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HIV-related knowledge and antiretroviral therapy (ART) outcomes in HIV-infected women initiating ART during pregnancy

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PREAMBLE

DECLARATION

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ABSTRACT

The characteristics of South Africa's HIV epidemic mean that approximately 28% of women presenting for antenatal care, are HIV-infected. Maternal HIV-infection can lead to mother-to-child transmission (MTCT) of HIV during pregnancy, labour, delivery or breastfeeding if viral load (VL) is not well controlled by antiretroviral therapy (ART). Globally, 90% of pediatric infections occur via MTCT, though lifelong ART is reducing the rate of new infections. Full benefits of ART can only be realized when ART adherence is high. Evidence from South Africa and elsewhere has shown that ART adherence in pregnant and postpartum women is suboptimal. Potential drivers of suboptimal adherence may include poor or inadequate knowledge of HIV and ART. This thesis investigates how HIV-infected pregnant and postpartum women's knowledge of HIV and ART-related information may be associated with ART adherence as evaluated by HIV VL measures.

Components of this thesis include the research protocol, a literature review of previous studies exploring the relationship between knowledge and HIV-related health outcomes in Sub-Saharan Africa and a manuscript describing the results of an investigation into predictors of HIV and ART-related knowledge and the association of knowledge with maternal vireamia (VL>1000copies/mL).

This data for analysis came from a cohort of 376 HIV-infected pregnant women, initiating ART during pregnancy, at a primary care antenatal facility in Gugulethu, South Africa. Participants were followed from their first antenatal visit until twelve months postpartum. Knowledge of HIV and ART-related information were assessed at three time points by two knowledge inventories and items were classified as either relating to general knowledge or prevention of MTCT. HIV VL was measured at delivery and twelve months postpartum. Demographic characteristics were surveyed at the first antenatal visit. Analyses included univariable and multivariable regression models to estimate potential predictors of

knowledge among demographic and clinical characteristics, as well as to estimate the association between knowledge and maternal vireamia at delivery and twelve months postpartum.

We found that HIV and ART knowledge increased marginally over the repeated study visits. Knowledge relating to general HIV or ART information was typically good while knowledge on PMTCT was lacking. Education (OR=-0.52; 95% CI=-0.83- -0.21; *P*=0.001), previous HIV diagnoses (OR=-0.36; 95% CI=-0.09-0.63; *P*=0.009), and weeks on ART at delivery (OR=-0.03; 95% CI=0.00-0.06; *P*=0.047) were statistically significant predictors of HIV knowledge in adjusted analyses. The associations between the various knowledge outcomes and vireamia at delivery and twelve months postpartum were mixed and generally not statistically significant.

In summary, HIV and ART knowledge both increased with increasing time in care and general knowledge was better than knowledge specific to MTCT. Education, timing of HIV diagnoses and time on ART were identified as potential predictors of HIV-related knowledge. Generally, knowledge of HIV or ART was not meaningfully associated with vireamia at delivery or at twelve months postpartum. There remain significant gaps in the knowledge of HIV-infected women, of childbearing age, around how HIV is transmitted and how to reduce the risk of MTCT.

LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ANC	Antenatal care
ART	Antiretroviral therapy
ARV	Antiretroviral
AZT	Azidothymidine
CD4	Cluster of differentiation-4, T lymphocyte
CI	Confidence interval
CHC	Community Health Centre
HIV	Human Immunodeficiency Virus
IQR	Interquartile range
JIAS	Journal of the International AIDS Society
KAB/P	Knowledge-Attitude-Behaviour/Practice
LTFU	Loss to follow-up
MCH-ART	Maternal & Child Health Antiretroviral Therapy Study
MOU	Midwife Obstetric Unit
MTCT	Mother-to-child transmission
NCBI	National Centre for Biotechnology Information
NHLS	National Health Laboratory Services
OR	Odds ratio
PMTCT	Prevention of mother-to-child transmission
SES	Socioeconomic status
UCT-HREC	University of Cape Town Human Research Ethics Committee
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	Viral load
WHO	World Health Organization

TABLE OF CONTENTS

LIST OF TABLES

PART A: RESEARCH PROTOCOL

PART B: STRUCTURED LITERATURE REVIEW

PART C: MANUSCRIPT

MANUSCRIPT SUPPLEMENTARY MATERIAL

LIST OF FIGURES

PART A: RESEARCH PROTOCOL

PART C: MANUSCRIPT

MANUSCRIPT SUPPLEMENTARY MATERIAL

PART A: RESEARCH PROTOCOL

BACKGROUND & RATIONALE

To date, HIV/AIDS is still one of the largest global public health concerns with an estimated 36.7 million people living with HIV in 2015 (1). To combat the AIDS epidemic, the Joint United Nations Programme on HIV/AIDS (UNAIDS) has set a new target (2). The goal is to ensure that by 2020; 90% of HIV-infected individuals are aware of their HIV status, 90% of these individuals are on lifelong antiretroviral therapy (ART) and 90% of those receiving ART are virally suppressed (2). It has been suggested, that if these targets are achieved, the AIDS epidemic can come to an end by 2030, resulting in major health and economic gains (2).

Achievement of the aforementioned goal hinges on the availability of HIV treatment to all those in need (2). One target population of particular interest is HIV-infected pregnant women and their HIV-exposed infants (1). The maternal care platform remains one of the most robust in Sub-Saharan Africa and many HIV-infected women are first identified during pregnancy. Moreover, the vast majority of the estimated 1.8 million children living with HIV, became infected as a result of mother-to-child transmission (MTCT) (vertical transmission), during pregnancy, labour, birth or breastfeeding (1). Prevention of mother-to-child transmission (PMTCT) is thus of major concern.

MTCT rates can be as high as 45% but with the use of successful interventions, transmission rates below 5% are achievable (3). The ultimate goal is to eliminate all MTCT and in some countries, such as Thailand and Belarus, this is already a reality (4). The use of combination ART during pregnancy, birth and the postpartum breastfeeding period has proved extremely effective for PMTC T (3). Intervention strategies thus primarily focus on ART and significant efforts have been made to reduce vertical transmission by extensive ART scale-up for pregnant women (3). Although HIV/AIDS is a global epidemic, individuals in low-and-middle-income countries are disproportionately affected (1) and 90% of HIV-infected children

reside in the countries of Sub-Saharan Africa (4). In South Africa specifically, a vertical transmission rate of 3.5% has been reported (28).

Total elimination of MTCT cannot be achieved solely through increased availability of ART. We need to consider that ART effectiveness is directly dependent on ART adherence which refers to taking correct medication doses at correct times in the correct manner (5). Studies have demonstrated that for ART to be clinically efficacious, an adherence rate of at least 95% is necessary (6). Without optimal ART adherence, drug resistant strains of HIV may develop but moreover HIV viral load (VL) cannot be suppressed (7). This is of particular concern for HIV-infected pregnant women because failure to suppress VL significantly increases the risk of MTCT (8).

It is, therefore, critical that mothers and their infants remain engaged in the full cascade of care, from entry into PMTCT services to infant HIV testing through to maternal re-entry into adult ART services (8). Despite significant efforts to eliminate MTCT and major advances in the cascade of PMTCT and ART services, ART adherence in pregnant and postpartum women is still suboptimal (9). As such, research on the determinants of ART adherence will be crucial in moving forward to realize the goal of eliminating vertical transmission. Various studies have sought to uncover both barriers to and enablers of ART adherence during pregnancy and the postpartum period (10). Barriers and enablers identified in the Sub-Saharan African setting include but are not limited to: age, fear, HIV-related stigma, access to health services, self-efficacy, HIV status disclosure, social support, education and knowledge of HIV and/or ART (10). These barriers and enablers have been researched to variable extents and further advancements are still required (10).

Of particular interest is the influence of knowledge on maternal ART adherence since improved knowledge can be easily achieved through educational programme interventions (11). The possible

mechanism by which knowledge may influence health outcomes is explained by the knowledge-attitude-behaviour/practice (KAB/P) model (12). Here knowledge refers to gaining information that can be used to make decisions, attitude refers to favourable or unfavourable feelings towards something and practice refers to behaviours that avert or delay disease (13). This model postulates that both knowledge and attitude can directly affect behaviour in a gradual manner (14). As an individual gains knowledge, their attitude changes (14). Over time these changes can accumulate and act as a motivational driver for behavior change (14). It is possible that HIV-infected pregnant and postpartum women who have sufficient knowledge about HIV and ART have more favourable attitudes towards health-seeking and health-promoting behaviour. They may, therefore, have increased motivation to behave in ways that lead to positive health outcomes.

In the Sub-Saharan African setting, few studies have investigated the relationship between HIV and ART-related knowledge and maternal health with inconclusive results. Studies in Ghana, Malawi, Kenya and South Africa have found associations between adequate knowledge and improved maternal health outcomes (5,15–17). Studies in Uganda, Ethiopia, Nigeria, Zimbabwe and additional South African studies have, however, found no evidence of similar associations (18–25). Health outcomes examined in these studies included access to ART, uptake of ART, use of antenatal services, retention in care and loss to follow-up, ART adherence and PMTCT and transmission risk behaviours (5,15–25). No studies have investigated the relationship between knowledge of HIV and ART-related information and maternal VL. A study of this nature would be particularly valuable since VL is the key outcome measure of ART and long-term health as well as the driving force behind MTCT risk (8,26).

In light of poor ART adherence and retention in PMTCT services in South Africa as well as research gaps, the Maternal & Child Health Antiretroviral Therapy (MCH-ART) study is underway (8). The MCH-ART study is set in Gugulethu, located in Cape Town, South Africa and aims to optimize ART services for

mothers and their infants (8). The study involves the assessment of HIV-infected pregnant women during antenatal and postnatal periods as well as their HIV-exposed infants (8). A wide array of measurements has been collected from this population including data on knowledge and VL (8). Cohort-specific vertical transmission risk has been documented at 1.3% and is significantly associated with increased VL (27). VL in this context can capture the essence of PMTCT service functioning, individual level behaviors including adherence as well as treatment effectiveness in a real setting (8). It has therefore been stated that VL is the most appropriate ART-related outcome measure in this setting (8).

Given the above, it is clear that more research on HIV-related knowledge and ART adherence in HIV-infected pregnant women in South Africa is warranted. It is also clear that VL is a key robust measure, encompassing ART adherence in this context. Moreover, VL has not been investigated as an outcome measure in any Sub-Saharan African knowledge association studies. A cohort of HIV-infected pregnant women from South Africa with data on HIV-related knowledge and VL is available. This provides the perfect opportunity for such research to be conducted.

AIMS & OBJECTIVES

Aim:

The overall aim of this study is to determine whether knowledge influences ART outcomes in women who initiate ART during pregnancy.

Objectives:

This study has three main objectives which are as follows:

1. To identify potential predictors of maternal HIV and ART knowledge.
2. To determine if knowledge of HIV influences maternal ART adherence as assessed by viral load.

3. To determine if knowledge of ART influences maternal ART adherence as assessed by viral load.

A priori hypotheses:

Regarding objectives 2 and 3, we hypothesize that:

- Increased knowledge of HIV is associated with improved ART adherence indicated by reduced viral load.
- Increased knowledge of ART is associated with improved ART adherence indicated by reduced viral load.

STUDY DESIGN

In order to address the study objectives, previously collected data will be analyzed (secondary data analysis). The parent study of this research is the MCH-ART study which aims to optimize ART services for maternal and child health by addressing several complex objectives (8). To achieve these objectives, MCH-ART followed HIV-infected pregnant women throughout antenatal and postnatal periods (8). Three different study designs, each represented by their own phase were employed (Figure A1) and are described below. In addition, the analysis set that will be utilized by the current study, including all three MCH-ART phases, is described.

Phase 1

Phase 1 was a cross-sectional study of consecutive HIV-infected pregnant women attending their first antenatal visit. The purpose of this phase was to assess the health statuses of and services received by HIV-infected pregnant women at the study clinic. Participants attended only one study visit at which they completed a questionnaire and had blood drawn.

Phase 2

Phase 2 was an observational cohort study including women from phase 1 who, according to local guidelines, were eligible to initiate ART. The purpose of this phase was to describe ART initiation as well as antenatal follow-up in the study population. In this phase, participants were followed from their second antenatal visit until their first postpartum visit and were assessed at three time points. Assessments took place at their second antenatal visit, in the third trimester of pregnancy and within a week after delivery (postpartum). At each study visit women completed relevant questionnaires and had blood drawn.

Phase 3

Phase 3 was a randomized trial to assess two methods of ART delivery during the postpartum period. It included a subset of phase 2 breastfeeding women. In this phase, women were randomized to receive either the ART standard of care, where they were referred to general adult ART services at 4-8 weeks postpartum, or to receive ART at the antenatal clinic with referral to general adult ART services only after breastfeeding had ceased. In this phase participants were assessed at 6 weeks, 3 months, 6 months, 9 months and 12 months postpartum. At each study visit women completed relevant questionnaires and had blood drawn.

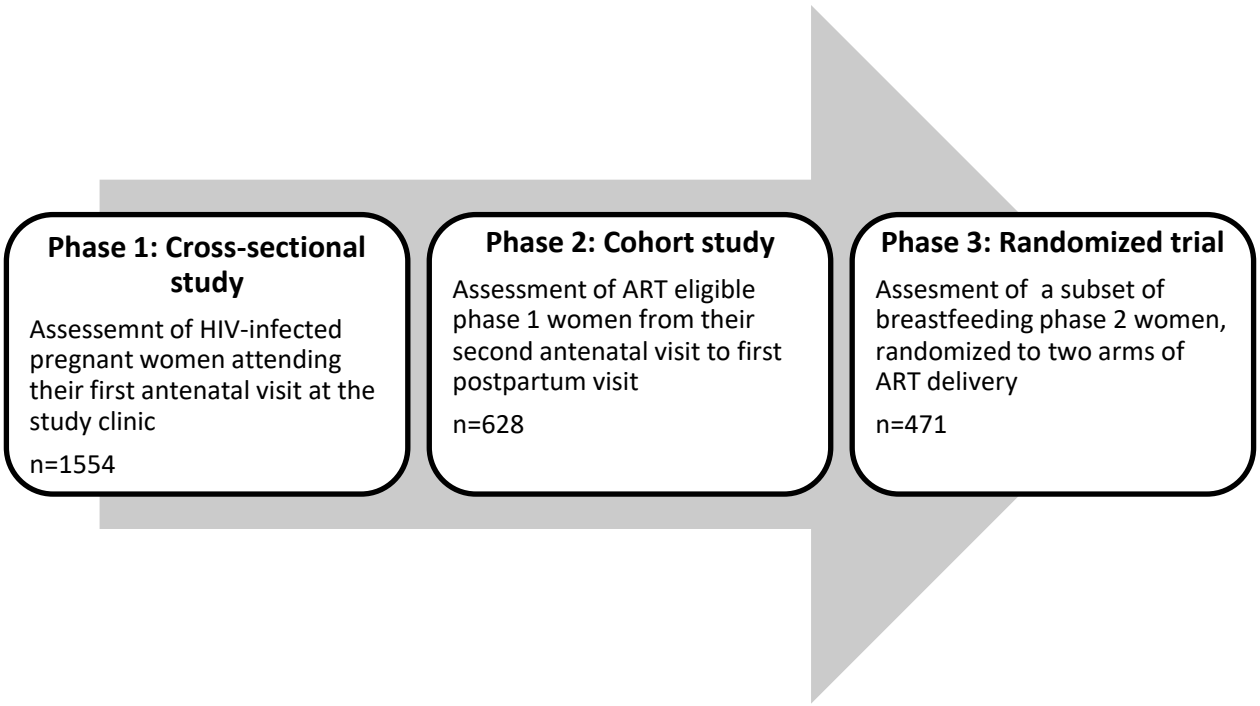

Figure A 1: MCH-ART study design.

Analysis set

The current study will be restricted to participants included in all three phases of the MCH-ART study who completed all knowledge-related questionnaires (n=376). The exposure of interest is HIV/ART knowledge while the outcome of interest is HIV vireamia (VL > 1000 copies/mL) which will be used to assess ART adherence. Moreover, demographic characteristics and participants' medical history which may influence the relationship between knowledge and vireamia are of interest.

STUDY POPULATION

The MCH-ART study enrolled HIV-infected pregnant women seeking antenatal services between April 2013 and June 2014 at the Gugulethu Midwife Obstetric Unit (MOU) situated at the Gugulethu Community Health Centre (CHC) in Cape Town, South Africa. Subgroups of these women were followed for extended periods as explained above. The Gugulethu MOU is a primary care facility in a peri-urban setting with extensive antenatal care (ANC) coverage (>95 %).

INCLUSION & EXCLUSION CRITERIA

Each MCH-ART phase had specific participant inclusion criteria while the exclusion criteria were general.

Inclusion Criteria

Phase 1

Participants must have been: (i) 18 years of age or older, (ii) HIV-infected (as confirmed by two finger prick rapid tests in those with unknown infection statuses or documentation of statuses in those who self-reported infection status), (iii)pregnant (as confirmed by a urine test, ultrasound or clinical exam), (iv) not receiving ART and (v) able to provide informed consent.

Phase 2

Participants must: (i) have consented to participate in phase 1, (ii) been eligible to initiate ART according to local guidelines, (iii) be initiating ART at the Gugulethu MOU during pregnancy (previous ART recipients must not have received treatment for at least six months) and (iv) have been able to provide informed consent.

Phase 3

Participants must have: (i) consented to participate in phase 2, (ii) initiated ART in the antenatal period, (iii) been breastfeeding, (iv) been willing to participate in the randomization process where they were allocated to one of two methods of ART delivery, (v) been willing to take part in postnatal visits and (vi) been able to provide informed consent.

Exclusion Criteria

Individuals were excluded from participation if they met any of the following criteria: (i) they were not pregnant or had experienced a miscarriage when inclusion criteria were assessed, (ii) they planned to permanently move out of Cape Town at some point during the study period, (iii) they had any medical, psychiatric or social conditions which investigators believed may affect ability to provide informed consent and/or efficiently participate in the study where participation barriers included ART refusal or HIV status denial.

RESEARCH PROCEDURES

All research procedures and data collection processes have already taken place and all data for the current study is readily available. All procedures took place during MCH-ART study measurement visits which were carried out separate from routine antenatal and postnatal clinic visits. The broad MCH-ART study included a multitude of measurements, however, only a small subset of these measurements is of interest in the current study. Measurements of interest include: HIV and ART knowledge, VL at delivery and 12 months postpartum and demographic characteristics and participants' medical history. The measurements of interest and the timing of their collection are summarized in Table A1 and described below.

HIV & ART Knowledge

Knowledge about HIV and ART were assessed and scored by two separate inventories (Appendix A). Instruments were administered to participants at the second antenatal visit (visit 2), the six week postpartum visit (visit 5) and the nine month postpartum visit (visit 8). Knowledge inventories were short and administered to participants along with various other questionnaires and a blood draw. The phase 1 study measurement visit had an approximate duration of 20 minutes, phase 2 study visits had an approximate duration of 30-45 minutes each and phase 3 study measurement visits had approximate durations ranging from 35-60 minutes each. In all instances, the instruments were administered by trained interviewers, able to assist participants' in their home language (isiXhosa).

HIV Viral Load

At each study visit (9 in total), 5mL of venous blood was collected from each participant into serum separating tubes, via venepuncture. As indicated above, study measurement visits for each phase, which included the blood draw, had a minimum duration of 20 minutes and a maximum duration of 60 minutes. Blood was transported to the National Health Laboratory Service (NHLS) for batched VL testing using the Abbott Molecular RealTime HIV-1 assay (Abbott Molecular, Illinois, USA). All blood draws were performed by trained phlebotomists and all VL testing was performed by individuals trained in the required laboratory techniques. Furthermore, all blood draws as well as specimen handling, processing, and storage was carried out according to routine protocols. Only VL measurements at delivery and at 12 months postpartum will be used as outcome variables in the current analyses.

Demographic Characteristics & Medical History

All demographic characteristics and medical history information was collected at the first study measurement visit. This information was collected by means of a short standardized questionnaire as

presented in Appendix B. Questionnaires were administered by trained interviewers in participants' home language (isiXhosa).

Table A 1: Measurements to be used in the current study and timing of their collection.

	Phase 1	**Phase 2**			**Phase 3**				
Visit Number	1	2	3	4	5	6	7	8	9
Visit timing	1st antenatal visit	2nd antenatal visit	Late 3rd trimester	< 7 days postpartum*	6 weeks postpartum	3 months postpartum	6 months postpartum	9 months postpartum	12 months postpartum
Questionnaire-based measures									
Demographics and medical history	✓								
HIV knowledge		✓			✓			✓	
ART knowledge		✓			✓			✓	
Laboratory measures									
Batched HIV viral load				✓					✓

*HIV viral load at <7 days postpartum is considered HIV viral load at delivery

RISKS & BENEFITS TO PARTICIPANTS

Since the current study involves only secondary data analysis, no new risks are posed to participants. This study is thus regarded as a minimal risk study. There are no direct benefits to study participants; however, identifying the relationships between HIV/ART knowledge and VL/ART adherence has the potential to yield indirect benefits. Better understanding of how knowledge affects VL/ART adherence may shed light on an important step in the PMTCT cascade which can be targeted for intervention to improve PMTCT services.

INFORMED CONSENT

All participants were required to sign informed consent, in accordance with the Declaration of Helsinki, before enrolling in any phase of the MCH-ART study. As such, three informed consent documents were necessary (Appendix C). All documents were verbally delivered to participants by specifically trained interviewers, following a standard script in participants' home-language (isiXhosa). The consent process detailed information regarding the study purpose, all study procedures as well as the risks and benefits of taking part in the research. During the consent processes and over the course of the study, interviewers made participants continuously aware that: (i) study participation was voluntary and would in no way affect the care they received and (ii) they could freely withdraw from the study at any time and that this would not affect their healthcare in any way. Details of each informed consent process are presented below:

Informed Consent 1

The first informed consent document was completed by HIV-infected pregnant women who were willing and eligible to participate in phase 1 of MCH-ART. This process provided information on the main study

purpose as well as information on completing the initial questionnaire (containing demographic and behavioral information), the blood draw, granting permission to abstract information from medical records and granting permission to be contacted for later research.

Informed Consent 2

The second informed consent document was completed by a subset of phase 1 women, eligible to initiate ART, who were willing to participate in phase 2 and deemed suitable according to the inclusion and exclusion criteria. This process provided information on the overall study purposes as well as information on all phase 2 specific procedures.

Informed Consent 3

The third informed consent document was completed by a subset of phase 2 breastfeeding women who were willing to participate in phase 3 and deemed suitable according to the inclusion and exclusion criteria. This process provided information on the overall study purposes as well as information pertaining to the two ART delivery methods being tested, the process of randomization and all further phase 3 specific procedures.

PRIVACY & CONFIDENTIALITY

The MCH-ART study made use of a variety of privacy and confidentiality measures. All pertinent measures will be upheld throughout the current study and include: (i) storing all participant information in secured cabinets at the Gugulethu study office or at the University of Cape Town, (ii) restricting participant identifiers to informed consent forms only accessible by project coordinators or principle investigators, (iii) using anonymous study identifiers on all study documents and (iv) ensuring all electronic records and electronic data communication are secured in password-protected files.

PARTICIPANT COMPENSATION

Since the current sub-study involves only secondary data analysis, participants will not receive any compensation specific to this study. Participants had, however, already received compensation for participation in the MCH-ART study. Participants received R20 per study visit to cover transportation costs, grocery vouchers to the value of R80 and refreshments up to the value of R50.

ANALYTIC CONSIDERATIONS

Data Source

All data to be used in the current study is from the MCH-ART study and has been previously collected.

Sample Size

The current study's sample size (n=376) and power is calculated based on the previously collected data from the MCH-ART study. The formula used for the power calculation is as follows: $n = \frac{\left(\sigma_1^2 + \sigma_2^2\right)(Z_{1-\alpha} + Z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}$ and all parameters are specified below (Table A2). Assuming 20% of HIV-infected women are vireamic and a standard deviation of 1.3, we can detect a 0.5 unit difference between groups with 84.4% power at a 5% significance level (α=0.05).

Table A 2: Parameters for the power calculation.

Study Parameter	Value
Alpha	0.05
Total N	376
N1	75
N2	301
N2/N1	4.01
Delta	0.50
Mean 1	6.00
Mean 2	6.50
Standard deviation	1.30
Estimated power	0.844

Data Analysis

All data will be analyzed using STATA V14.0 (Stata Corporation, College Station, Texas, USA). The characteristics of participants will be described using medians and interquartile ranges (IQR) or by frequencies (%).HIV knowledge and ART knowledge will be described by frequencies of item-specific correct answers, means of total correct answers and cumulative number correct. Univariable and multivariable linear regression models will be used to estimate associations between demographic/clinical variables and knowledge scores. Univariable and multivariable logistic regression models will be used to estimate associations between knowledge scores and vireamia at delivery and 12 months postpartum. Coefficients, odds ratios and 95% confidence intervals will be reported. For all analyses, statistical significance will be set at α=0.05.

ETHICAL COMPLIANCE

Ethical approval was obtained for the MCH-ART study from the Human Research Ethics Committee of the Faculty of Health Sciences within the University of Cape Town (HREC: 451/2012) (Appendix D) and the Columbia University Medical Centre Institutional Review Board. The current study protocol and required documentation will be reviewed and approved by the Human Research Ethics Committee of the Faculty of Health Sciences within the University of Cape Town (HREC: 707/2017). As highlighted: (i) all participants completed informed consent documents and were aware that they could freely withdraw from the study without any repercussions, (ii) this study is considered a minimal risk study in which benefits outweigh risks, (iii) extensive measures have and will continue to be taken to assure data confidentiality and (iv) participants were not excessively compensated. Furthermore, study collaborators will agree on all results to be disseminated and no funding bodies may influence which/how results will be presented or published.

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PART B: STRUCTURED LITERATURE REVIEW

INTRODUCTION

In 2015 an estimated 36.7 million people were living with HIV (1). More than 70% of the HIV-infected population resides in Sub-Saharan Africa with the greatest prevalence found in South Africa, where women are disproportionately affected (2, 3). Furthermore, it has been noted than among pregnant women in this region, approximately 28% are HIV-infected (4). This is of major concern since mother-to-child transmission (MTCT) accounts for about 90% of new pediatric infections (5).

HIV-infected women can transmit HIV to their infants during pregnancy, labour, delivery or breastfeeding (6). Without preventative measures MTCT rates can be as high as 45% (7). Interventions aimed at preventing mother-to-child transmission (PMTCT) can, however, reduce these rates to <5% as shown in high income countries (7, 66). In recent years, policy changes increasing the availability of and access to maternal antiretroviral therapy (ART) have had a major impact on reducing MTCT (8). Many Sub-Saharan African countries, including South Africa, have adopted the World Health Organization's (WHO) "Option B+" strategy which calls for universal initiation of lifelong ART among pregnant and breastfeeding women irrespective of CD4 count, stage of disease or gestational age (8,9). Consequently, there has been a large increase in women initiating ART during pregnancy and the postpartum period in South Africa as the maternal care platform is one of the most robust among Sub-Saharan African countries (8).

The role of ART in maternal health is three-fold: ART improves the health status of the mother, reduces the risk of MTCT and reduces the risk of horizontal HIV transmission to sexual partners (10,11). These benefits arise because ART acts to suppress viral load (VL) (12). This, however, can only be achieved through optimal ART adherence where adherence rates of at least 95% are required for clinical efficacy (13). Evidence from Sub-Saharan Africa suggests that HIV-infected pregnant women have lower rates of

retention in care (a precursor to ART adherence) than non-pregnant women and men (14,15). Moreover, ART adherence is strongly associated with reaching viral suppression (16,17) while non-adherence is associated with viremia (VL>1000copies/mL) – the driving force behind MTCT (18).

With the influx of pregnant and postpartum women initiating ART (8), their low retention rates (14,15) and the high rate of adherence necessary to maintain viral suppression (13), HIV-infected pregnant and postpartum women have become the focus of much research (8). Several studies have investigated maternal HIV-related health outcomes and their possible determinants (19). One such determinant, gaining attention in recent years, is knowledge (19). This topic forms the basis of the following review.

OBJECTIVE

The main objective of this literature review is to review and evaluate previous work which has examined associations between HIV, ART, and MTCT/PMTCT knowledge and maternal HIV-related health outcomes in Sub-Saharan Africa.

SEARCH STRATEGY

The PubMed databases hosted by the National Centre for Biotechnology Information (NCBI) were searched using the following two sets of search terms: “(HIV OR MTCT OR ART) AND (pregnancy OR postpartum) AND knowledge AND Sub-Saharan Africa” and ”(adherence OR retention OR viremia) AND option B+ AND Sub-Saharan Africa”. Titles and abstracts of the resultant literature were reviewed to select core articles. Reference lists of these articles were reviewed to obtain additional relevant articles. Where appropriate, reference lists of these additional articles were used to acquire further literature.

SUMMARY OF THE LITERATURE

Retention, adherence and viral control among pregnant & postpartum women initiating ART under Option B+ in Sub-Saharan Africa

Option B+ is potentially far superior to its preceding strategies due to its non-discriminatory and permanent nature (9). Since it is a universal strategy, there is no need for CD4 count measures or any additional assessment of disease progression or gestational age (20,21). In resource limited settings, it is generally considered simpler to implement which has a major impact on regions of Sub-Saharan Africa where HIV is considered to be a generalized epidemic (20–22).

Nonetheless, implementation of Option B+ is not without challenges. To fully benefit, women often initiating ART when healthy, must remain in care and on treatment for the rest of their lives (8). Consequently, evidence suggests that retention and engagement in ART services is imperfect (3,8,23–28). A number of studies have investigated retention in care and/or loss to follow-up (LTFU) as well as adherence to ART following Option B+ implementation (3,8,23–28). Evaluation of these outcomes depends on the definitions used and difficulty arises due to the close relationship between retention, which is generally regarded as a precursor to adherence, and adherence (8). As with many pragmatic measures carried out in resource limited settings, obtaining accurate estimates can depend on the study resources. For example, women may be incorrectly identified as LTFU when they could simply be receiving care at another facility (8). Problems also arise when retention is used as a proxy for adherence since a women may be adherent if receiving care elsewhere, although defined as not retained (8). While these issues should be noted, the umbrella term 'engagement in ART services' has been suggested to encompass retention in care and adherence following which, viral control can be achieved (8).

Retention

Since the introduction of Option B+, studies from Malawi, Cameroon, Mozambique, Zimbabwe and Ethiopia have investigated retention and/or LTFU rates (10, 21, 22, 29-32). In a national Malawian study, Tenthani *et al* found that 82% of 21 939 mothers remained in care after six months (29). A further analysis including pregnant (n=3320) and breastfeeding (n=2037) women as well as women initiating ART for their own health (n=6177) found six month retention rates of 70.6%, 83.9% and 90.4%, respectively (29). A later Malawian study, including much the same cohort, noted 12, 24 and 36 month retention rates of 76.8% , 70.8% , 69.7%, respectively (30). In an urban based Cameroon cohort of pregnant and breastfeeding women (n=268), Atanga *et al* found six month retention rates of 88.0% reducing to 81.1% at 12 months, 74.2% at 18 months and 73.3% after 24 months (10). In Ethiopia, Mitiku *et al* found retention in care to be 88.1% at six months, 84.3% at 12 months and 77.4% at 24 months, among 346 pregnant and breastfeeding women in an urban setting (31).

Rural cohorts in Mozambique and Zimbabwe had worse rates of retention although comparability with urban cohorts is problematic due to different health systems and practices. In Mozambique Llenas-Garcia *et al* found poor 12 month retention rates among pregnant (41.8%) and lactating women (40.4%) (n=308) (21).Similarly Erlwanger *et al* found 12 month retention rates of 67.7% among a large Zimbabwean cohort (n=1113) of pregnant women (32). A much smaller study (n=157) in Zimbabwe estimated a six month retention rate of 83% among pregnant and breastfeeding women (22).

Overall, findings indicate that six month retention, where estimated, is fairly high and similar across study settings, ranging from 82% to 88%. Twelve month retention rates were far more variable, ranging from 40% to 84%. This is largely due to very low retention rates in Mozambique (21). If data from Mozambique are excluded, a narrower range is observed (68% - 84%). Two year retention rates were only available for Malawi, Cameroon and Ethiopia and ranged from 71 to 77%. Only a single study

considered retention at 36 months which was estimated to be 70% (Malawi) (30). As evidence by these studies, retention of pregnant and postpartum women is suboptimal and declines consistently.

Adherence

Ugandan and Zimbabwean studies have investigated ART adherence under Option B+ (20,32). In Uganda Schnack *et al* found a median pill count adherence of 95.7% in 124 pregnant women (20). Furthermore they noted that 21.1%, 27.6% and 51.3% of women had low (<80%), moderate (80-94.9%) and adequate (>95%) adherence rates, respectively (20). In Zimbabwe Erlwanger *et al* found a one year adherence rate of 39.1% in women initiating ART during pregnancy (n=1113) (32).In this study adherence was measured by dispensary records and a medication possession ratio (32). In comparison it appears that adequate adherence rates were ~10% higher in Uganda. Both studies were conducted in rural settings so perhaps discrepancies are the result of inter-country differences or different methodologies. It is difficult to draw conclusions on adherence from such limited data; nonetheless, adherence rates appear suboptimal and worse than retention rates.

Viral Control

Use of and health system capacity to carry out routine VL monitoring is limited in Sub-Saharan Africa (8). As such, three of five identified studies that utilized VL measurements were based in South Africa, with one each in Malawi and Rwanda (33–37). In South Africa, viral suppression (VL<50copies/mL) of 574 pregnant women already on ART was 78% at the time of their first antenatal visit (33). Of the remaining 22%, 13% had VLs >1000copies/mL and 7% had VLs >10 000copies/mL (33). In a linked study (same clinic population), viral suppression among 620 women initiating ART during pregnancy was evaluated (34). At delivery, 73% of these women were virally suppressed and a cumulate 91% had VLs <1000 copies/mL, posing a minimal MTCT risk (34). Postpartum follow-up of an overlapping cohort indicated that 70% of

women sustained viral suppression through 12 months postpartum, 8% of women experienced a minor vireamic episode (VL: 50-1000copies/mL) and 22% at least one major vireamic episode (VL>1000copies/mL) (35).

In a large study (n=1269) based in Malawi, 84% of pregnant or breastfeeding women had VLs <1000copies/mL six months after treatment initiation (36). The remaining 16% were considered to have virologic failure (36). Among 608 pregnant and postpartum women in Rwanda, most of whom were on ART prior to entry into antenatal care, 85% of women had VLs <1000copies/mL during late pregnancy or the early postpartum period (37). It was also noted that VL tended to be higher in those who had been on ART for more than three years (37).

The evidence from South Africa indicates that VL increases with increased ART duration throughout the gestational and postpartum period (33–35). Given that the studies in Malawi and Rwanda analyzed VL at different time points, it is difficult to compare results across the three settings (36,37). Even so, evidence suggests that viral control during pregnancy and the postpartum period is suboptimal.

HIV, ART and PMTCT knowledge among pregnant & postpartum women in Sub-Saharan Africa

Lack of knowledge about HIV, ART and/or MTCT/PMTCT has been hypothesized to contribute to poor health outcomes (38–46). This is of particular concern in key populations such as women of childbearing age and pregnant and postpartum women due to the increased risk of HIV-acquisition during pregnancy and the risk of MTCT if HIV-infected (8,47). Nine South African studies evaluating knowledge in these key populations were identified (38–45), as well as a number of studies from other Sub-Saharan African countries (3,48–53).

In a small 2013 study of 67 women of childbearing age (22% HIV-infected) in rural South Africa, most participants (>90%) were aware of major HIV transmission methods but there were several misconceptions surrounding transmission by other means (38). Only 67.2% of participants knew progression of HIV to AIDS could be prevented by ART and 35.8% of participants thought HIV could be cured (38). Most participants (>90%) knew about MTCT but far fewer were aware that vertical transmission could occur during pregnancy (55%), labour/delivery (27%) or breastfeeding (29%) (38).

Five studies included pregnant women from South Africa (39–43). Between 2006 and 2007, among 160 women receiving PMTCT services in a peri-urban setting, Futterman *et al* found that overall knowledge was generally reasonable but knowledge on CD4 counts and VL was lacking (39). Three studies including the same pregnant women, attending antenatal services in a rural setting, found that women and their partners (n=478) possessed moderate HIV-related knowledge (40–42). In addition, when knowledge of these participants was evaluated by in-depth interviews, participants were considered to have "some" knowledge of HIV and PMTCT (43).

Among the studies carried out in postpartum women, a 2006 study in rural South Africa (n=202 HIV-infected) found high levels of HIV transmission (98%) and prevention (94%) knowledge (44). As with other groups, PMTCT knowledge was poor with only 56% and 73% of participants assessed to have appropriate knowledge on vertical transmission and its prevention, respectively (44). A larger study in 2008 (n=815), among mothers in a PMTCT programme in rural South Africa, found that only 71% of participants were aware of MTCT (45). Furthermore, while 54% of participants were aware that MTCT occurs sometimes, over 30% thought that MTCT always occurs between an HIV-infected mother and her infant (45). A qualitative study has provided additional insight on postpartum women's HIV/ART knowledge (42). A 2016 study of 15 postpartum mothers receiving PMTCT services revealed that most participants knew that a mother could infect her infant at various stages but were not sure how and did

not understand how transmission after birth occurs. These participants were however aware that prevention methods for MTCT existed and that adhering to ART was critical for PMTCT (42).

Work from other Sub-Saharan African countries supports the findings from South Africa. In rural Mozambique, only 56% of 27 HIV-related questions were answered correctly by 348 women receiving antenatal care (48). A study carried out at the same time (2011) in rural Uganda, among a general population of women of childbearing age (n=100), found very low rates of knowledge, with 7% having adequate MTCT knowledge (49). In 2011 in Ghana, among 229 HIV-infected women of reproductive age, 90% had inadequate ART and PMTCT knowledge (3). A 2011 study in Cameroon found PMTCT knowledge among 477 pregnant women was good overall but this was likely due to HIV and PMTCT talks routinely given at the clinic (50). In 2012 national data from Tanzania showed that 45% of HIV-uninfected (n=9737) and 56% of HIV-infected women (n=562) had adequate knowledge on MTCT and PMTCT (51). In 2014 in rural Nigeria, 78% of pregnant women in care (n=450) had adequate knowledge on MTCT but only 28% of women knew that ART was a means to prevent MTCT (52). In rural Ethiopia in 2014, 63.8% of 542 pregnant women, some of whom were in care, had appropriate knowledge of HIV while 19% had comprehensive MTCT knowledge (53).

Overall, this research indicates that HIV, ART and MTCT/PMTCT knowledge among both women of childbearing age and pregnant and postpartum women is imperfect. In particular, knowledge of vertical transmission seems to be poor. Although difficult to assess from the available literature, there is some evidence that knowledge is improving as scale-up in ART services takes place and that knowledge of MTCT is better among women who are pregnant or breastfeeding than the general population. It is also worth noting that the majority of the published findings have occurred in rural populations. As such, they may not generalize, especially to urban populations who typically have more consistent access to healthcare and information about healthcare.

Mechanisms through which knowledge may impact ART outcomes

A lack of knowledge may act as a substantial barrier to accessing healthcare, remaining in healthcare and adhering to medication. However, enhancing knowledge is considered one of the easiest interventions to evoke behavioural change and the identified gaps in knowledge may represent an opportunity for meaningful interventions (54,55). Social-cognitive theory suggests that improving knowledge can lead to behaviour change and the applied focus is on social-cognitive methods that lead to health promotion and disease prevention (55). The theory identifies health determinants, their mechanisms and best methods for translating knowledge into action (55). Determinants typically include: (i) knowledge about health risks and practices, (ii) self-efficacy, (iii) expected outcomes, (iv) personal goals and (v) barriers to and facilitators of change (55). Analyzing this theory in its entirety is beyond the scope of this review but it is important to note that knowledge is at the forefront and can be considered a prerequisite for behaviour change to occur (55).

Improvement to knowledge has typically been approached through various formal and informal educational interventions (55). Moreover, education has long been considered an important component of HIV-programmes (56). A theoretical model of health education, known as the knowledge-attitude-behaviour/practice (KAB/P) model, has been developed (57). In the KAB/P model, knowledge is defined as gaining information, by means of education or experiences, which can be retained and utilized to make decisions (58). Attitude is a psychological construct and is denoted by having favourable or unfavourable feelings towards something (58). Finally, practice refers to health-related behaviours which lead to disease aversion or delayed progression of disease (58). This model postulates that behaviour and practice can be directly influenced by both knowledge and attitudes (59). It further suggests that knowledge acquisition and attitude modulation are gradual and accumulative, potentially leading to long-term behaviour modification as they become a motivational driver for change (59). The

relationship between these three constructs is not straight-forward but dynamic and multidirectional (60). Knowledge may inform an individual's attitude and these feelings may alter behaviour but the converse is also possible (60). Behaviours may influence attitudes which then influence perceptions and potentially the amount of knowledge acquired (60).

Associations between HIV, ART and/or MTCT/PMTCT knowledge and HIV-related health outcomes in Sub-Saharan Africa

The literature search identified 11 studies investigating the relationship between HIV, ART and/or MTCT/PMTCT knowledge and HIV-related health outcomes (Table B1). Three studies explored retention in care or defaulting from care, four studies explored medication adherence and individual studies considered access to ART, uptake of ARVs, use of antenatal care and PMTCT and transmission risk behaviours. No studies investigated HIV VL as a clinical outcome.

Retention in Care/Defaulting

Of the three studies investigating this outcome, two found significant associations (3, 25). In Ghana, women with inadequate ART/PMTCT knowledge had a significantly higher risk of defaulting compared to those with adequate knowledge (OR=3.5, 95% CI:1.89-6.21) (3). This study included 206 HIV-infected women of reproductive age, measured knowledge by a questionnaire and classified defaulting as missing at least two consecutive ART appointments (3). In Malawi, high ART knowledge scores were associated with an increased odds of retention in care (OR=1.60, 95% CI:1.15-2.23, *P*=0.004) among women on ART, 82% of which were pregnant (25). Knowledge was measured by a questionnaire, cases (n=50) were individuals out of ART for more than 60 days and controls (n=153) were individuals remaining in care for at least 12 months (25). In Uganda, no discrepancies between knowledge among

those in care and ART defaulters were noted (23). This qualitative study included 45 HIV-infected pregnant women and measured knowledge by in-depth interviews (23).

General limitations of these studies included self-reported measures vulnerable to recall bias and social desirability bias (answering questions to conform to norms (23)) as well as potential questionnaire limitations. Questionnaires may hinder the ability to comprehensively test knowledge since closed-ended questions allow participants to recognize correct answers. This may ultimately lead to measurement of passive knowledge rather that active knowledge that could influence behaviour (3). In Ghana specifically, few women had adequate knowledge (n=17), the cross-sectional nature makes it impossible to ascertain whether knowledge preceded non-defaulting and ART counseling across facilities was not accounted for (3). In Malawi there were low numbers of defaulters (n=50) and no corrections for multiple testing (25). In Uganda the study was small and qualitative in nature (23).

Table B 1: Summary of knowledge and HIV-related health outcome associations in Sub-Saharan Africa.

Author	Country	Time period	Sample size	Population	Option B+	Study design	Method of knowledge assessment	Type of knowledge assessed	Outcome	Main finding
Duff *et al* (23)	Uganda	2010	45	HIV+ pregnant women	No	Cross-sectional	In-depth interviews & focus groups	HIV, HAART	Retention/ defaulting	No association
Boateng *et al* (3)	Ghana	2011	206	HIV+ women of childbearing age	No	Cross-sectional	Questionnaire& classification into adequate and inadequate	ART & PMTCT	Retention/ defaulting	Defaulting rate significantly higher in those with inadequate knowledge compared to those with adequate knowledge
Hoffman *et al* (25)	Malawi	2014-2015	203	HIV+ women initiated on ART	Yes	Case-control	Questionnaire	ART, PMTCT	Retention/ defaulting	Knowledge scores significantly higher among non-defaulters
Peltzer *et al* (45)	South Africa	2008-2009	215	HIV+ mothers with infants of 3-6 months	No	Cross-sectional	Questionnaire & scores	MTCT	Adherence	Increased MTCT knowledge associated with increased maternal adherence
Peltzer *et al* (27)	South Africa	2009	746	HIV+ antenatal and postnatal women	No	Cross-sectional	Questionnaire & scores	MTCT	Adherence	No association
Ekama *et al* (28)	Nigeria	2009	170	HIV+ pregnant women	No	Cross-sectional	Questionnaire & classification as good or poor	HIV, ART	Adherence	No association
Ebuy *et al* (24)	Ethiopia	2014	277	HIV+ pregnant women	Yes	Cross-sectional	Questionnaire & classification into high, moderate low	HIV, ART, PMTCT	Adherence	No association
Kohler *et al* (61)	Kenya	2011	247	HIV+ postpartum women	No	Cross-sectional	Questionnaire & scores	HIV, PMTCT	ARV uptake	HIV prevention knowledge and PMTCT knowledge associated with increased uptake of ARVs
Muchedzi *et al* (61)	Zimbabwe	2008	147	HIV+ women from PMTCT programs	No	Cross-sectional	Questionnaire & classification as <50 or >50	PMTCT	Access to care	No association
Sahlu *et al* (63)	Ethiopia	2011	7392	HIV- and HIV+ postpartum women (116 HIV+)	No	Cross-sectional	Questionnaire& classification into high and low	MTCT	ANC use	No association
Futterman *et al* (39)	South Africa	2006-2007	71	HIV+ pregnant women	No	Case-control	Questionnaire & scores	HIV, ART	PMTCT/ Transmission risk behaviour	No association

Adherence

Only one of four studies identified a significant knowledge-adherence association (45). In South Africa, Peltzer *et al* found MTCT knowledge to be associated with increased adherence to nevirapine (an ARV) for PMTCT (OR=1.67, 95% CI:1.28-1.68, *P*<0.001) (45). This study included 815 HIV-infected mothers, measured knowledge and ART adherence by questionnaires and defined non-adherence as not taking nevirapine as prescribed or not at all (45).

Studies that found no association included a later South African study (Peltzer *et al*), a Nigerian study (Ekama *et al*) and an Ethiopian study (Ebuy *et al*) (24,27,28). Peltzer *et al* examined factors associated with adherence to nevirapine and AZT (ARVs) among HIV-infected antenatal (n=139) and postnatal women (n=607) (27). They measured knowledge by a questionnaire and adherence by self-report where non-adherence to nevirapine was defined as not taking it as prescribed or not at all while adherence to AZT was defined as never missing a dose (27). Ekama *et al* examined determinants of adherence in 170 pregnant women accessing PMTCT services (28). ART knowledge was classified as 'good' or 'not good' based on questionnaire scores greater or less than 70%, respectively. Adherence was measured using the percentage of doses taken based on three day recall and rates ≥95% were considered good (28). Ebuy *et al* investigated factors associated with adherence to Option B+ among 277 women (24). They measured PMTCT and ARV knowledge as well as adherence by questionnaires (24). Knowledge was classified as low, moderate or high while adherence was classified as good or poor (24). All four of these studies were limited by the use of self-report to measure adherence and potentially minor issues surrounding the use of questionnaires. Peltzer's studies were further limited by not randomly selecting participants, hindering generalizability (27, 45).

Uptake of ARVs, Access to ART & Use of Antenatal care

An association was only found between knowledge and ARV uptake (61). In Kenya, Kohler *et al* found that increased knowledge was associated with increased ARV uptake among 247 HIV-infected mothers (61). Knowledge was assessed and scored by a questionnaire and HIV status and ARV uptake were measured by self-report (61). In Zimbabwe, Muchedzi *et al* found no association between PMTCT knowledge and access to care (62). They included 147 women in PMTCT programmes with referral to ART services, measured and categorized knowledge (>51% or <51%) using a questionnaire and defined access to care as successful registration at a referral clinic (62). In Ethiopia, Sahlu *et al* found no association between HIV or MTCT knowledge and the use of antenatal care among 7392 HIV-infected women who had given birth in the previous five years (63). MTCT knowledge was measured using a questionnaire and classified as high or low if women answered all questions correctly or not. Antenatal care was measured by self-report (63).

In general, these studies were limited by their cross-sectional nature and possibly social desirability bias. More specifically, the Kenyan study was limited by self-reported measures (61), the Zimbabwean study was limited by the sample size and LTFU (23%) (62) and the Ethiopian study was limited by self-report and not accounting for different types and qualities of antenatal care (63).

PMTCT-related and Transmission Risk Behaviours

In addition to PMTCT-related behaviours, transmission risk behaviors which may include a lack of condom use, no knowledge of sexual partners' HIV status or having multiple sexual partners, is of special concern. This is because hormonal changes make pregnant women especially vulnerable to HIV-infection and because of the incidental implications of perinatal infections (39,47,64). In South Africa, Futterman *et al* found no association between general HIV knowledge and PMTCT and transmission

behaviours (39). This small intervention study included 160 HIV-infected pregnant women at two maternity clinics where the intervention arm included additional peer-support and learning sessions aimed at improving health (39). The intervention significantly increased knowledge scores six months post-delivery (among the 44% retained) as measured by a questionnaire (39). PMTCT and transmission behaviours between the two groups, however, did not differ (39). This study was not randomized, LTFU rates were high and measurements were based on self-report so findings may reflect aspects of bias in the resulting sample.

Summary

The evidence is inconclusive with respect to knowledge-retention and knowledge-adherence associations. While some studies found positive associations (3,25,45), others failed to demonstrate an association (23,24,27,28). The variation in findings could be due to the utilization of different methodologies, different study settings or individual study limitations, particularly the use of cross-sectional data. Evidence from single studies investigating other health outcomes, is insufficient to draw any valid conclusions (39, 61–63). Furthermore, with very few studies investigating knowledge as a potential factor in clinical outcomes and none evaluating HIV VL, conclusions cannot be drawn about the impact of knowledge on clinically measurable health outcomes. This lack highlights the need for further research that specifically interrogates the potential association between knowledge and viral control. While VL is not an explicit measure of ART adherence it is the primary clinical biomarker of ART-related outcomes (e.g. adherence) and HIV disease progression (8,12).Moreover, in pregnant and breastfeeding women who are at risk of HIV transmission to infants, VL is the chief determinant of that risk (8,35).

CONCLUSION & FUTURE DIRECTIONS

Option B+ lifelong ART for all HIV-infected pregnant and postpartum women has dramatically increased the number of women in ART and PMTCT services, reducing the rate of MTCT and improving health outcomes (8). While provision of ART in pregnancy and breastfeeding periods has a theoretical potential to nearly eliminate new pediatric HIV-infections, this can only become a reality if women remain engaged in care and achieve sustained viral suppression (13,65). This review highlights that retention in care, adherence and viral control in women initiating ART, under Option B+, in Sub-Saharan Africa is suboptimal. This review revealed gaps in HIV-related, ART and particularly MTCT/PMTCT knowledge among women of childbearing age as well as pregnant and postpartum women in Sub-Saharan Africa. This lack of knowledge may be a potential driver of the observed suboptimal outcomes.

In Sub-Saharan Africa poor knowledge has been investigated as a determinant of retention in care, adherence, ART uptake, access to ART, use of antenatal care and PMTCT/transmission risk behaviour but the results as yet cannot yield any definite conclusions. Unraveling the association between knowledge and HIV-related health outcomes is of importance since it can inform interventions to improve maternal health. In general, further research on knowledge and HIV-related health outcomes is warranted. More importantly, a major research gap is the absence of data on the relationship between knowledge and maternal VL outcomes. VL is the key outcome influenced by ART and the main driver of MTCT (8,35). It has also been proposed as the gold standard measure for evaluating ART (8), thus an analysis of this nature would be invaluable.

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PART C: MANUSCRIPT

HIV/ART knowledge and viral load outcomes in HIV-infected women initiating antiretroviral therapy (ART) during pregnancy

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ABSTRACT

Introduction: HIV infection during pregnancy and breastfeeding can result in mother-to-child transmission (MTCT) of HIV if viral load (VL) is not well controlled. In South Africa, where almost one third of pregnant women are HIV-infected, this is a major concern. Maternal lifelong antiretroviral therapy (ART) is reducing new pediatric infections by controlling VL but to ensure clinical efficacy adherence must be extremely high. Empirical evidence shows that ART adherence in pregnant and breastfeeding women is suboptimal. HIV and ART knowledge among these women is also lacking, potentially driving suboptimal adherence and subsequent poor viral control. To better understand this, we investigated the association between knowledge and maternal ART adherence as evaluated by vireamia (VL>1000 copies/mL).

Methods: We followed a cohort of 376 HIV-infected pregnant women from their first antenatal visit until 12 months postpartum. HIV and ART knowledge were assessed at three time points by separate knowledge inventories categorized into general and prevention of MTCT (PMTCT) knowledge. An overall, general and PMTCT knowledge score was calculated from each inventory. HIV VL at delivery and at 12 months postpartum was measured and demographic characteristics were surveyed. Univariable and multivariable regression models were used to assess potential demographic/clinical knowledge predictors and to estimate the associations between knowledge scores and vireamia.

Results: Participants were Black African women. Almost half had prior HIV diagnoses (44.7%) and 4.3% had previously received ART. HIV and ART knowledge increased slightly over the study period. General knowledge about HIV and ART was typically good while knowledge about PMTCT was lacking. Previous HIV diagnoses (OR=-0.36;95% CI=-0.09-0.63;*P*=0.009), weeks on ART at delivery (OR=-0.03;95% CI=0.00-0.06;*P*=0.047) and level of education (OR=-0.52;95% CI=-0.83- -0.21;*P*=0.001) were statistically

significant predictors of HIV knowledge outcomes after adjusting for demographic/clinical variables. Associations between knowledge scores and vireamia at delivery and 12 months postpartum were mixed and generally not statistically significant.

Conclusion: General knowledge was good while knowledge specific to PMTCT was comparatively poor. Timing of HIV diagnoses, time on ART and education were identified as potential predictors of HIV-related knowledge. Neither HIV nor ART knowledge was meaningfully associated with vireamia or adherence at delivery or at 12 months postpartum.

INTRODUCTION

Mother-to-child transmission (MTCT) of HIV accounts for 90% of new pediatric infections and can occur during pregnancy, labour, delivery or breastfeeding when viral load (VL) is not suppressed (1,2). Prevention of MTCT (PMTCT) interventions are thus aimed at sustaining viral suppression through the use of antiretroviral therapy (ART) (3). In South Africa, where approximately 28% of pregnant women are HIV-infected (4), the World Health Organization's (WHO) Option B+ ART strategy for PMTCT has been implemented (3). Option B+ endorses initiation of lifelong ART for all pregnant and breastfeeding women regardless of clinical disease stage, gestational age or CD4 count (5). This has consequently resulted in an increase of pregnant and postpartum women entering into ART services for the first time (3). While Option B+ has the potential to transform MTCT rates, its success depends on optimal ART adherence (≥95%) (6). Empirical evidence has demonstrated that women who initiate ART during pregnancy in Sub-Saharan Africa, do not remain engaged in ART services (7–19). This can include being lost from care or not adhering to medication, resulting in uncontrolled VLs and increased risk of MTCT (3).

Researchers have postulated that a lack of knowledge may in part, be responsible for these suboptimal HIV-related health outcomes (20). There has been debate as to whether knowledge influences health outcomes such as adherence, particularly in Sub-Saharan Africa. The knowledge-attitude-behaviour/practice (KAB/P) model best explains the mechanism through which this might occur (21). Knowledge may result in attitude changes which can act as a motivational driver, ultimately leading to behavioural changes (21). It is quite possible that women with poor HIV/ART knowledge have negative or neutral attitudes towards health-improving behaviour and lack the motivation to remain engaged in ART services.

A limited number of studies in Sub-Saharan Africa have investigated knowledge and maternal HIV-related health outcomes with inconclusive findings (22–30). In Ghana, Malawi and Uganda, studies have been undertaken to assess the relationship between knowledge and retention in care but yielded mixed results (22–24). Increased knowledge was found to be associated with improved maternal ART adherence in South Africa but subsequent studies on this association in South Africa, Ethiopia and Nigeria did not support the conclusions (25–27). Increased knowledge has been associated with improved ARV uptake in Kenya (31) but not with access to care in Zimbabwe (28), the use of antenatal care in Ethiopia (29) nor PMTCT and transmission risk behaviours in South Africa (30). Many of these studies had several limitations and comparability is difficult due to the lack of standardized methodology, highlighting the need for further research.

Data on the association between knowledge and VL or any similar clinical outcome in Sub-Saharan Africa are scarce. This is surprising since VL is the primary measure of successful ART adherence and long term health in HIV-infected persons (3). VL is also the key driver of vertical transmission where high VL is associated with an increased risk of transmission in a dose-response manner (3). On this basis, VL has been proposed as the gold-standard for evaluating ART-related outcomes (3).Given the conflicting evidence and lack of data, we investigated how the knowledge of HIV-infected pregnant and postpartum women may be associated with their ART adherence as evaluated by HIV vireamia (VL>1000 copies/mL).

METHODS

This is a sub-study of the Maternal & Child Health Antiretroviral Therapy (MCH-ART) study (32). MCH-ART is a 3 phase implementation science study with the aim of optimizing ART services for pregnant and postpartum women and their infants (ClinicalTrials.gov NCT01933477). Phase 1 was a cross-sectional study of consecutive HIV-infected pregnant women attending their first antenatal visit (n=1554). Phase 2

was an observational cohort study including women from phase 1, initiating ART (n=628). Phase 3 was a randomized trial to assess two methods of ART delivery during the postpartum period (n=471). MCH-ART was conducted at the Gugulethu Midwife Obstetric Unit (MOU) within the Gugulethu Community Health Centre (CHC) in Cape Town, South Africa. This is a primary healthcare facility in a peri-urban setting with antenatal care (ANC) coverage exceeding 95%. The study has been described previously by Myer *et al* (32).

Participants

Participants included in the reported results were recruited and followed as part of the MCH-ART study. This analysis is restricted to participants who were retained throughout the MCH-ART study period and completed all three study phases. Moreover, analyses were further restricted to participants for which all knowledge-related data were available (n=376) (Supplementary Figure D1). Recruitment and follow-up occurred between April 2013 and November 2015. Between April and June 2013 women were ART eligible if their clinical disease stage was III/IV or if they had CD4 counts that did not exceed 350cells/mL, according to South African national guidelines at the time. For the remainder of the study period all women initiated ART irrespective of disease stage or CD4 count as per WHO's Option B+ strategy, which was adopted by South Africa in July 2013. The ART regimen consisted of a fixed dose combination of tenofovir 300mg, emtracitabine 300mg and efavirenz 600mg, once daily. All ART initiation and follow-up occurred as part of routine care.

All participants signed written informed consent in accordance with the declaration of Helsinki. MCH-ART ethical approval was granted by the Human Research Ethics Committee of the Faculty of Health Sciences within the University of Cape Town (HREC: 451/2012) and the Columbia University Medical Centre Institutional Review Board. In addition, the current study obtained ethical approval from the

Human Research Ethics Committee of the Faculty of Health Sciences within the University of Cape Town (HREC: 707/2017).

Study Measurements

All data collection took place as part of MCH-ART study measurement visits, carried out separately from routine care. In total, a maximum of nine study measurement visits were attended by each participant. These included: two antenatal visits, a visit in the third trimester, a visit within seven days postpartum as well as visits at 6 weeks, 3 months, 6 months, 9 months and 12 months postpartum. Window periods up until the midpoint of the prior or following visit were allowed for participants who arrived before or after expected visit dates. Various study measurements were collected during these visits, subsets of which were included in this research (32).

HIV-related knowledge was assessed by an eight item inventory while ART-related knowledge was assessed by a nine item inventory. The timing of knowledge assessments and number of participants completing each is indicated in Supplementary Figure D1. Each inventory was subdivided into general knowledge items and PMTCT knowledge items. Scores for each inventory and subcategory were then calculated by the sum of correct responses, leading to six knowledge scores per knowledge assessment visit. Inventories were administered by trained interviewers in participants' home language (isiXhosa). HIV VL at delivery and at 12 months postpartum was assessed via blood tests performed on 5mL of venous blood which was collected from each participant into serum separating tubes. Batched VL testing was conducted using the Abbott Molecular RealTime HIV-1 assay (Abbott Molecular, Illinois, USA). VL measures below the lower detectable limit were recorded as 39copies/mL. Blood draws were performed by trained phlebotomists and VL testing was performed by trained individuals. Participant demographic characteristics and medical history were assessed by a questionnaire. This was administered in isiXhosa by trained interviewers at the second antenatal visit.

Statistical Analyses

Participant descriptive summaries were by medians and interquartile ranges (IQR) or by frequencies (%) as well as χ^2 tests for comparisons. HIV and ART knowledge was summarized by frequencies of item-specific correct answers and inventory scores, mean scores and cumulative number correct. The internal consistency of the knowledge inventory scales was assessed using Cronbach's alpha (α). Univariable and multivariable linear regression models were used to estimate associations of demographic/clinical variables with knowledge scores at the first knowledge assessment. Covariates for inclusion in multivariable models were selected *a priori.* Univariable and multivariable logistic regression models were used to estimate associations between vireamia at delivery and 12 months postpartum and knowledge scores at the first knowledge assessment. Sensitivity analyses were conducted to estimate these associations after excluding women with very poor knowledge. Coefficients, odds ratios and 95% confidence intervals are reported. Data was analyzed using STATA V14.0 (Stata Corporation, College Station, Texas, USA) and statistical significance was set at $\alpha=0.05$ for all analyses.

RESULTS

Participant Characteristics

Participant characteristics are summarized in Table C1. A total of 471 participants completed every phase of the MCH-ART study. Of these, 376 participants completed all three knowledge assessments and are included in the analyses. Demographics were similar between those who completed every MCH-ART phase and the subset that completed all knowledge assessments (Table C1). All participants were Black African women; most had less than a secondary level education (75.5%) and most were unemployed (60.9%). Participants were generally evenly distributed between socioeconomic status (SES) categories (low: 26.6%, moderate: 34.8%, high: 38.6%) and poverty categories (least disadvantaged: 33.5%, moderately disadvantaged: 33.5%, most disadvantaged: 33.0%). Most participants were multiparous (84.6%) and the majority of pregnancies were unplanned (70.2%). Approximately half the participants had been previously diagnosed with HIV (44.7%) but only 4.3% had previously received ART. At study enrolment, 85.1% of participants had elevated VLs (median: 9907.0; IQR: 2539.0-36494.5 copies/mL). At the time of delivery, this percentage was 6.4% (median: 39.0; IQR: 39.0-48.0 copies/mL) but increased to 32.2% at 12 months postpartum (median: 39.0; IQR: 39.0-680.0 copies/mL).

In a comparison between the subset of women who experienced vireamia at 12 months postpartum (n= 88, 23%) and the study population as a whole (Supplementary Table D1), variables that appeared appreciably different were: employment, nature of pregnancy, relationship status and VL at enrolment. Those with vireamia at 12 months postpartum were more likely to be unemployed, not married/cohabitating, have unintended pregnancies and experience vireamia at enrolment compared to those without vireamia at 12 months postpartum.

Table C 1: Descriptive characteristics of HIV-infected pregnant women completing all three phases of MCH-ART and the subset who completed all knowledge assessments.

Variable	Median (IQR) or n (%)		
	All 3 phases of MCH-ART (n=471)	All knowledge assessments (n=376)	*P*-value
Age (years)	28.0(24.0-32.0)	28.0(25-32.5)	0.353
Ethnicity			
Black/African	469(99.6)	376(100)	0.206
Other	2(0.4)	0(0)	
Education			
Less than secondary level	354(75.2)	284(75.5)	0.901
Secondary/tertiary level	117(24.8)	92(24.5)	
Employment			
Employed	184(39.1)	147(39.1)	0.993
Unemployed	287(60.9)	229(60.9)	
Socioeconomic status category			
Low	134(28.5)	100(26.6)	0.780
Moderate	165(35.0)	131(34.8)	
High	172(36.5)	145(38.6)	
Poverty category			
Least disadvantaged	149(31.6)	126(33.5)	0.805
Moderately disadvantaged	158(33.6)	126(33.5)	
Most disadvantaged	164(34.8)	124(33.0)	
Relationship status			
Not married/not cohabiting	278(59.0)	223(59.3)	0.933
Married/cohabiting	193(41.0)	153(40.7)	
Primigravida			
Yes	82(17.4)	58(15.4)	0.440
No	389(82.6)	318(84.6)	
Nature of pregnancy			
Intended	133(28.2)	112(29.8)	0.621
Unintended	338(71.8)	264(70.2)	
Timing of HIV diagnosis			
Newly diagnosed	268(56.9)	208(55.3)	0.645
Previously diagnosed	203(43.1)	168(44.7)	
Previous ART use			
No	452(96.0)	360(95.7)	0.872
Yes	19(4.0)	16(4.3)	
HIV viral load (copies/mL)			
At enrollment	*n=471*	*n=376*	
Median (IQR)†	9829(2279.0-36353.0)	9907(2539.5-36494.5)	
<50	22(4.7)	15(4.0)	0.825
50-1000	55(11.7)	41(10.9)	
>1000	394(83.7)	320(85.1)	
Delivery	*n=471*	*n=376*	
Median (IQR)†	39(39.0-48.0)	39(39.0-48.0)	
<50	355(75.4)	285(75.8)	0.988
50-1000	85(18.1)	67(17.8)	
>1000	31(6.6)	24(6.4)	
12 months postpartum	*n=411*	*n=373*	
Median (IQR)†	39(39.0-1349.0)	39(39.0-680.0)	
<50	272(66.2)	255(68.4)	0.732
50-1000	32(7.8)	30(8.0)	
>1000	107(26.0)	88(32.2)	

† VLs below the lower detectable limit were set at 39copies/mL

HIV & ART Knowledge

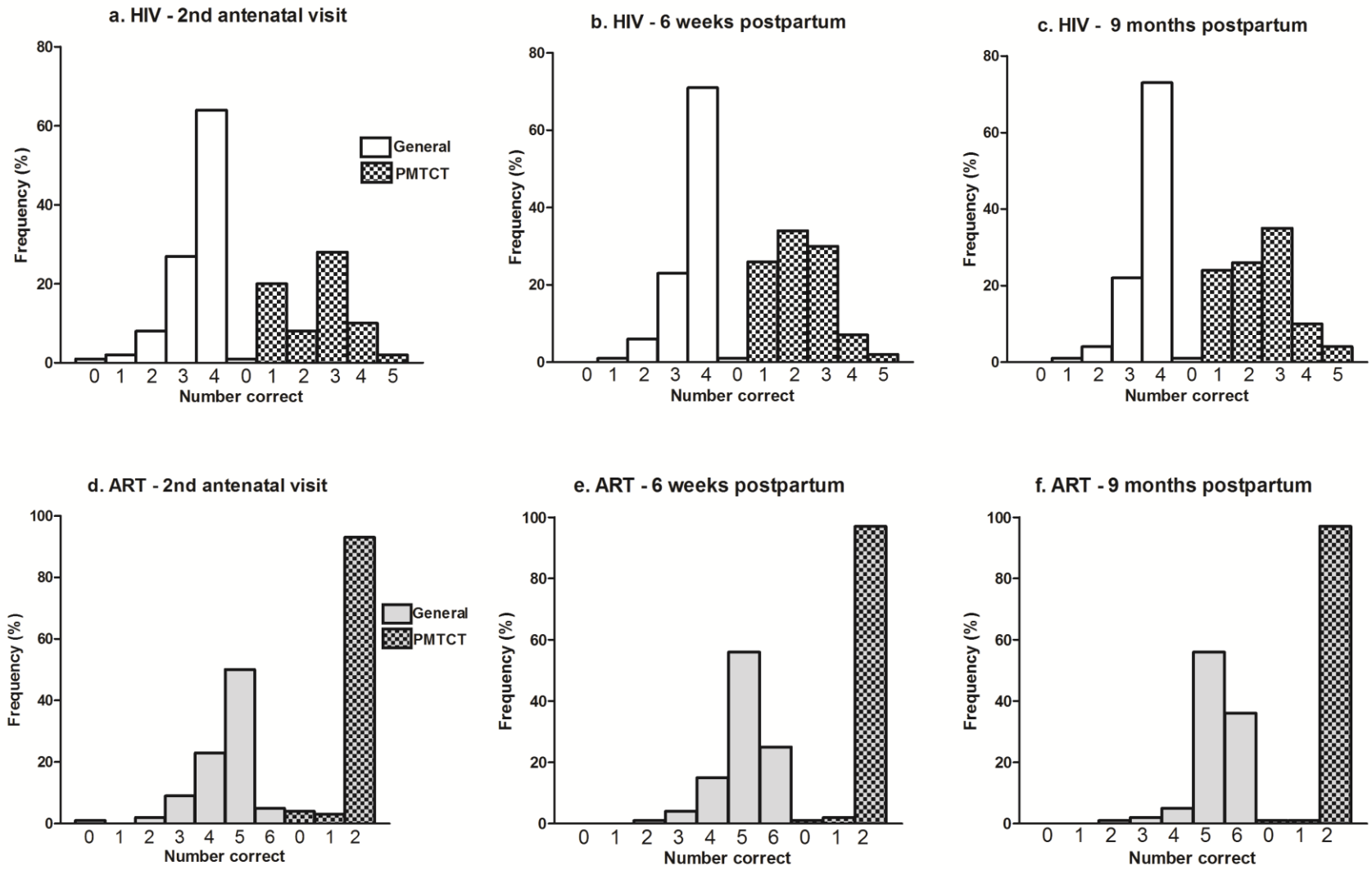
All HIV (Cronbach's alpha (α): 0.39) and ART (Cronbach's alpha (α): 0.53) knowledge inventory items are described in Table C2.HIV general knowledge slightly increased over time (% achieving max score: 64 to 73%). HIV PMTCT knowledge also increased over time (% achieving max score: 2 to 4%). HIV general knowledge was typically better than HIV PMTCT knowledge as shown by frequencies of those obtaining maximum scores for each subcategory (Figure C1 a-c). The overall mean scores for HIV knowledge were similar across assessments (Table C2). The mean HIV general knowledge score increased over time by less than a single point. The mean HIV PMTCT score decreased at six weeks postpartum and then improved both by less than a single point. Supplementary Figure D2 (a-c) shows item-specific frequencies of correct answers for HIV knowledge over time. Over the study period, items that were poorly answered were 7, 8 and 9 which all related to PMTCT knowledge.

ART general knowledge improved over time as the frequency of individuals answering five or six questions (maximum score) correctly increased (Figure C1 d-f). ART PMTCT knowledge also increased over time as the frequency of individuals answering two (maximum score) questions correctly increased (Figure C1 d-f). ART PMTCT knowledge was better than ART general knowledge, in contrast to the HIV general/PMTCT findings. These findings were confirmed by mean scores over the study period (Table C2). Overall mean scores for ART knowledge increased over time (second antenatal visit: 6.5; 6 weeks postpartum: 7.0; 9 months postpartum: 7.2), driven by ART general knowledge (second antenatal visit: 4.6; 6 weeks postpartum: 5.0; 9 months postpartum: 5.3). Supplementary Figure D2 (d-f) illustrates item-specific frequencies of correct answers for ART knowledge items over the study period. Item 8, which concerned transmission knowledge, was consistently poorly answered. Generally, ART knowledge appeared better than HIV knowledge.

178 **Table C 2: HIV and ART knowledge mean scores and item-specific frequencies of correct answers at the three knowledge assessments.**

179

Item	Question/statement	2nd Antenatal visit (n=376) Correct n(%)	6 weeks postpartum (n=376) Correct n(%)	9 months postpartum (n=376) Correct n(%)
	HIV knowledge			
	General			
1	Is HIV/AIDS spread by kissing?	364(96.8)	372(98.9)	369(98.1)
2	Must a person have many different partners to get HIV/AIDS?	333(88.6)	332(88.3)	336(89.4)
4	Is HIV the virus that causes AIDS?	293(77.9)	313(83.2)	317(84.3)
5	Is there a cure for HIV/AIDS?	332(88.3)	354(93.2)	363(96.5)
	Mean number correct	3.5	3.7	3.7
	PMTCT			
3	Can a pregnant woman give HIV/AIDS to her baby?	266(70.7)	240(63.8)	248(66.0)
6	Are there medications that a woman can take to protect her baby from getting HIV/AIDS?	370(98.4)	370(98.4)	369(98.1)
7	Can a woman give HIV/AIDS to her baby during breastfeeding?	124(33.0)	132(35.1)	175(46.5)
8	Does formula feeding reduce the risk of a baby getting HIV?	89(23.7)	71(18.9)	81(21.5)
9	Do caesarian sections reduce the risk of a baby getting HIV?	38(10.1)	27(7.2)	39(10.4)
	Mean number correct	2.4	2.2	2.4
	Overall mean number correct	5.9	5.9	6.1
	ART knowledge			
	General			
1	Antiretroviral medication aims to reduce or suppress the activity of the HIV virus in the body.	367(97.6)	375(99.7)	375(99.7)
2	Taking antiretroviral medications on schedule helps keep the right amount of medicine in one's system.	356(94.7)	360(95.7)	370(98.4)
3	Viral load measures the amount of HIV virus in the blood.	269(71.5)	307(91.7)	355(94.4)
4	Sometimes lab results say that a person's viral load is "undetectable." This means that there is no virus left.	305(81.1)	347(92.3)	362(96.3)
5	Taking antiretroviral therapy exactly as prescribed is likely to reduce viral load.			
8	If a person takes antiretroviral therapy and has a low viral load, they may be less likely to transmit the virus	362(96.3)	370(98.4)	370(98.4)
	through having sex with an HIV-negative partner.	83(22.1)	122(32.5)	149(39.6)
	Mean number correct	4.6	5.0	5.3
	PMTCT			
6	Taking antiretroviral therapy can reduce a child's risk of becoming HIV infected during pregnancy and delivery.	357(95.0)	370(98.4)	370(98.4)
7	Taking antiretroviral therapy can reduce a child's risk of becoming HIV infected during breastfeeding.	353(93.9)	364(96.8)	367(97.6)
	Mean number correct	1.9	2.0	2.0
	Overall mean number correct	6.5	7.0	7.2



181 **Figure C 1: Frequencies of HIV knowledge scores (a-c) and ART knowledge scores (d-f) at the second antenatal visit, 6 weeks postpartum and 9 months postpartum. White bars pertain to HIV general knowledge, black and white checked bars pertain to HIV PMTCT knowledge, grey bars pertain to ART general knowledge and grey and black checked bars pertain to ART PMTCT knowledge.**

Analysis of Knowledge Predictors

Regarding overall and general HIV knowledge, education, SES and previous HIV diagnosis were all significant predictors in univariable analyses (Table C3). In multivariable analyses, low education and previous HIV diagnoses remained significant predictors of improved overall and general HIV knowledge. In univariable analyses of HIV PMTCT knowledge, SES was a significant predictor (β=-0.25; 95% CI=-0.46 - -0.03; *P*=0.023). In multivariable analyses of HIV PMTCT knowledge, the only significant predictor was weeks on ART at delivery (β=0.03; 95% CI=-0.00 - 0.06; *P*=0.047).

Regarding ART knowledge, gestational age at enrolment and previous ART use were significant predictors of overall ART knowledge in univariable analyses (Table C4). Age and timing of ART diagnosis were marginally significant predictors of ART general knowledge in univariable analyses. Gestational age at enrolment and time on ART were significant predictors of ART PMTCT knowledge in univariable analyses. In multivariable analyses, no variables remained statistically significant with respect to any ART knowledge outcomes.

Table C 3: Coefficient estimates, 95% confidence intervals (CI) and *P*-values for univariable and multivariable linear regression models of the predictors of HIV knowledge scores.

	HIV Overall		HIV General		HIV PMTCT	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Univariable						
Age	0.01(-0.02-0.03)	0.603	0.00(-0.01-0.02)	0.802	0.01(-0.01-0.02)	0.619
Education						
Primary	Reference					
Secondary/tertiary	-0.51(-0.82- -0.21)	**0.001**	-0.28(-0.45—0.12)	**0.001**	-0.23(-0.47-0.01)	0.056
Employment						
Employed	Reference					
Unemployed	-0.15(-0.42-0.12)	0.282	-0.07(-0.22-0.08)	0.378	-0.08(-0.30-0.13)	0.447
SES						
High	Reference					
Moderate	-0.27(-0.54-0.01)	0.062	-0.02(-0.18-0.14)	0.816	-0.25(-0.46- -0.03)	**0.023**
Low	-0.31(-0.61- -0.01)	**0.045**	-0.20(-0.37- -0.03)	**0.021**	-0.11(-0.34-0.12)	0.358
Poverty category						
Least disadvantaged	Reference					
Moderately disadvantaged	-0.24(-0.52-0.04)	0.092	-0.11(-0.27-0.05)	0.182	-0.13(-0.35-0.08)	0.221
Most disadvantaged	-0.25(-0.53-0.04)	0.086	-0.04(-0.20-0.12)	0.658	-0.21(-0.43-0.00)	0.055
Relationship status						
Married/cohabitating	Reference					
Not married/cohabitating	0.05(-0.22-0.32)	0.697	0.05(-0.10-0.21)	0.483	0.00(-0.21-0.21)	0.994
Primigravida						
Yes	Reference					
No	0.20(-0.17-0.57)	0.289	0.04(-0.17-0.24)	0.710	0.16(-0.12-0.44)	0.265
Nature of pregnancy						
Intended	Reference					
Unintended	0.01(-0.30-0.28)	0.932	-0.03(-0.19-0.14)	0.736	0.02(-0.21-0.24)	0.892
Gestational age at enrolment	-0.01(-0.03-0.01)	0.216	0.00(-0.01-0.01)	0.587	-0.01(-0.02-0.01)	0.223
Previous HIV diagnosis	0.32(0.06-0.59)	**0.017**	0.20(0.05-0.35)	**0.010**	0.13(-0.08-0.33)	0.227
Previous ART	0.46(-0.20-1.12)	0.173	0.24(-0.13-0.61)	0.195	0.21(-0.29-0.72)	0.407
Time on ART†	0.00(-0.02-0.02)	0.756	0.00(-0.01-0.01)	0.857	0.00(-0.01-0.02)	0.590
Time on ART‡	0.00(-0.020.01)	0.627	0.00(-0.01-0.01)	0.902	0.00(-0.02-0.01)	0.585
Multivariable						
Age	0.00(-0.02-0.02)	0.945	0.00(-0.02-0.01)	0.831	0.00(-0.02-0.02)	0.807
Education						
Primary	Reference					
Secondary/tertiary	-0.52(-0.83- -0.21)	**0.001**	-0.30(-0.47- -0.12)	**0.001**	-0.23(-0.47-0.02)	0.066
Employment						
Employed	Reference					
Unemployed	-0.10(-0.38-0.18)	0.481	-0.04(-0.19-0.12)	0.653	-0.06(-0.28-0.15)	0.560
Previous HIV diagnosis	0.36(0.09-0.63)	**0.009**	0.23(0.07-0.38)	**0.004**	0.14(-0.07-0.34)	0.202
Time on ART†	0.03(-0.01-0.06)	0.169	0.00(-0.02-0.02)	0.773	0.03(0.00-0.06)	**0.047**
Time on ART‡	-0.02(-0.06-0.01)	0.110	0.00(-0.02-0.02)	0.981	-0.02(-0.05-0.00)	0.038

† Delivery

‡ 12 months postpartum

Table C 4: Coefficient estimates, 95% confidence intervals (CI) and *P*-values for univariable and multivariable linear regression models of the predictors of ART knowledge scores.

	ART overall		ART General		ART PMTCT	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Univariable						
Age	0.02(-0.00-0.04)	0.118	0.02(0.00-0.04)	**0.045**	0.00(-0.01-0.01)	0.795
Education						
Primary	Reference					
Secondary/tertiary	-0.09(-0.37-0.19)	0.540	-0.08(-0.31-0.15)	0.481	0.00(-0.11-0.10)	0.939
Employment						
Employed	Reference					
Unemployed	0.06(-0.18-0.31)	0.615	0.05(-0.16-0.25)	0.663	0.02(-0.07-0.11)	0.698
SES						
High	Reference					
Moderate	0.13(-0.13-0.38)	0.327	0.14(-0.07-0.35)	0.182	-0.02(-0.11-0.08)	0.731
Low	-0.10(-0.37-0.17)	0.482	-0.10(-0.32-0.13)	0.385	0.00(-0.10-0.11)	0.963
Poverty category						
Least disadvantaged	Reference					
Moderately disadvantaged	-0.08(-0.33-0.17)	0.538	-0.07(-0.28-0.14)	0.521	-0.01(-0.10-0.08)	0.814
Most disadvantaged	0.10(-0.15-0.36)	0.438	0.10(-0.11-0.31)	0.341	0.00(-0.09-0.09)	0.970
Relationship status						
Married/cohabitating	Reference					
Not married/cohabitating	-0.10(-0.34-0.14)	0.412	-0.07(-0.27-0.13)	0.510	-0.03(-0.12-0.05)	0.451
Primigravida						
Yes	Reference					
No	0.23(-010-0.56)	0.175	0.18(-0.10-0.45)	0.204	0.05(-0.07-0.17)	0.403
Nature of pregnancy						
Intended	Reference					
Unintended	0.12(-0.14-0.28)	0.371	0.09(-0.13-0.30)	0.428	0.03(-0.06-0.13)	0.514
Gestational age at enrolment	-0.02(-0.03-0.00)	**0.037**	-0.01(-0.02-0.00)	0.128	-0.01(-0.01-0.023)	**0.023**
Previous HIV diagnosis	0.27(0.03-0.51)	**0.025**	0.20(0.00-0.40)	**0.048**	0.07(-0.01-0.16)	0.103
Previous ART	-0.02(-0.62-0.57)	0.941	0.12(-0.37-0.61)	0.626	-0.14(-0.36-0.07)	0.189
Time on ART†	0.01(0.00-0.03)	0.157	0.00(-0.01-0.02)	0.549	0.01(0.00-0.01)	**0.011**
Time on ART‡	0.01(-0.01-0.02)	0.456	0.00(-0.01-0.01)	0.934	0.01(0.00-0.01)	0.062
Multivariable						
Age	0.02(-0.01-0.04)	0.147	0.02(0.00-0.04)	0.063	0.00(-0.01-0.01)	0.807
Education						
Primary	Reference					
Secondary/tertiary	-0.12(-0.41-0.16)	0.404	-0.10(-0.34-0.13)	0.399	-0.02(-0.12-0.08)	0.713
Employment						
Employed	Reference					
Unemployed	0.10(-0.15-0.35)	0.435	0.07(-0.14-0.28)	0.502	0.03(-0.06-0.12)	0.537
Previous HIV diagnosis	0.24(-0.01-0.48)	0.061	0.18(-0.03-0.38)	0.092	0.06(-0.03-0.15)	0.192
Time on ART†	0.02(-0.01-0.06)	0.151	0.02(-0.01-0.04)	0.332	0.01(0.00-0.02)	0.084
Time on ART‡	-0.01(-0.04-0.02)	0.376	-0.01(-0.03-0.01)	0.414	0.00(-0.01-0.01)	0.567

† Delivery

‡ 12 months postpartum

Analysis of Knowledge and Vireamia

Cumulative frequencies of correct HIV and ART knowledge items were similar across VL categories at delivery (VL<50; VL: 50-1000; VL>1000) (Supplementary Figure D3). This was also true for VL categories at 12 months postpartum (Supplementary Figure D4).

Figure C2 shows a forest plot of the coefficient estimates and 95% confidence intervals of knowledge variables in logistic regression models for vireamia outcomes. The majority of estimated associations were positive, though few were statistically significant. None of the HIV knowledge scores were significantly associated with vireamia at delivery in any analyses (Table C5). HIV overall knowledge was significantly associated with vireamia at 12 months postpartum, in adjusted and unadjusted analyses (OR=1.25; 95% CI=1.04-1.51; *P*=0.019†, OR=1.30; 95% CI=1.06-1.58; *P*=0.011‡, OR=1.30; 95% CI=1.06-1.60; *P*=0.012§ respectively). HIV general knowledge was significantly associated with vireamia at 12 months postpartum, in adjusted analyses only (OR=1.52; 95% CI=1.03-2.25; *P*=0.034‡, OR=1.53; 95% CI=1.03-2.28; *P*=0.037§). HIV PMTCT knowledge was not significantly associated with vireamia at 12 months postpartum in any analyses.

ART overall and ART PMTCT knowledge were not significantly associated with vireamia at delivery in adjusted or unadjusted analyses (Table C5). ART general knowledge was significantly associated with vireamia at delivery when adjusting for demographic variables (OR=1.71; 95% CI=1.03-2.87; *P*=0.043). None of the ART knowledge outcomes were significantly associated with vireamia at 12 months postpartum in any models.

Supplementary Table D2 and Table D3 indicate that most participants, across all VL categories, scored at least four on the HIV (n=359) and/or ART (n=365) knowledge inventory scales. A sensitivity analysis was carried out to investigate the knowledge-vireamia associations after excluding women who scored less than four on these inventories (Supplementary Table D4). All odds ratio estimates decreased in these

analyses. The only significant positive associations that remained were those for overall HIV knowledge and vireamia at 12 months postpartum in adjusted analyses (OR=1.27; 95% CI=1.02-1.57; *P*=0.032‡, OR=1.26; 95% CI=1.00-1.58; *P*=0.044[§]). In addition, ART PMTCT knowledge became negatively associated with vireamia at 12 months postpartum in adjusted and unadjusted analyses (OR=0.51; 95% CI=0.27-0.98; *P*=0.045†, OR=0.47; 95% CI=0.24-0.93; *P*=0.030‡, OR=0.42; 95% CI=0.21-0.87; *P*=0.019[§]).

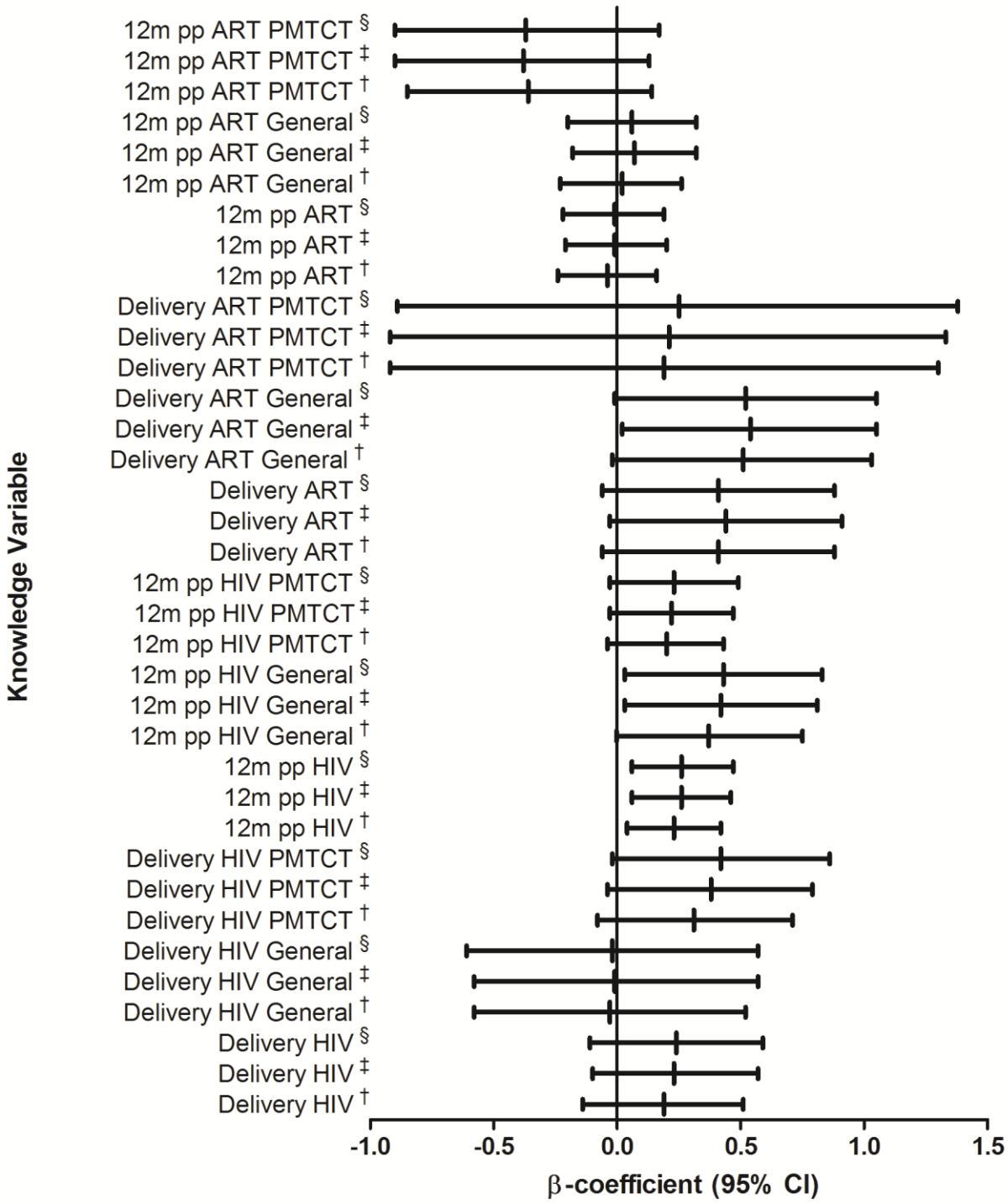


Figure C 2: Forest plot of β-coefficient estimates and 95% confidence intervals (CI) for the knowledge score variables in unadjusted and adjusted regression models for the outcome variables vireamia (VL>1000 copies/mL) at delivery and 12 months postpartum (pp).

231 † Crude
232 ‡ Adjusted for demographic variables (age, education, poverty category)
233 § Adjusted for demographic and clinical variables (age, education, poverty category, previous ART use, pregnancy
234 intention, gestational age at enrolment, VL at enrolment, time on ART)
235
236

Table C 5: Odds ratios, 95% Confidence intervals (CI) and *P*-values for knowledge score variables at the second antenatal visit in adjusted and unadjusted logistic regression models for the outcome variables vireamia (VL>1000 copies/mL) at delivery and 12 months postpartum.

		OR (95% CI) †	*P*-value	OR (95% CI) ‡	*P*-value	OR (95% CI) §	*P*-value
HIV Knowledge							
Delivery	Overall	1.20 (0.87-1.66)	0.260	1.26(0.90-1.77)	0.174	1.28(0.90-1.81)	0.171
	General	0.97(0.56-1.68)	0.913	0.99(0.56-1.76)	0.982	0.98(0.54-1.77)	0.949
	PMTCT	1.37(0.92-2.04)	0.122	1.46(0.96-2.21)	0.076	1.53(0.98-2.37)	0.061
12 months postpartum	Overall	1.25(1.04-1.51)	**0.019**	1.30(1.06-1.58)	**0.011**	1.30(1.06-1.60)	**0.012**
	General	1.45(1.00-2.11)	0.051	1.52(1.03-2.25)	**0.034**	1.53(1.03-2.28)	**0.037**
	PMTCT	1.22(0.96-1.54)	0.103	1.25(0.98-1.60)	0.078	1.26(0.97-1.63)	0.077
ART Knowledge							
Delivery	Overall	1.51(0.94-2.42)	0.087	1.55(0.97-2.48)	0.068	1.50(0.94-2.41)	0.090
	General	1.66(0.99-2.80)	0.057	1.71(1.02-2.87)	**0.043**	1.68(0.99-2.86)	0.056
	PMTCT	1.21(0.40-3.65)	0.739	1.23(0.40-3.80)	0.722	1.28(0.41-3.97)	0.671
12 months postpartum	Overall	0.96(0.79-1.17)	0.680	0.99(0.81-1.22)	0.947	0.99(0.80-1.21)	0.900
	General	1.02(0.80-1.30)	0.893	1.07(0.84-1.38)	0.576	1.06(0.82-1.37)	0.659
	PMTCT	0.70(0.43-1.15)	0.156	0.68(0.41-1.14)	0.142	0.69(0.41-1.18)	0.178

† Crude

‡ Adjusted for demographic variables (age, education, SES)

§ Adjusted for demographic and clinical variables (age, education, SES, previous ART use, pregnancy intention, gestational age at enrolment, VL at enrolment, time on ART)

DISCUSSION

Previous studies have estimated associations between HIV, ART and MTCT/PMTCT knowledge and maternal health outcomes (22–31). None have investigated the relationship between knowledge and maternal VL – the critical measure of effective ART use and central determinant of MTCT risk (3). In light of this, we investigated HIV/ART/PMTCT knowledge and vireamia in HIV-infected women initiating ART during pregnancy. We found that while HIV and ART knowledge increased over time and that there were significant predictors of knowledge, HIV and ART knowledge were not consistently associated with maternal vireamia.

During the study period HIV and ART knowledge showed some improvement, with the mean score increasing by an average of one point. Women had relatively high general knowledge about HIV, for

example by nine months postpartum more than 80% of participants knew that HIV/AIDS was not spread by kissing. Women had relatively low HIV PMTCT knowledge, for example by nine months postpartum only 46.5% of participants knew that a women could transmit HIV via breastfeeding and only 10.4% were aware that caesarians could reduce MTCT risk. General knowledge about ART was also typically high. More than 90% of women were knowledgeable on the purpose of ART, the importance of taking ART as prescribed, and about VLs. Knowledge about transmission was poor, only 39.6% of participants knew that taking ART and having a low VL could reduce the risk of transmission to sexual partners. These findings are broadly in line with earlier South African knowledge studies where general HIV/ART knowledge was acceptable but knowledge on vertical transmission was comparatively poor. Futterman *et al,* Jones *et al* and Griesell *et al* all found HIV general knowledge to be reasonable in pregnant or postpartum women (30,33–36). Similarly, Peltzer *et al* and Ramoshaba *et al* found that MTCT knowledge was generally lacking in HIV-infected postpartum women (37,38).

We identified timing of HIV diagnoses and level of education as predictors of overall and general knowledge about HIV in adjusted analyses. We also identified duration on ART at delivery as a predictor of HIV PMTCT knowledge in adjusted analyses. Higher scores were significantly more likely among those who had previously been diagnosed with HIV and in those with longer durations on ART, suggesting improved knowledge with longer time in care. Higher scores were also more likely among those who had not completed any secondary or tertiary education compared to those that had. This association is contradictory to findings in Mozambique, Tanzania and Ghana which found higher education to be correlated with better HIV and MTCT/PMTCT knowledge (22,39,40).

For the most part we did not identify any relevant associations between knowledge outcomes and maternal vireamia. We found similar cumulative frequencies of correct knowledge items across VL categories, suggesting knowledge did not alter VL. Nonetheless, in some instances we found increased

knowledge to be associated with worse health outcomes in regression models. Overall and general HIV knowledge scores were positively associated with vireamia at 12 months postpartum in adjusted analyses. In addition, ART general knowledge was associated with vireamia at delivery after adjusting for demographics. Except for the associations between ART knowledge and vireamia at 12 months postpartum, odds ratios for the knowledge-vireamia associations exceeded one with relatively large effect sizes, although generally not significant. In sensitivity analyses, when we restricted our sample to women achieving a score of at least four on the relevant knowledge inventory, the effect sizes were reduced and in some cases associations were reversed. Nevertheless, some positive relationships between knowledge and vireamia persisted.

Overall, these findings are counterintuitive and unlikely. Previous work has found positive relationships between increased HIV, ART or MTCT/PMTCT knowledge and better health outcomes or no evidence of a relationship. Many of the potential confounders identified in prior research were controlled for in the current study but some factors such as male partner involvement were not (27). If additional data were collected, perhaps further analyses adjusting for additional confounders may result in more accurate estimates of these knowledge-vireamia associations in our study sample.

The major strength of this study is that it investigates the association between HIV and ART knowledge and maternal vireamia – a research area in which data are sparse. Vireamia is a clinically measurable outcome unlike many other health outcomes measured by self-report, limiting validity and reliability by the potential introduction of recall and response bias. This study had limitations in terms of sample size, methods used to measure knowledge and adherence, possible bias introduced by loss to follow-up, and generalizability. While the total sample size was relatively large, few participants were noted to have viremia at delivery (n=24) and at 12 months postpartum (n=88). This may have undermined the power of the study. Although questionnaires are the most commonly utilized method of knowledge

assessment, one cannot rule out the possibility that individuals may be able to recognize correct answers (22). This may overestimate knowledge since recognition does not necessarily translate to knowledge in practice (22). Moreover, Cronbach's alpha calculated for the knowledge inventories were quite low (HIV knowledge: α=0.39; ART knowledge: α=0.53), suggesting potential issues with our scale. We did not consider maternal attitudes towards HIV, ART and PMTCT which are likely important intermediates in the KAB/P framework for the influence of knowledge on behaviour. It is also possible that VL is not a perfect measure of adherence since VL may be influenced by additional factors. Finally, the study population included HIV-infected women seeking antenatal care at a single primary healthcare facility in a peri-urban setting in South Africa. Generalization of these results to different settings must be approached with caution.

As the implementation of lifelong ART for all pregnant and breastfeeding women (Option B+) increases across Sub-Saharan African countries, more women will initiate ART for the first time (3). Poor ART adherence will continue to threaten the success of this strategy if barriers to adherence are not identified and reduced by effective interventions. Improving knowledge is thought to be a straight-forward intervention that can lead to behavioural change and this is likely relevant in the context of HIV (41). Pregnant and postpartum women with adequate knowledge may have more favourable attitudes towards health-seeking and health-promoting behaviour. This could potentially result in increased motivation to behave in ways culminating in positive health outcomes such as increased ART adherence and improved viral control. While we did not find evidence that increased knowledge improved maternal viral control, we did identify gaps in pregnant and postpartum women's knowledge of HIV transmission.

CONCLUSION

Understanding the association between knowledge and maternal health outcomes can inform interventions aimed at improving the health of HIV-infected pregnant and postpartum women. This novel study investigated HIV and ART-related knowledge among women initiating ART during pregnancy as well as its association with vireamia at delivery and 12 months postpartum. Women's general HIV and ART knowledge were high but knowledge on aspects of vertical transmission were lacking. Previous HIV diagnoses, time on ART and education were identified as possible knowledge predictors. Knowledge was not meaningfully associated with vireamia, thus it follows that knowledge was not associated with adherence either. Further investigation of this relationship is required in the current sample as well as in additional study populations.

COMPETING INTERESTS

The authors declare no conflict of interests.

AUTHORS' CONTRIBUTIONS

KB carried out data analysis and drafted the manuscript. ML and LM conceptualized this research and directed data analyses and interpretation of results. The final manuscript was approved by all authors.

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ADDITIONAL FILES

Table D 1: Descriptive characteristics of all HIV-infected pregnant women included in the study and the subset of women with viral loads exceeding 1000 copies/mL at 12 months postpartum.

Table D 2: HIV and ART knowledge scores by viral load category at delivery.

Table D 3: HIV and ART knowledge scores by viral load category at 12 months postpartum.

Table D 4: Odds ratios, 95% Confidence intervals (CI) and P-values for knowledge score variables in adjusted and unadjusted logistic regression models for the outcome variables vireamia (VL>1000 copies/mL) at delivery and 12 months postpartum in the subset of women scoring at least four on the HIV and/or ART knowledge inventories.

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LIST OF ABBREVIATIONS

ANC	Antenatal care
ART	Antiretroviral therapy

365	CD4	Cluster of differentiation-4, T lymphocyte
366	CI	Confidence interval
367	CHC	Community Health Centre
368	HIV	Human Immunodeficiency Virus
369	IQR	Interquartile range
370	KAB/P	Knowledge-Attitude-Behaviour/Practice
371	MCH-ART	Maternal & Child Health Antiretroviral Therapy Study
372	MOU	Midwife Obstetric Unit
373	MTCT	Mother-to-child transmission
374	NHLS	National Health Laboratory Services
375	OR	Odds ratio
376	PMTCT	Prevention of mother-to-child transmission
377	SES	Socioeconomic status
378	UCT-HREC	University of Cape Town Human Research Ethics Committee
379	VL	Viral load
380	WHO	World Health Organization

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SUPPLEMENTARY TABLES AND FIGURES

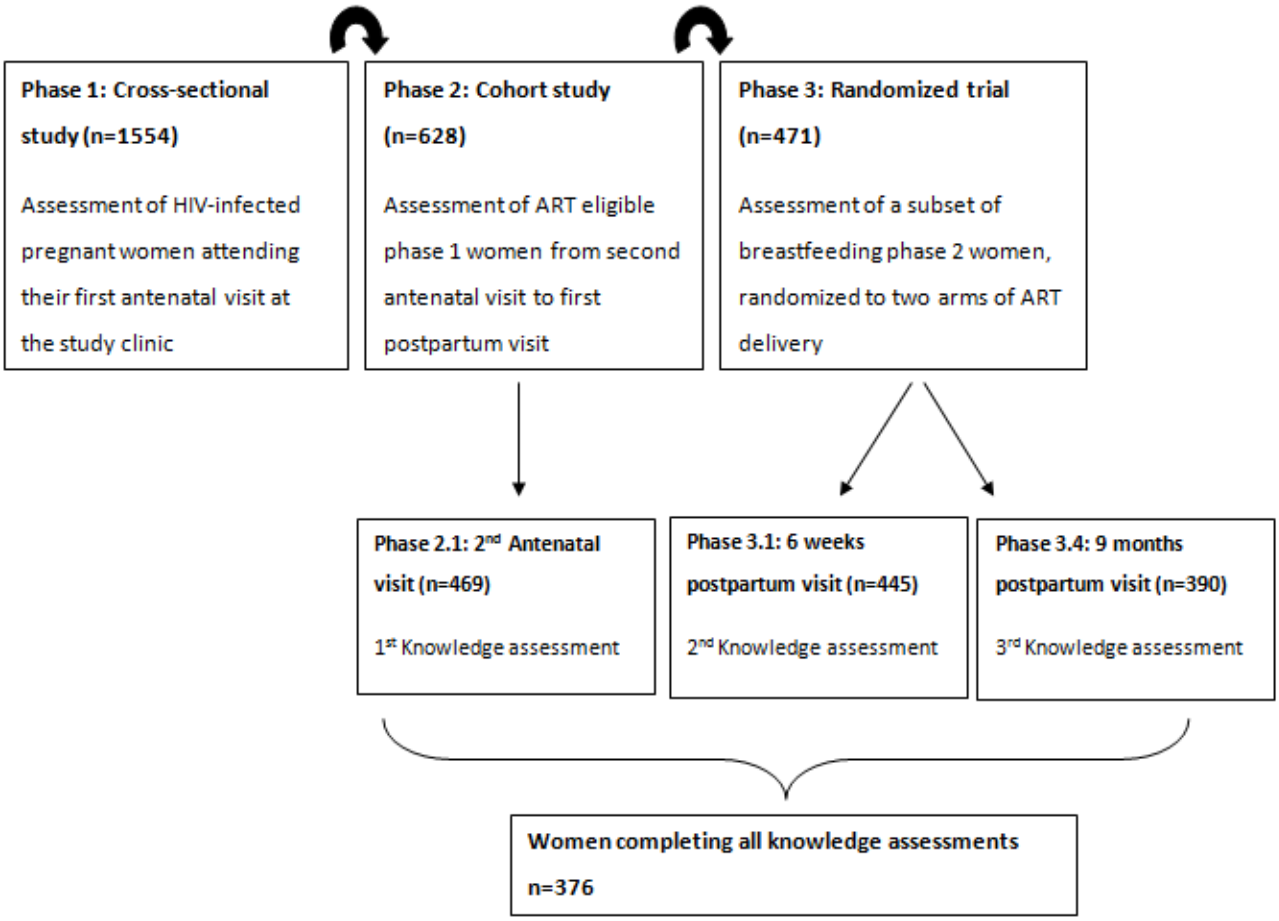

Figure D 1: Design of the current research indicating the timing of knowledge assessments and the numbers of participants who completed each (n).

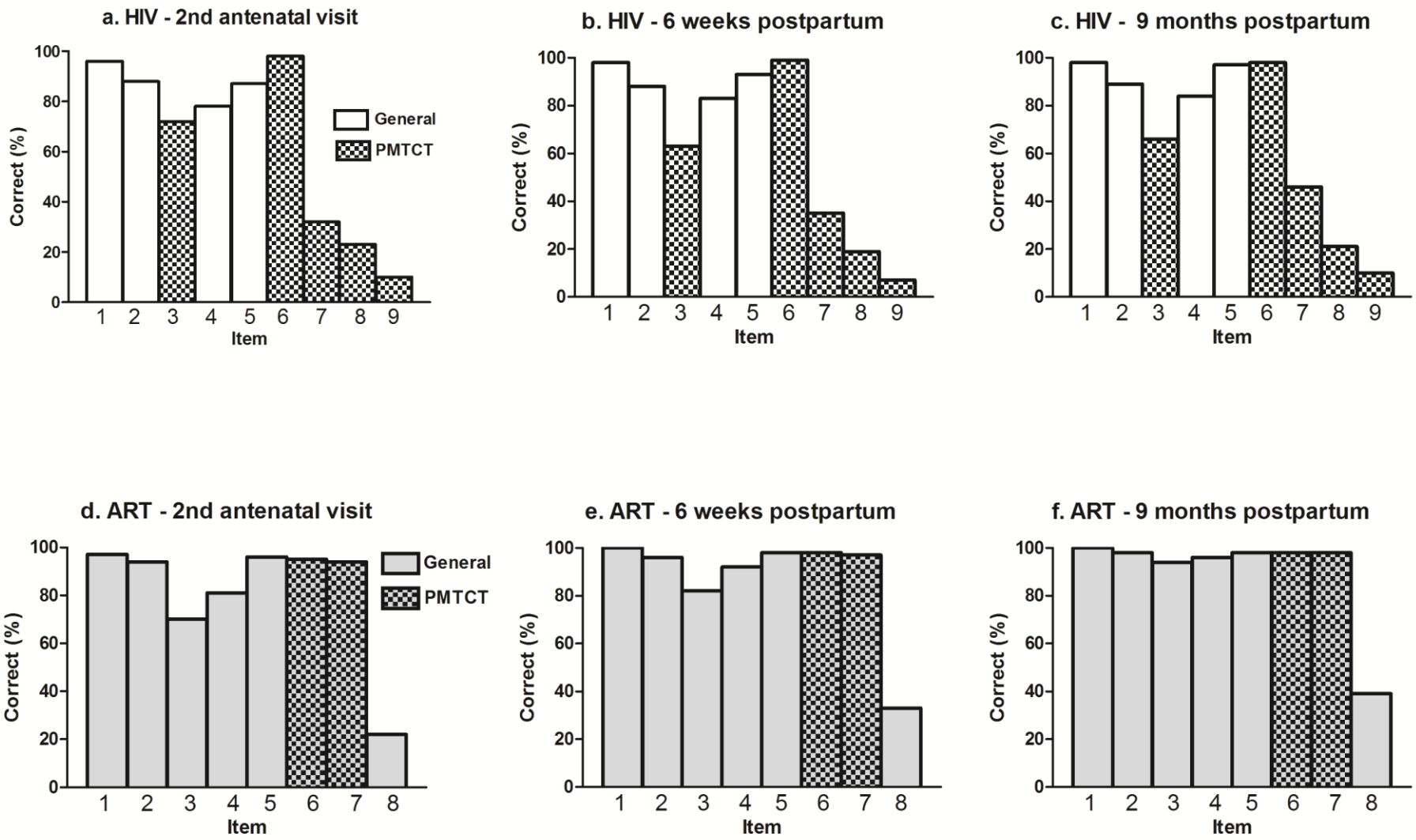

Figure D 2: Item-specific frequencies of correct answers for HIV knowledge (a-c) and ART knowledge (d-f) at the second antenatal visit, 6 weeks postpartum and 9 months postpartum. White bars indicate HIV general knowledge items, black and white checked bars indicate HIV PMTCT knowledge items, grey bars indicate ART general knowledge items and grey and black checked bars indicate ART PMTCT knowledge items.

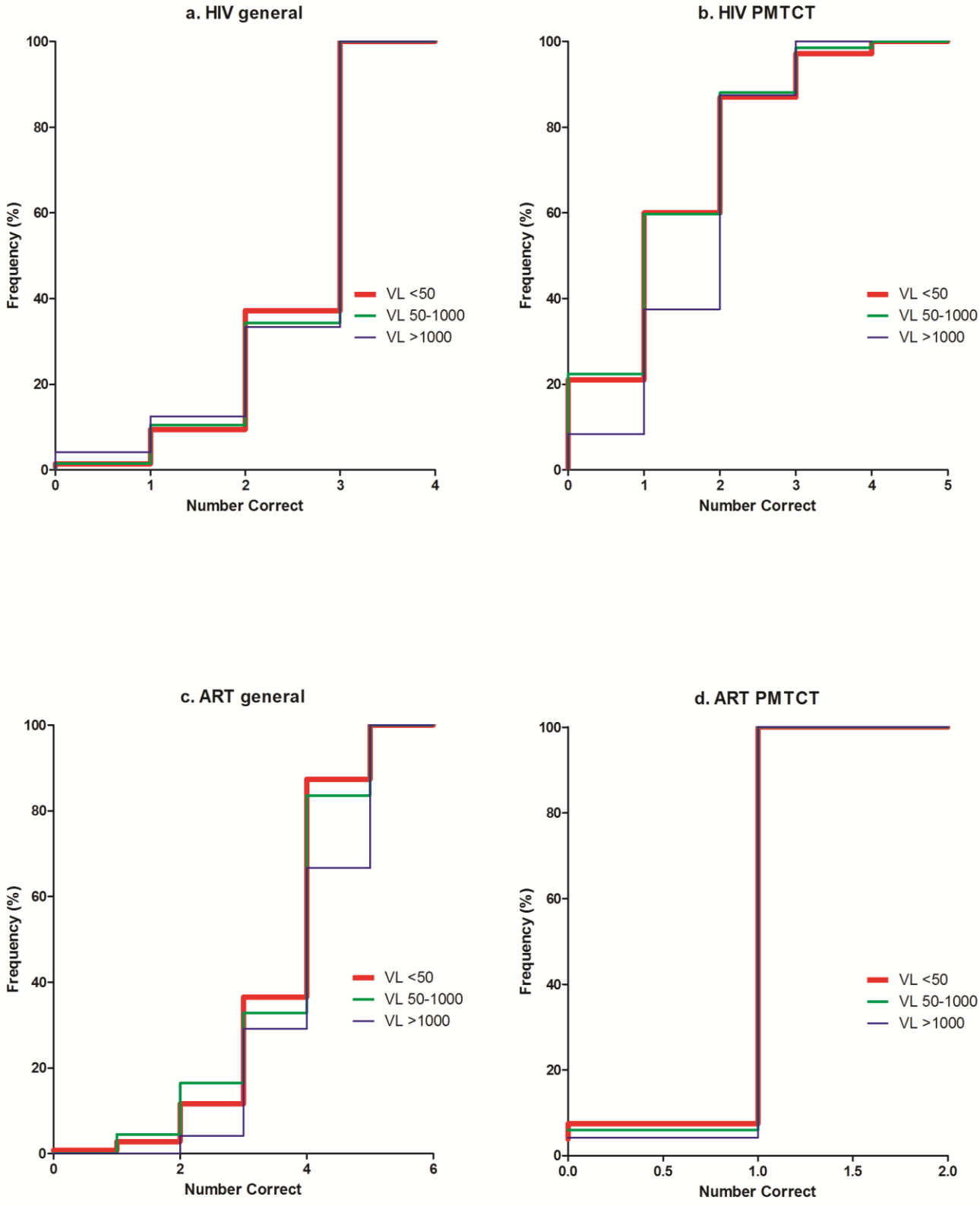

Figure D 3: Cumulative frequencies of correct knowledge items for HIV general (a) and PMTCT (b) knowledge as well as ART general (c) and PMTCT (d) knowledge stratified by viral load category at delivery. Red lines indicate VL< 50copies/mL, green lines indicate VL: 50-1000 copies/mL and blue lines indicate VL>1000 copies/mL.

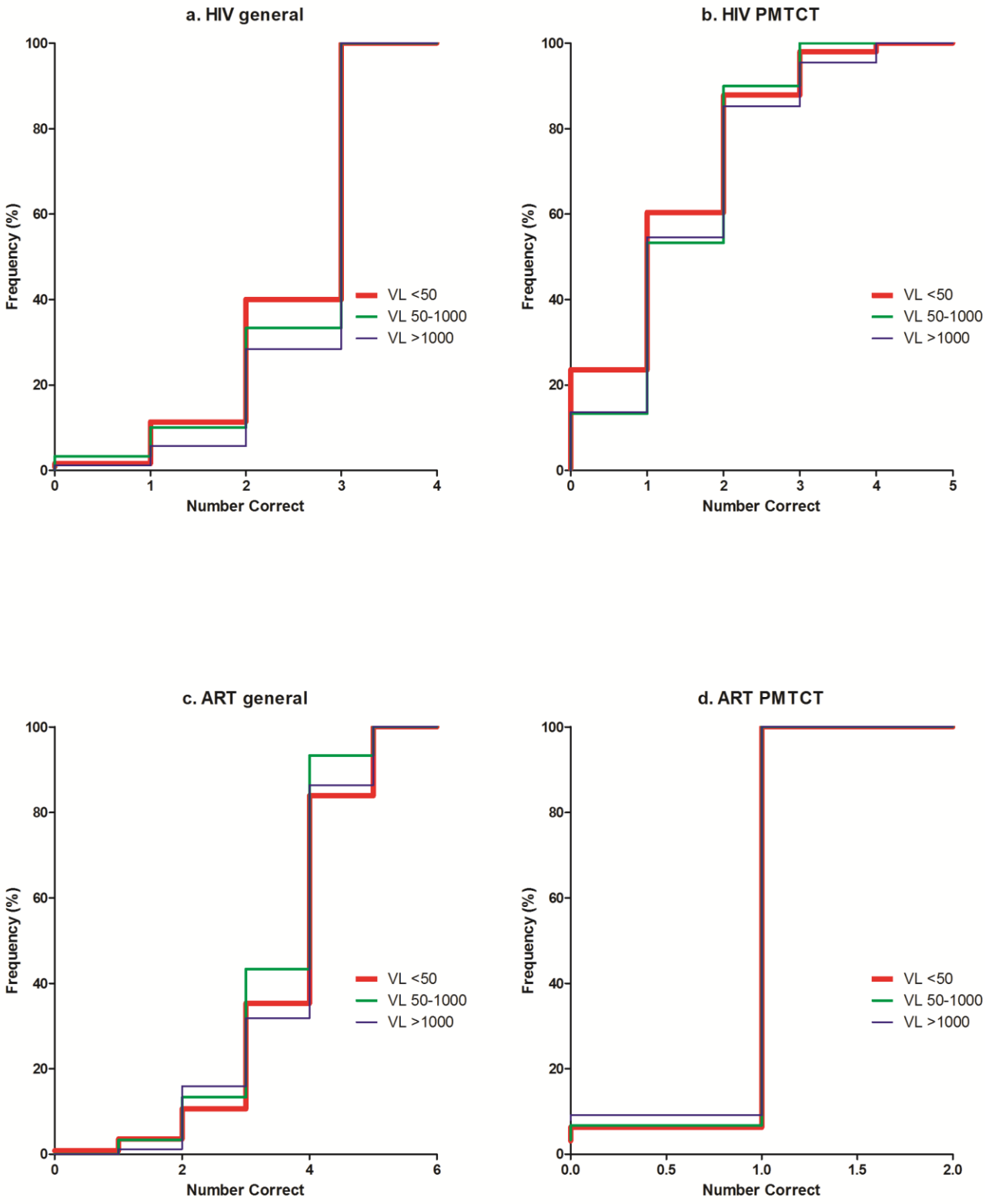

Figure D 4: Cumulative frequencies of correct knowledge items for HIV general (a) and PMTCT (b) knowledge as well as ART general (c) and PMTCT (d) knowledge stratified by viral load category at 12 months postpartum. Red lines indicate VL< 50copies/mL, green lines indicate VL: 50-1000 copies/mL and blue lines indicate VL>1000 copies/mL.

Table D 1: Descriptive characteristics of all HIV-infected pregnant women included in the study and the subset of women with viral loads exceeding 1000 copies/mL at 12 months postpartum.

Variable	Median (IQR) or n (%)		
	All women	**Women with VL≥1000**	***P*-value**
n	376	88	
Age (years)	28.0(25-32.5)	26.5(22.5-31.0)	0.076
Ethnicity			
Black/African	376(100)	88(100)	1.000
Other	0(0)	0(0)	
Education			
Less than secondary level	284(75.5)	66(75.0)	0.917
Secondary/tertiary level	92(24.5)	22(25.0)	
Employment			
Employed	147(39.1)	26(29.6)	0.095
Unemployed	229(60.9)	62(70.5)	
Socioeconomic status category			
Low	100(26.6)	27(30.7)	0.724
Moderate	131(34.8)	28(31.8)	
High	145(38.6)	33(37.5)	
Poverty category			
Least disadvantaged	126(33.5)	36(40.9)	0.313
Moderately disadvantaged	126(33.5)	23(26.1)	
Most disadvantaged	124(33.0)	29(33.0)	
Relationship status			
Not married/not cohabiting	223(59.3)	61(69.3)	0.083
Married/cohabiting	153(40.7)	27(30.7)	
Primigravida			
Yes	58(15.4)	15(17.1)	0.707
No	318(84.6)	73(82.9)	
Nature of pregnancy			
Intended	112(29.8)	16(18.2)	0.028
Unintended	264(70.2)	72(81.8)	
Timing of HIV diagnosis			
Newly diagnosed	208(55.3)	44(50.0)	0.367
Previously diagnosed	168(44.7)	44(50.0)	
Previous ART use			
No	360(95.7)	82(93.2)	0.309
Yes	16(4.3)	6(6.8)	
HIV viral load (copies/mL)			
At enrollment	*n=376*	*n=88*	
<50	15(4.0)	0(0)	0.046
50-1000	41(10.9)	5(5.7)	
>1000	320(85.1)	83(94.3)	
Delivery	*n=376*	*n=88*	
<50	285(75.8)	49(55.7)	<0.001
50-1000	67(17.8)	23(26.1)	
>1000	24(6.4)	16(18.2)	
12 months postpartum	*n=373*	*n=88*	
<50	255(68.4)	0(0)	<0.001
50-1000	30(11.0)	0(0)	
>1000	88(32.2)	88(100)	

Table D 2: HIV and ART knowledge scores by viral load category at delivery.

		Viral load (copies/mL)		
n=376	**Score**	<50 n=285	50-1000 n=67	>1000 n=24
HIV knowledge	0	0(0)	0(0)	0(0)
	1	1(0.4)	0(0)	0(0)
	2	0(0)	1(1.5)	0(0)
	3	11(3.9)	1(1.5)	0(0)
	4	29(10.2)	5(7.5)	3(12.5)
	5	70(24.6)	17(25.4)	3(12.5)
	6	86(30.2)	24(35.8)	7(29.2)
	7	57(20.0)	15(22.4)	9(37.5)
	8	25(8.8)	3(4.5)	2(8.3)
	9	6(2.1)	1(1.5)	0(0)
ART knowledge	0	1(0.4)	0(0)	0(0)
	1	1(0.4)	0(0)	0(0)
	2	1(0.4)	2(3.0)	0(0)
	3	5(1.8)	1(1.5)	0(0)
	4	6(2.1)	2(3.0)	0(0)
	5	27(9.5)	7(10.5)	1(4.2)
	6	71(24.9)	10(14.9)	7(29.2)
	7	137(48.1)	34(50.8)	9(37.5)
	8	36(12.6)	11(16.4)	7(29.2)

Table D 3: HIV and ART knowledge scores by viral load category at 12 months postpartum.

		Viral load (copies/mL)		
n=373	**Score**	<50 n=255	50-1000 n=30	>1000 n=88
HIV knowledge	0	0(0)	0(0)	0(0)
	1	1(0.4)	0(0)	0(0)
	2	0(0)	0(0)	1(1.4)
	3	11(4.3)	1(3.3)	0(0)
	4	27(10.6)	2(6.7)	8(9.1)
	5	67(26.3)	5(16.7)	17(19.3)
	6	76(29.8)	13(43.3)	27(30.7)
	7	51(20.0)	7(23.3)	23(26.1)
	8	19(7.5)	2(6.7)	8(9.1)
	9	3(1.2)	0(0)	4(4.6)
ART knowledge	0	1(0.4)	0(0)	0(0)
	1	1(0.4)	0(0)	0(0)
	2	1(0.4)	1(3.3)	1(1.1)
	3	5(2.0)	0(0)	1(1.1)
	4	7(2.8)	0(0)	1(1.1)
	5	15(5.9)	4(13.3)	16(18.2)
	6	65(25.5)	8(26.7)	13(14.8)
	7	119(46.7)	15(50.0)	45(51.1)
	8	41(16.1)	2(6.7)	11(12.5)

Table D 4: Odds ratios, 95% Confidence intervals (CI) and *P*-values for knowledge score variables in adjusted and unadjusted logistic regression models for the outcome variables vireamia (VL>1000 copies/mL) at delivery and 12 months postpartum in the subset of women scoring at least four on the HIV and/or ART knowledge inventories.

		OR (95% CI) †	*P*-value	OR (95% CI) ‡	*P*-value	OR (95% CI) §	*P*-value
HIV Knowledge (n=359)							
Delivery	Overall	1.14 (0.81-1.61)	0.459	1.20(0.84-1.73)	0.319	1.21(0.83-1.76)	0.325
	General	0.79(0.43-1.46)	0.458	0.81(0.43-1.54)	0.520	0.78(0.40-1.53)	0.463
	PMTCT	1.32(0.88-1.98)	0.177	1.41(0.92-2.15)	0.113	1.46(0.93-2.30)	0.098
12 months postpartum	Overall	1.23(1.00-1.51)	0.051	1.27(1.02-1.57)	**0.032**	1.26(1.00-1.58)	**0.044**
	General	1.40(0.91-2.13)	0.122	1.46(0.94-2.27)	0.093	1.44(0.91-2.27)	0.116
	PMTCT	1.18(0.93-1.51)	0.174	1.21(0.94-1.56)	0.135	1.21(0.93-1.58)	0.159
ART Knowledge (n=365)							
Delivery	Overall	1.46(0.88-2.41)	0.143	1.50(0.91-2.47)	0.115	1.24(0.86-1.77)	0.261
	General	1.60(0.93-2.75)	0.091	1.64(0.96-2.82)	0.071	1.59(0.90-2.78)	0.108
	PMTCT	0.83(0.27-2.58)	0.749	0.84(0.26-2.65)	0.763	0.79(0.25-2.54)	0.698
12 months postpartum	Overall	0.88(0.68-1.14)	0.345	0.92(0.70-1.20)	0.530	0.88(0.67-1.16)	0.374
	General	0.97(0.73-1.28)	0.826	1.02(0.77-1.36)	0.877	0.99(0.74-1.32)	0.942
	PMTCT	0.51(0.27-0.98)	**0.045**	0.47(0.24-0.93)	**0.030**	0.42(0.21-0.87)	**0.019**

† Crude

‡ Adjusted for demographic variables (age, education, SES)

§ Adjusted for demographic and clinical variables (age, education, SES, previous ART use, pregnancy intention, gestational age at enrolment, VL at enrolment, time on ART)

PART D: APPENDICES

APPENDIX A: HIV & ART KNOWLEDGE QUESTIONNAIRES

Visit Date: __ __/__ __ __/__ __ __ __

HIV/AIDS KNOWLEDGE INVENTORY *:*
We are now going to ask you some questions about HIV/AIDS. Please circle your answer to each question below:

	Score	0	1	2	4
1.	Is HIV/AIDS spread by kissing?	No	Yes	Don't Know	Refuse
2.	Must a person have many different partners to get HIV/AIDS?	No	Yes	Don't Know	Refuse
3.	Can a pregnant woman give HIV/AIDS to her baby?	No	Yes	Don't Know	Refuse
4.	Is HIV the virus that causes AIDS?	No	Yes	Don't Know	Refuse
5.	Is there a cure for HIV/AIDS?	No	Yes	Don't Know	Refuse
6.	Are there medications that a woman can take to protect her baby from getting HIV/AIDS?	No	Yes	Don't Know	Refuse
7.	Can a woman give HIV/AIDS to her baby during breast feeding?	No	Yes	Don't Know	Refuse
8.	Does formula feeding reduce the risk of a baby getting HIV?	No	Yes	Don't Know	Refuse
9.	Do caesarian sections reduce the risk of a baby getting HIV?	No	Yes	Don't Know	Refuse

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

Date of QC: _ _ /_ _ _ / _ _ _ _ Signed measurement nurse: _____

Visit Date: __ __/__ __ __/__ __ __ __

HIV/AIDS TREATMENT KNOWLEDGE INVENTORY

We are now going to ask you some questions about HIV/AIDS treatment. Are the following statements TRUE or FALSE? Indicate by circling your answer for each statement.

	Score	0	1	2	4
1	Antiretroviral medication aims to reduce or suppress the activity of the HIV virus in the body.	TRUE	FALSE	Don't know	Refuse
2	Taking antiretroviral medications on schedule helps keep the right amount of medicine in one's system.	TRUE	FALSE	Don't know	Refuse
3	Viral load measures the amount of HIV virus in the blood.	TRUE	FALSE	Don't know	Refuse
4	Sometimes lab results say that a person's viral load is "undetectable." This means that there is no virus left.	TRUE	FALSE	Don't know	Refuse
5	Taking antiretroviral therapy exactly as prescribed is likely to reduce viral load.	TRUE	FALSE	Don't know	Refuse
6	Taking antiretroviral therapy can reduce a child's risk of becoming HIV infected during pregnancy and delivery.	TRUE	FALSE	Don't know	Refuse
7	Taking antiretroviral therapy can reduce a child's risk of becoming HIV infected during breastfeeding.	TRUE	FALSE	Don't know	Refuse
8	If a person takes antiretroviral therapy and has a low viral load, they may be less likely to transmit the virus through having sex with an HIV-negative partner.	TRUE	FALSE	Don't know	Refuse

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

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

APPENDIX B: DEMOGRAPHIC CHARACTERISTICS AND MEDICAL HISTORY QUESTIONNAIRE

			Visit Date: __ __/__ __ __/__ __ __ __
1.	What is your date of birth?		Day:____ Month :_____ Year:_____
2.	What is your age?		Age:_____ (years)
3.	What population group do you belong to?		African = 1 Indian = 2 Coloured = 3 White = 4 Other = 5, specify: _____
4.	What language do you speak at home?		isiXhosa = 1 isiZulu = 2 Afrikaans = 3 English = 4 Other = 5 specify: _____
5.	What is the highest level of schooling/education that you have completed?		Grade:_____/ Standard:_____ Postsecondary:_____
6.	Are you currently working and or studying?		No = 0 → **SKIP to Q8** Yes = 1
7.	If yes, which of one the following best describes what you do? *Choose one only*		Employed full-time = 1 Employed part-time = 2 Informal job/hawker = 3 Attending school/learner = 4 Attending tertiary education facility = 5
8.	What is the MAJOR source of income for your household? *Choose one only*		None = 0 Full-time employment = 1 Part-time employment = 2 Informal employment = 3 Disability grant = 4 Social grant = 5 Pension = 6 Other grant = 7, specify type: _____ Other = 8, specify:_____ Don't know = 9
9.	What kind of home do you live in?		Shack/informal dwelling = 1 Formal house = 2 Flat/council home = 3 Other = 4, specify: _____
10.	Does your house have the following: *Read and answer for all*	a. A toilet inside	No = 0 Yes = 1
		b. Running water inside	No = 0 Yes = 1

		c. Electricity inside	No = 0 Yes = 1
		d. A refrigerator	No = 0 Yes = 1
		e. A telephone	No = 0 Yes = 1
		f. A television	No = 0 Yes = 1
11.	Including yourself, how many people (adults and children) live in your house?		# of people: _____
12.	How many adults (aged 16 or older), including you, live in your house?		# of adults:_____
13.	How many children (aged 15 and under) live in your house?		# of children: _____
14.	How many times have you been pregnant (including current pregnancy)?		# of pregnancies: _____
15.	Were you trying to have a baby when you found out you were pregnant (in this pregnancy)?		No = 0 Yes = 1 Don't Know = 9
16.	How many children have you given birth to?		# of children: _____ **If 0, SKIP to Q21**
17.	How many of these children are living?		# of children: _____
18.	How many of these children currently live with you?		# of children: _____
19.	How many of your children have tested HIV-positive?		# of HIV-positive children: _____
20.	How many of these children who have tested HIV- positive are currently living?		# of HIV-positive children currently alive: ___
21.	Are you currently in a relationship?		No = 0 → **SKIP to Q26** Yes = 1
22.	How would you describe your current relationship?		Married = 1 Not married, living together = 2 Married, not living together = 3 Not married, not living together = 4 Other = 5, specify:_____
23.	How long have you been in this relationship?		Duration in: Months_____ Years _____
24.	Is your current partner the parent of any of your children? (including current pregnancy)		No = 0 Yes = 1
25.	Have you disclosed your HIV status to your current partner?		No = 0 Yes = 1
26.	In the last 12 months have you had sexual relationships/sexual partners with people other than this partner?		No = 0 → **SKIP to Q 29** Yes = 1

27.	What is the nature of your other relationship(s)? *Mark all that apply.*	a. Spouse/ married b. Boyfriend c. Casual Partner/One Night Stands d. Other, specify:_____
28.	Have you disclosed your HIV status to any of these other sexual partners?	No = 0 Yes = 1
29.	Did you first test HIV positive <u>in this pregnancy</u> or <u>before this pregnancy</u>?	In his pregnancy = 1 → **SKIP to 33** Before this pregnancy = 2
30.	When did you 1st test HIV-positive?	Day:____ Month: _____Year:_____

31.	Why was this test conducted?	Tested during pregnancy = 1 VCT/Wanted to be tested = 2 Diagnosed with TB = 3 Admitted to the hospital = 4 Other = 5, specify: _____
32.	Were you pregnant when you first tested HIV-positive?	No = 0 Yes = 1
33.	Have you ever tested negative on an HIV test?	No = 0 → **SKIP to Q37** Yes = 1
34.	When did you last test HIV-negative?	Day:____ Month:_____Year:_____
35.	Why did you test at that time?	Tested during pregnancy = 1 VCT/Wanted to be tested = 2 Diagnosed with TB = 3 Admitted to the hospital = 4 Other = 5, specify: _____
36.	Were you pregnant at the time of that test?	No = 0 Yes = 1
37.	Have you told <u>anyone</u> that you are HIV-positive?	No = 0 → **SKIP to Q40** Yes = 1
38.	Which of your family members have you told about your HIV status? Please answer this question for each of the family members listed below.	
a.	Husband/partner	No = 0 Yes = 1 N/A = 9
b.	Mother	No = 0 Yes = 1 N/A = 9
c.	Father	No = 0 Yes = 1 N/A = 9
d.	Sister	No = 0 Yes = 1

		N/A = 9
e.	Brother	No = 0 Yes = 1 N/A = 9
f.	Daughter	No = 0 Yes = 1 N/A = 9
g.	Son	No = 0 Yes = 1 N/A = 9
h.	Uncle	No = 0 Yes = 1 N/A = 9
i.	Aunt	No = 0 Yes = 1 N/A = 9
j.	Male cousin	No = 0 Yes = 1 N/A = 9
k.	Female cousin	No = 0 Yes = 1 N/A = 9
l.	Other male family member	No = 0 Yes = 1 N/A = 9
m.	Other female family member	No = 0 Yes = 1 N/A = 9
39.	Aside from family members listed above, who else have you told about your HIV status? (read and answer for all)	
a.	Health professionals	No = 0 Yes = 1
b.	Support group	No = 0 Yes = 1
c.	A sexual partner who does not live with you	No = 0 Yes = 1
d.	Friends	No = 0 Yes = 1
e.	Spiritual leader	No = 0 Yes = 1
f.	Current or former employer	No = 0 Yes = 1
g.	Public disclosure/ community	No = 0 Yes = 1

h.	Other, specify _____	No = 0 Yes = 1
40.	Have you ever been pregnant before this pregnancy?	No = 0 → **SKIP to Q 46** Yes = 1
41.	When you were pregnant before this pregnancy were you ever been given medication at the clinic to keep your baby from getting HIV infected?	No = 0 → **SKIP to Q 46** Yes = 1
42.	If yes, during how many pregnancies have you received medication for this purpose?	# of pregnancies: _____
43.	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?	Only at Delivery (Nevirapine) #:_____ While you were pregnant (AZT)? #: _____
44.	When was the last time that you received medication for this purpose?	Day:____ Month:_____Year:_____
45.	Where did you receive the medication the last time?	Name of clinic: _____
46.	Aside from when you were pregnant, have you ever taken ART in the past?	No = 0 → **END** Yes = 1
47.	If yes, where did you receive ART the last time?	Name of clinic_____
48.	When did you start taking ART?	Day:____ Month:_____Year:_____
49.	Are you still on ART?	No = 0 Yes = 1→ **END**
50.	If No, when did you stop taking ART?	Day:____ Month:_____Year:_____
51.	Why did you stop taking ART? *Circle all that apply*	a. I ran out of medicine and didn't go for refills b. The medicine tastes bad c. I just forgot d. I was worried about the side effects e. I did not want others to notice me taking the medicine f. I was ill g. Didn't think I needed it anymore h. Can stay healthy without it i. I felt the medicine might be harmful to me j. I felt depressed k. I was well l. There was too much medicine to take m. I was away from home n. I was busy with other things o. I learned that there are other ways to treat or cure HIV

Date completed: _ _ /_ _ _ / _ _ _ _

Signed counsellor completing CRF: _____

Date of QC: _ _ /_ _ _ / _ _ _ _

Signed Measurement Nurse: _____

APPENDIX C: INFORMED CONSENT DOCUMENTS

Document 1

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. 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-infected 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 and previous use of HIV drugs.
- Have 5mLs (1 teaspoon) of blood drawn from your arm so that we can check your viral load (this is the amount of HIV in your blood)

NOTE: Blood drawn today for viral load testing is not part of your routine health care. This blood will be stored and tested 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 reviewing and abstracting information from your medical records. We are interested in learning about the HIV care and treatment that you receive during your pregnancy and after you delivered. We also want to learn about the pregnancy care you received as well as information about your delivery.

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 to take part in additional study visits like this one. At that time, you would be asked to review and sign another consent form. You can choose to not take part in these additional visits if you are asked.

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 the standard of care for all HIV-positive pregnant women.

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.

WILL I BE GIVEN ANYTHING FOR TAKING PART?
No, there is no compensation for participating 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:
We are specifically looking at your use of antiretroviral therapy during this study, and in particular the amount of HIV in your blood. However, the information and samples being collected from all participants may also help answer other questions about HIV in the future. If there is leftover blood at the end of this study, we may want to use your leftover blood so that other research studies can be done in the future. If you agree to let us keep your leftover 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.

_____ (initial) I agree to have my specimens stored for future research by the investigators who are conducting this study.

_____ (initial) I do **NOT** agree to the storage of my blood after the end of this study.

DO YOU HAVE ANY QUESTIONS?
If there is anything that is unclear or if you need further information, please ask us and we will provide it.

Do you have any questions?

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

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

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

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

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, or a tick if you would prefer.

_____

Signature of Volunteer [tick optional] Date

_____

Signature of study staff Date

Thank you.

Document 2

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. 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-infected women during their pregnancy and after they deliver the baby.

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

You are being asked to take part in this study because you are a pregnant woman with known HIV infection who is about to start taking HIV drugs (antiretroviral therapy). The purpose of this consent form 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 come in for up to 3 visits. These visits will take place today while you are in the clinic, during your third trimester and within one week of delivering your baby. Each visit will take about 30-45 minutes.

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

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

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

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

NOTE: Blood drawn today for viral load testing is not part of your routine health care. This blood will be stored and tested 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.

Contact for future study
After the completion of the visit one week after delivery, it is possible that we will ask to see whether you would like to participate in a further research study that aims to understand how best to deliver health care services to HIV-positive mothers and their children. At that time, you will be asked to review and sign another consent form. You can choose to not take part in these additional visits if you are asked.

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

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

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

WHAT ARE THE ALTERNATIVES TO TAKING PART?
The alternative to taking part in this study is to continue with the standard of care for all HIV-positive pregnant women.

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.

WILL I BE GIVEN ANYTHING FOR TAKING PART?
At the end of each visit, you will be given a R150 grocery voucher.

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:
We are specifically looking at your use of antiretroviral therapy during this study, and in particular the amount of HIV in your blood. However, the information and samples being collected from all participants may also help answer other questions about HIV in the future. If there is leftover blood at the end of this study, we may want to use your leftover blood so that other research studies can be done in the future. If you agree to let us keep your leftover 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.

_____ (initial) I agree to have my specimens stored for future research by the investigators who are conducting this study.

_____ (initial) I do **NOT** agree to the storage of my blood after the end of this study.

DO YOU HAVE ANY QUESTIONS?
If there is anything that is unclear or if you need further information, please ask us and we will provide it.

Do you have any questions?

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

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

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

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

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, or a tick if you would prefer.

_____

Signature of Volunteer [tick optional] Date

_____

Signature of study staff Date

Thank you.

Document 3

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. 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 compare two different ways of providing HIV treatment to women after they deliver a baby.

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

You are being asked to take part in this study because you are a pregnant woman with known HIV infection who is about to start taking HIV drugs. The purpose of this consent form 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 be randomized (like a flip of a coin) to one of two places to receive your ART, as described below:

1. MCH-focused ART services group: Women assigned to this group will continue to receive HIV care and medicines here, at the MOU, as they did during their pregnancy. When they have stopped breastfeeding, women in this group will be referred to their nearest general ART clinic.

2. General ART services group: Women assigned to this group will be referred to the nearest ART clinic for HIV care and to continue their HIV medicines.

"Randomised" means that you will have a 50% chance of being in the group that will receive on-site care. You will also have a 50% chance of being in the group that receives referred care. Neither the study staff nor you can choose which group you will be assigned to. The decisions are made by a computer and put into an envelope. The staff does not know which group is in each envelope.

This randomization will occur today and you will then come in for up to 4 additional study measurement visits at 6 weeks after delivery and 6, 9, and 12 months after delivery. Each visit will take about 30-60 minutes.

These visits will include the following:

- Answer questions about your recent pregnancy- and HIV-related health care, HIV disclosure, and use of HIV drugs (including side effects and adherence).
    - At selected visits, we will ask you additional questions about HIV, stigma, and mental health (including drug and alcohol use), family planning, infant feeding practices, infant health care and how you feel about the HIV care that you have received.

- Have 5mLs (1 teaspoon) of blood drawn from your arm so that we can check your viral load (amount of HIV in your body)

NOTE: Blood drawn today for viral load testing is not part of your routine health care. This blood will be stored and tested 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.

At the last visit, we will also draw blood from your baby:

- Baby will undergo a heelstick to collect blood to check your baby's HIV status.
    - We will return the results of this test to you as soon as it is available.

WHAT ARE THE POTENTIAL RISKS?

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

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

WHAT ARE THE POTENTIAL BENEFITS?

There is no direct benefit to you if you take part in this study, 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. In addition, 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 the standard of care for all HIV-positive pregnant women, which means you will be referred from the MOU to your nearest general ART clinic as soon as possible.

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.

WILL I BE GIVEN ANYTHING FOR TAKING PART?
At the end of each visit, you will be given a R150 grocery voucher.

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:
We are specifically looking at your use of antiretroviral therapy during this study, and in particular the amount of HIV in your blood. However, the information and samples being collected from all participants may also help answer other questions about HIV in the future. If there is leftover blood at the end of this study, we may want to use your leftover blood so that other research studies can be done in the future. If you agree to let us keep your leftover 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.

_____ (initial) I agree to have my specimens stored for future research by the investigators who are conducting this study.

_____ (initial) I do **NOT** agree to the storage of my blood after the end of this study.

DO YOU HAVE ANY QUESTIONS?
If there is anything that is unclear or if you need further information, please ask us and we will provide it.

Do you have any questions?

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

Dr Landon Myer
School of Public Health and Family Medicine
Faculty of Health Sciences, University of Cape Town

Tel: 021 406 6661; email: Landon.Myer@uct.ac.za

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

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

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, or a tick if you would prefer.

_____

Signature of Volunteer [tick optional] Date

_____

Signature of study staff Date

Thank you.

APPENDIX D: MCH-ART ETHICAL CLEARANCE

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • **Facsimile** [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

13 January 2011

HREC REF: 030/2011

A/Prof L Myer
Public Health & Family Medicine

Dear A/Prof Myer

PROJECT TITLE: STRATEGIES FOR THE RAPID INITIATION OF ANTIRETROVIRAL THERAPY IN PREGNANCY.

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

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

Approval is granted for one year till the 30th January 2012.

Please submit an annual progress report (FHS016) if the research continues beyond the approval period. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note a minor typo on pages 8 and 9 in the consent forms: You will (not) ill be asked to…

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

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.

S Thomas

APPENDIX E: STUDY ETHICAL CLEARANCE

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6526
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

10 October 2017

HREC REF: 707/2017

Dr Maia Lesosky
Public Health & Family Medicine
Level 3
Falmouth Building

Dear Dr Lesosky

PROJECT TITLE: HIV-RELATED KNOWLEDGE AND ANTIRETROVIRAL THERAPY OUTCOMES (ART) IN HIV INFECTED WOMEN INITIATING ART DURING PREGNANCY (SUB-STUDY LINKED TO 451/2012) MASTER'S CANDIDATE – MS K BROWN

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

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

Approval is granted for one year until the 30 October 2018.

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.

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, where necessary, before the research may occur.

The HREC acknowledge that the student, Karryn Brown will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (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 F: JIAS AUTHOR GUIDELINES

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

Author Guidelines

Sections

1. SUBMISSION

Please carefully read through the Instructions for Authors and prepare your manuscript according to the guidelines, including structuring it manuscript based on the chosen article category. Manuscripts that do not follow the instructions may be returned to the authors for corrections.

Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

Once the submission materials have been prepared in accordance with the Author Guidelines, manuscripts should be submitted online at https://mc.manuscriptcentral.com/jias. The submission system will prompt authors to use an ORCID iD (a unique author identifier) to help distinguish their work from that of other researchers. Click here to find out more.
You will be asked to 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.

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2. AIMS AND SCOPE

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

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

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

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

3. MANUSCRIPT CATEGORIES AND REQUIREMENTS

The *JIAS* accepts submissions in the following categories:

• Research
• Short report
• Review
• Debate
• Commentary
• Letter to the Editor
• Viewpoint

Research - full reports of data from original research studies

Headings: Introduction, Methods, Results, Conclusions
Word limit: 350 words

Main text:
Headings: Introduction, Methods, Results, Discussion, Conclusions
Word limit: 3500 words
Numbers of figures and tables: Unlimited
Additional files: Yes
Download the manuscript template

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

Abstract:
Headings: Introduction, Methods, Results and discussion, Conclusions
Word limit: 350 words

Main text:
Headings: Introduction, Methods, Results and discussion, Conclusions
Word limit: 2500 words
Numbers of figures and tables: 4
Additional files: No
Download the manuscript template

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

Abstract:
Headings: Introduction, Methods (if applicable), Results and discussion (if applicable, otherwise Discussion only), Conclusions
Word limit: 350 words

Main text:
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
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Debate - presentation of an evidence-based argument

Abstract:
Headings: Introduction, Discussion, Conclusions
Word limit: 350 words

Main text:
Headings: Introduction, Discussion, Conclusions
Word limit: 3500 words
Numbers of figures and tables: 4
Additional files: No
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Commentary - focused and opinionated articles on important and timely issues, no original data

Abstract:
Headings: Introduction, Discussion, Conclusions

Word limit: 350 words

Main text:
Headings: Introduction, Discussion, Conclusions
Word limit: 2500 words
Numbers of figures and tables: 1
Additional files: No
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Letter to the Editor - comments on and responses to published articles

Abstract:
None

Main text:
Headings: None
Word limit: 500 words
Numbers of figures and tables: None
Additional files: No
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Viewpoint - constructive, stand-alone views on current topics

Abstract:
None

Main text:
Headings: None
Word limit: 1000 words
Numbers of figures and tables: 1
Additional files: No
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4. PREPARING THE SUBMISSION

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 .and declare any competing interests (see Editorial Policies and Ethical Considerations)

Parts of the Manuscript

The manuscript should be submitted as a main text file including figures and appendices and supporting information should be supplied as separate files.

Main Text File

The text file should be presented in the following order:

1. Title page;
2. Keywords;
3. Abstract;
4. Main text;
5. Conflict of Interest Statement;
6. Authorship;
7. Acknowledgments;
8. References;
9. Tables;
10. Figures;

Title page

The title should not contain abbreviations, except commonly used abbreviations such as HIV or AIDS (see Wiley's best practice SEO tips).

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.

*Keywords*l

Pease provide six keywords. Keywords should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser list at https://www.nlm.nih.gov/mesh/. 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 above), 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

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.

Conflict of Interest Statement

Authors will be asked to provide a conflict of interest statement during the submission process. For details on

what to include in this section, see the ‘Conflict of Interest’ section in the Editorial Policies and Ethical Considerations section below. Submitting authors should ensure they liaise with all co-authors to confirm agreement with the final statement.

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Please refer to the journal’s Authorship policy in the Editorial Policies and Ethical Considerationssection for details on author listing eligibility. 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. An example of a suitable statement is: “S.W., N.J., D.W. and S.S. performed the research. S.W., N.J., H.H. and T.L. designed the research study. H.H. and S.S. contributed essential reagents or tools. S.W., N.J. and D.W. analysed the data. S.W. and N.J. wrote the paper.” Please see the ‘Authorship’ section in the Editorial Policies and Ethical Considerations section below for what constitutes authorship.

Acknowledgments

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

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.

Tables

They should be supplied as editable files, not pasted as images. Tables should be inserted into the text. They 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. 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. Tables should be self-contained and complement, not duplicate, information contained in the text. 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. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

Figures

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.

Although authors are encouraged to send the highest-quality figures possible, for peer-review purposes, a wide variety of formats, sizes, and resolutions are accepted. Click here for the basic figure requirements for figures submitted with manuscripts for initial peer review, as well as the more detailed post-acceptance figure requirements.
Figure legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement. If several figures are included, please ensure that symbols are used consistently.

Additional Files

Appendices

Appendices will be published after the references. For submission, they should be supplied as separate files but referred to in the text.

Supporting Information

Supporting information is information that is not essential to the article, but provides greater depth and background. It is hosted online and appears without editing or typesetting. It may include tables, figures, videos, datasets, etc. Click here for Wiley's FAQs on supporting information.

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The following points provide general advice on formatting and style:

• **Abbreviations:** In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Initially, use the word in full, followed by the abbreviation in parentheses. Thereafter use the abbreviation only.

• **Acronyms:** Acronyms should be used sparingly, and not in headings or in the Abstract. Only commonly known acronyms may be used, and they should be spelt out at first use followed by the abbreviation in brackets. SI units should be used, with litre and molar being permitted.

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• **Numbers:** Numbers under 10 are spelt out, except for: measurements with a unit (8mmol/l); age (6 weeks old), or lists with other numbers (11 dogs, 9 cats, 4 gerbils).

• **Trade Names:** Chemical substances should be referred to by the generic name only. Trade names should not be used. Drugs should be referred to by their generic names. If proprietary drugs have been used in the study, refer to these by their generic name, mentioning the proprietary name and the name and location of the manufacturer in parentheses.

• **Footnotes:** Footnotes are not allowed in the text, the information shall be included directly into the text, where it fits best, and if these are references, to include in the reference section at the end.

• **Language**: 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.

• **General recommendation:** Use line spacing of 1.5 and an easily readable font, for example, Times New Roman, size 12. Your manuscript should contain line numbers to facilitate editors' and reviewers' comments

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The *Journal of the International AIDS Society* expects that data supporting the results in the paper will be archived in an appropriate public repository. Whenever possible the scripts and other artefacts used to generate the analyses presented in the paper should also be publicly archived. Exceptions may be granted at the discretion of the editor for sensitive information such as human subject data or the location of endangered species. Authors are expected to provide a data accessibility statement, including a link to the repository they have used, to accompany their paper.

Protein and nucleotide sequences

For nucleic acid sequences, protein sequences or atomic coordinates, which are cited in the manuscript, and the accession number, together with the database where the information was deposited, should be cited in square brackets in the text, for example, [EMBL:AB026295, EMBL:AC137000, DDBJ:AE000812, GenBank:U49845, PDB:1BFM, Swiss-Prot:Q96KQ7, PIR:S66116]. Relevant databases are: EMBL Nucleotide Sequence Database (EMBL), DNA Data Bank of Japan (DDBJ), GenBank at the NCBI (GenBank), Protein Data Bank (PDB), Protein Information Resource (PIR) and the Swiss-Prot Protein Database (Swiss-Prot).

Mass spectrometry

Mass spectrometry data should be provided in the mzML format according to the HUPO Protein Standards Initiative Mass Spectrometry Standards Working Group guidelines. The data should also be deposited in the ProteomeExchange through the PRIDE website, and protein interaction data can be deposited through members of the IMEx consortium.

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Chemical structures and assays

Structures of chemical substances can be deposited with PubChem Substance. Bioactivity screens of chemical substances can be deposited with PubChem BioAssay.

Functional genomics data (such as microarray or CHIP-Seq data)

Please refer to standards proposed by the Functional Genomics Data Society and deposit your microarray data in MIAME-compliant format in one of the public repositories, for example, ArrayExpress or Gene Expression Omnibus (GEO). Deposition of high-throughput functional genomics sequencing data (such as RNA-Seq or ChIP-Seq data) with ArrayExpress or GEO in compliance with MINSEQE is also needed.

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Please prepare models of biochemical reaction networks using the Systems Biology Markup Language and submit your model to the BioModels database, as well as providing it as an additional file with your submission.

Plasmids

Please submit copies of your plasmids as DNA or bacterial stocks with Addgene, a non-profit repository, or PlasmID, the Plasmid Information Database at Harvard.

Ethical approval – Human and animal studies

Human Studies and Subjects

For manuscripts reporting medical studies that involve human participants, a statement identifying the ethics committee that approved the study and confirmation that the study conforms to recognized standards is required, for example: Declaration of Helsinki; US Federal Policy for the Protection of Human Subjects; or European Medicines Agency Guidelines for Good Clinical Practice.

A statement on the ethical aspects, including the consent procedure followed, must be included in the Methods section of the manuscript. The Editors may reject manuscripts where the research has not been carried out within an ethical framework. Images and information from individual participants will only be published where the authors have obtained the individual's free prior informed consent. Confidentiality of study participants must be ensured at all stages of research and reporting. Authors do not need to provide a copy of the consent form to the publisher; however, in signing the author license to publish, authors are required to confirm that consent has been obtained. Wiley has a standard patient consent form available for use.

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A statement indicating that the protocol and procedures employed were ethically reviewed and approved, as well as the name of the body giving approval, must be included in the Methods section of the manuscript. Authors are encouraged to adhere to animal research reporting standards, for example the The Gold Standard Publication Checklist from Hooijmans and colleagues or theARRIVE reporting guidelines for reporting study design and statistical analysis; experimental procedures; experimental animals and housing and husbandry. Authors should also state whether experiments were performed in accordance with relevant institutional and national guidelines for the care and use of laboratory animals:

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The journal requires that clinical trials are prospectively registered in a publicly accessible database and clinical trial registration numbers should be included in all papers that report their results. Authors are asked to include the name of the trial register and the clinical trial registration number at the end of the abstract. If the trial is not registered, or was registered retrospectively, the reasons for this should be explained.

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Standard 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), interventional trials (SPIRIT), qualitative research (COREQ), systematic reviews (PRISMA), observational studies (STROBE), economic evaluations of health interventions (CHEERS), meta-analyses of observational studies (MOOSE) and diagnostic / prognostic studies (STARD and TRIPOD). 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' Handbookfor an example of how a search strategy should be presented.

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Submitting authors shall include data disaggregated by sex (and, whenever possible, by race) and provide an 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. 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. If the research study was specific to one sex/gender, the reasons for this should be clearly stated. Please refer to the SAGER guidelines for more information

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Upon its first use in the title, abstract, and text, the common name of a species should be followed by the scientific name (genus, species, and authority) in parentheses. For well-known species, however, scientific names may be omitted from article titles. If no common name exists in English, only the scientific name should be used.
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