authors of the manuscript within the past five years, should not be current collaborators, and should not be members of the same institution. Suggested reviewers will be considered alongside potential reviewers identified by the Editorial team.

Members of the International AIDS Society receive a 15% discount on the publication fee. Authors should include their valid membership number in the cover letter upon submission.

**Title page**

On the title page, you should mention the title of the manuscript, list all authors' names in full, and list any study groups if applicable. Each authors' affiliation should be numbered in superscript consecutively and listed underneath, including department, institution, city and country. The corresponding author should be marked with the symbol § in superscript and full contact details should be provided, including a telephone number with country code. Authors who have contributed equally to the work should be marked with the symbol * in superscript. Deceased authors should be marked with the symbol ^ in superscript. The email addresses of all authors should be listed by their initials. A list of six to eight keywords should be provided, preferably alternate words to those found in the abstract in order to improve search hits for the article in repositories.

**Abstract**

The Abstract should not exceed 350 words and should be structured according to the headings of the selected article category (see below), excluding the heading, Discussion for Research articles. Avoid using abbreviations and do not cite references in the Abstract. If you are reporting results from a controlled health care intervention, please include your trial registry, together with your unique identifying number at the end of the Abstract. For randomized controlled trials, follow the CONSORT extension for abstracts.

**Main text**

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

**Article categories**

Research - full reports of data from original research studies

Headings: Introduction, Methods, Results, Discussion, Conclusions

Word limit: 3500 words

Numbers of figures and tables: Unlimited

Additional files: Yes

Manuscript template

Short report - brief reports of data from original research, such as follow-up or confirmatory studies, case series and negative results

Headings: Introduction, Methods, Results and discussion, Conclusions

Word limit: 2500 words

Numbers of figures and tables: 4

Additional files: No

Manuscript template

Review - comprehensive, authoritative descriptions and summaries of a specific subject area providing a systematic and substantial overview of the field

Headings: Introduction, Methods (if applicable), Results and discussion (if applicable, otherwise Discussion only), Conclusions

Word limit: 5000 words

Numbers of figures and tables: Unlimited

Additional files: Yes
Article sections

Introduction
The Introduction section should introduce the topic to readers without specialist knowledge in that area and must clearly outline the current state of knowledge in this field, the motivation and the aim of the study or the article.

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

All studies involving humans or animals require a statement on ethical approval, and for the former, the consent procedure that was followed. Please include the names of the ethics review board(s) that approved the study. If the research study was specific to one sex/gender, the reasons for this should be clearly stated.

Results
This section should include only data and findings from the authors’ study. Presentation of statistical results should mention confidence intervals and levels of significance where appropriate. Quotes from qualitative study participants
of less than three lines should be quoted in the text using quotation marks. For quotes longer than three lines, place the quote in a separate, indented paragraph and introduce it with a colon. No quotation marks are needed in this case. Details of the participant can be added in round brackets following the quote, but should not contain identifiable information to ensure confidentiality. Clarifications within the quotation should be placed in square brackets.

Submitting authors are strongly encouraged to include data disaggregated by sex (and, whenever possible, by race) and provide a comprehensive analysis of gender and racial differences. The authors should include the number and percentage of men, women and, if appropriate, transgender persons who participated in the research study. Anatomical and physiological differences between men and women (height, weight, body fat-to-muscle ratios, cell counts, hormonal cycles, etc.), as well as social and cultural variables (socio-economic, education, access to care, etc.), should be taken into consideration in the presentation of data and/or analysis of the results.

Discussion
In the Discussion section, you should discuss your main findings and place these within the context of the current body of knowledge in the field. Limitations of the study, for example, selection bias, can also be discussed, and should address how these influence the results and conclusions. If statistically significant differences were found between men and women or between different racial or cultural groups in the effects of the studied intervention, the implications, if any, for clinical and/or public health should be adequately discussed.

Conclusions
In your Conclusions section, state your key messages from the study and explain their importance and relevance, as well as implications. Future studies and recommendations can be included in this section. The conclusions drawn must be strictly based on the data provided.

Figures
Figures should be integrated into the text at the appropriate place. Figures should be cropped as closely as possible and have the header: "Figure 1. Title of figure". All figures need to be cited in the text in consecutive order. Legends should be provided underneath the figures, listing any abbreviations or meanings of symbols used. If several figures are included, please ensure that symbols are used consistently. Sufficient information needs to be provided for the figure to stand alone, including labels of axes. Please ensure that figures are legible in black and white print and also compatible with colour blindness. If figures are copied or adapted from another source, authors must seek permission prior to publication and these should be clearly cited as such. If the complete figure spans more than one page, authors should upload the figure as an additional file instead. High-resolution illustrations are recommended for optimal viewing performance in the final article.

Tables
Tables must be created within the word file in the correct place and should have the header: "Table 1. Title of table". All tables should be cited in the text in consecutive order. The tables should not contain colour or shading, and no vertical, visible lines. A legend can be provided underneath the title, listing any abbreviations or meanings of symbols used. If several tables are included, please ensure that symbols are used consistently. If tables are copied or adapted from another source, permission must be sought by the authors prior to publication and these should be clearly cited as such. If a table spans more than one page, authors may want to consider uploading the table as an additional file instead.

References
All external sources of information should be referenced within the text, the tables and figures, using consecutive numbering in square brackets, e.g. [1], [3-5], [3,4]. The references should be up to date and adequately reflect the current state of knowledge in the field. Citation bias, for example, by country or point of view must be avoided. Numbers of references are unlimited for all article categories and should be formatted in standard Vancouver style; see Sample references from ICMJE. Unpublished observations, personal communications and manuscripts currently under consideration should be cited in the text in round brackets and not in the reference list.
ADDITIONAL SECTIONS FOR MANUSCRIPTS

Competing interests - required
Please use authors’ initials, and list any competing interests for each author. If there are no declarations to be made, you should state that the authors have (or the author has) no competing interests to declare. See the Competing interests section for further details.

Acknowledgements and funding - required
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Authors' contributions - required
The individual contributions of each author must be specified in the Authors' contributions section. Please use authors' initials and state that all authors have read and approved the final manuscript. See the Authorship section for further details.

Additional files - optional
Supporting data or supplementary files can be included in the submission as additional files. A section listing the additional files numbered consecutively should be provided as "Additional file 1", "Additional file 2", etc. and all files need to be referenced in the main text in round brackets. Please specify the file format used and a short description of the data under each title. Additional files will be linked to the published article in the same format as originally submitted by the authors, but will not be displayed within the article. Please use file formats that readers can access using free or widely available tools.

Author information - optional
This section can be used to include additional information on the author(s) that may be useful for readers' interpretation of the article and their understanding of the viewpoint presented.

List of abbreviations - optional
A list of all abbreviations presented in alphabetical order can be provided in a separate section.

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