Antiretroviral therapy use during pregnancy and adverse birth outcomes in South African women

Thokozile Rosemary Malaba
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School of Public Health and Family Medicine
Faculty of Health Sciences, University of Cape Town

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Supervisor:
Professor Landon Myer
School of Public Health and Family Medicine
Faculty of Health Sciences
University of Cape Town

PREAMBLE

DECLARATION

I, Thokozile Rosemary Malaba, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work or any part thereof has been, is currently being, or is to be submitted for another degree at this or any other university. I further declare that this work was not published prior to my registration for the degree of Master of Public Health (Epidemiology).

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ABSTRACT

Background

Studies suggest antiretroviral therapy (ART) use during pregnancy may be associated with adverse pregnancy outcomes. Given the large numbers of pregnancies exposed to ART, better understandings of potential associations with commonly used ART regimens and adverse pregnancy outcomes is critical. With the number of women on ART initiated before conception rapidly increasing, understanding how current recommended regimens and timing of ART initiation may influence pregnancy outcomes is critically important.

Methods

This mini-dissertation presents a research protocol (Section A), literature view (Section B) and journal-formatted manuscript (Section C) for a study of ART use and birth outcomes among HIV-infected women and a comparator cohort of HIV-uninfected women. Pregnant women seeking care at the Gugulethu MOU, a primary-level antenatal care facility in Cape Town, South Africa were enrolled between March 2013 and August 2015. Pregnancy dating was based on research ultrasound, or last menstrual period/clinical exam where ultrasound was unavailable. Women were followed from their 1st antenatal visit through delivery. Analyses compared birth outcomes (preterm (PTD), low birthweight (LBW) and small for gestational age (SGA) deliveries) between HIV-infected and uninfected women; and between women on ART initiated before conception versus those initiating ART during pregnancy.

Results

In 1554 women with live singleton births (mean birthweight, 3079g; 21% preterm; 13% LBW; 12% SGA), a higher prevalence of PTD (22% vs 13%, p=0.001) and LBW (14% vs 9%, p=0.030) were observed in the HIV-infected compared to HIV-uninfected women. Adverse birth outcomes (PTD, LBW and SGA) did not vary systematically among the HIV-infected women regardless of ART initiation timing (initiated ART before conception or initiated ART to during pregnancy). The absence of associations between the adverse birth outcomes and timing of ART initiation persisted after adjusting for maternal age, parity, height, CD4 cell count and viral load at 1st visit.

Conclusions

Levels of adverse birth outcomes, in particular PTD, remain high among HIV-infected women, however our findings from a routine care cohort demonstrate that the timing of initiation of widely used regimens before conception or during pregnancy do not appear to be associated with an increased risk in adverse pregnancy outcomes.

LIST OF ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
AGA	Appropriate for Gestation Age
ANC	Antenatal Care
AOR	Adjusted Odds Ratio
ARR	Adjusted Relative Risk
ART	Antiretroviral Therapy (triple drug)
ARV	Antiretroviral
CD4	Cluster of differentiation-4, T lymphocyte
CI	Confidence Interval
D4T	Stavudine
EDD	Expected Date of Delivery
EFV	Efavirenz
FTC	Emtricitabine
FDC	Fixed Dose Combination
GA	Gestational Age
HIV	Human Immunodeficiency Virus
IQR	Inter-Quartile Range
IUGR	Intrauterine Growth Restriction
LBW	Low Birth Weight
LGA	Large for Gestational Age
LMIC	Low to Middle Income Countries
LMP	Last Menstrual Period
LPV/r	Lopinavir/ritonavir
MCH-ART	Maternal-Child Health Antiretroviral Therapy study
MOU	Midwife Obstetric Unit
MTCT	Mother-to-Child Transmission
MUAC	Middle Upper Arm Circumference
NA	Not Applicable
NR	Not Reported
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine

OR	Odds Ratio
PI	Protease Inhibitor
PMTCT	Prevention of Mother-to-Child Transmission
PTD	Preterm Delivery
RCT	Randomized Control Trial
RR	Relative Risk
SD	Standard Deviation
SFH	Symphysis-Fundal Height
SGA	Small for Gestational Age
SSA	Sub-Saharan Africa
US	Ultrasound
VL	Viral Load
VLBW	Very Low Birth Weight
VPTD	Very Preterm Delivery
WHO	World Health Organization
ZDV	Zidovudine

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SECTION A: RESEARCH PROTOCOL

1. INTRODUCTION

1.1 Background

Antiretroviral therapy (ART) is a principal intervention ensuring maternal and child health in the context of HIV infection. World Health Organisation (WHO) recommends the use of ART for all HIV-infected women during pregnancy and breastfeeding, regardless of CD4 cell count or WHO disease stage, to be continued as lifelong treatment (Option B+) (1).

In South Africa and other similar low and middle-income countries (LMIC), large and increasing proportions of HIV-infected pregnant women are accessing ART – increasing the number of fetuses exposed to antiretroviral (ARV) drugs during their early developmental stages. With this increased ART use during pregnancy, concern has been raised about the possibility of adverse birth outcomes (preterm delivery (PTD), low birth weight (LBW) and small-for-gestational age (SGA)), associated with *in utero* ART exposure; with no consensus about the effect on these birth outcomes. Untreated, advanced HIV disease has already been shown to be associated with these adverse birth outcomes (2, 3). The effect of ART on adverse birth outcomes adds further complexity to deciphering the relationship between HIV infection, ART use and birth outcomes.

The first reports linking adverse birth outcomes to ART came from European studies showing an association between ART exposure and both PTD and LBW (4, 5). Associations were less clear in American studies, with some of these studies only finding associations with protease inhibitor (PI) - based regimens (6, 7). Although a number of studies in different settings have investigated the effect of different ART regimens on birth outcomes, the presence and nature of any association remains contentious.

Several factors have been proposed as explanations for the apparently conflicting conclusions. First, a frequently hypothesized explanation pertains to heterogeneity in study populations. Most studies have been conducted in high income countries; however the majority of women requiring ART in pregnancy are in LMIC, where the impact of adverse birth outcomes is greater, owing to insufficient obstetric and neonatal services. Study populations in different settings are also likely to differ in terms of risk factor prevalence and background rates of adverse birth outcomes.

Second; different methodological approaches complicate comparisons of individual studies, with the choice of comparison groups used in the studies usually dictated by available data or the current treatment guidelines. HIV treatment and practice guidelines in pregnancy have shifted over time, towards more effective regimens and longer periods of antenatal ART coverage. The resulting use of different regimens and timing of initiation, depending on the setting, impacts on comparisons. Additionally, data is mostly available from high income countries where ART initiation occurred regardless of HIV disease stage, and regimens were primarily PI-based because of their tolerability in pregnancy. Less data has been generated from LMIC, particularly Africa, which carries a significant burden of the disease. Studies in sub-Saharan Africa (SSA) suggest an association between ART and risk of PTD/LBW (8, 9); as well as increased risk of stillbirth, PTD, SGA and early neonatal death (10). However, regimens used in these studies did not include the current WHO recommended first-line regimen (tenofovir (TDF) + lamivudine (3TC)/emtricitabine (FTC) + efavirenz (EFV)). Recent reports from a national program in which pregnant women were initiated on TDF+FTC+EFV suggested no increased risk of adverse birth outcomes when compared to other commonly used PMTCT regimens including zidovudine (ZDV) monotherapy (11). This is reassuring following concern raised by results of the PROMISE study, which reported more severe adverse birth outcomes among women initiated on triple drug regimens compared to ZDV monotherapy (12).

Third, differences in study design and implementation are directly related to the type and quality of data collected. Differences or compromises in outcome ascertainment methods in the different

studies, through the use of imprecise assessment methods for birthweight (abstraction of clinic records) and gestational age (menstrual history and clinical examinations) determination, can affect the detection of the magnitude of associations. Additionally, the degree of potential measurement error of the exposures, outcomes and/or risk factors can also be affected. Unmeasured or inaccurately measured risk factors compromise the controlling of their effects resulting in residual cofounding. The non-random allocation and misclassification of exposures (timing of ART initiation or type of regimen), particularly in observational studies, can result in reductions in power and decreased likelihood of detection of true associations. Consequently, limiting measurement error through the use of robust measures with fewer errors in future studies is vitally important.

Given these challenges, more data are required to elucidate the relationship between ART and adverse birth outcomes. Additionally, the local background rates of adverse birth outcomes are often unknown, so more studies including HIV-uninfected comparators are required. Given the increasing population of HIV-infected pregnant women in our setting, we aim to investigate birth outcomes in a well characterized population of pregnant women undergoing routine antenatal care (ANC) using commonly used regimens at a large public sector primary care facility in Cape Town, South Africa.

1.2. Rationale

Whilst there is indisputable benefit of ART to both mother and infant, evidence indicating that ART use during pregnancy could play a role in increasing the risk of adverse birth outcomes has raised concern. Data from Africa, where most ART use in pregnancy occurs, is limited by the poor quality of pregnancy dating as well as limited data on the effects of the most commonly used non-nucleoside reverse transcriptase (NNRTI)-based regimens. Consequently, further research is required in countries such South Africa, which has the largest treatment program with 3.4 million people on ART (13), because of the far reaching implications for infant morbidity and mortality. Findings from a randomized control trial (RCT) in Botswana demonstrated that HIV-exposed preterm infants (compared to term infants) had a 5-fold increased risk of death and higher rates of severe lower

respiratory tract infections (8). Additionally PTD, LBW and SGA have long term consequences for child development, educational attainment (14), and quality of life. In view of these long term consequences of adverse birth outcomes it is essential to quantify their associations with ART use in high prevalence LMIC in order to facilitate risk-benefit assessment of ART and the different regimens (15).

2. AIMS AND OBJECTIVES

2.1 Aim

The aim of the proposed study is to examine the association between ART use and birth outcomes in a population of pregnant women undergoing routine ANC at a large public sector primary care facility in Cape Town, South Africa.

2.2 Objectives

1. To describe the clinical and demographic characteristics of pregnant women seeking ANC.
2. To describe the prevalence of adverse birth outcomes (PTD, LBW and SGA) among pregnant women booking for ANC.
3. To examine the association between adverse birth outcomes among pregnant women seeking ANC by (i) HIV status (i.e comparing HIV-infected vs HIV-uninfected) and (ii) Timing of ART initiation (i.e comparing ART Initiation before conception vs ART initiation during pregnancy).

3. METHODS

3.1 Study Design

The proposed study will be a sub-study of the MCH-ART trial, a community-based study of antiretroviral services for HIV-infected women during pregnancy and postpartum (https://clinicaltrials.gov/ct2/show/NCT01933477). The MCH-ART trial has been described in detail elsewhere (16); however in brief the primary objective of this multicomponent trial was the

comparison between the maternal-and-child health focused ART services and the general adult ART services during the postpartum period. Phase 1 was a cross-sectional evaluation of consecutive HIV-infected women and the primary aim of this phase was the characterization of the health status of HIV-infected pregnant women, including maternal and infant outcomes.

Analysis for this proposed study will draw on data collected between March 2013 and August 2015 during the first phase of MCH-ART as well as a comparator cohort of HIV-uninfected women.

3.2 Study Setting

The setting for parent study was the Gugulethu Midwife Obstetric Unit (MOU), a primary care facility in the peri-urban area of Gugulethu in Cape Town, South Africa. The MOU provides antenatal and obstetric care for low-risk pregnancies; women with history of pregnancy complications or those requiring specialist review and/or intervention are referred to secondary (Mowbray Maternity Hospital) or tertiary (Groote Schuur Hospital) obstetric facilities. The catchment population of the MOU is approximately 350 000 and uptake of ANC services is very high in this population with coverage consistently reported at greater than 95% (17). In 2014 the antenatal HIV seroprevalence at the MOU was estimated at 30% (17). PMTCT services are integrated into ANC services resulting in near universal routine HIV testing in pregnancy using HIV rapid antibody tests. All women without a previous HIV diagnosis undergo HIV counselling and testing at their first ANC visit. Women who test HIV negative are retested prior to or at delivery.

During the study period, women who tested positive and had a CD4 cell count <350 cells/µl or WHO clinical stage 3 or 4 conditions were eligible to initiate ART during pregnancy for maternal treatment. In July 2013, local PMTCT guidelines changed to recommend initiation of triple-drug ART for all HIV-infected pregnant women regardless of CD4 cell count (Option B+). ART primarily consisted of a fixed dose combination of TDF+FTC+EFV as first-line therapy for the majority of HIV-infected pregnant women initiating ART.

3.3 Study Population and Sampling

Pregnant women seeking ANC services at the Gugulethu MOU between March 2013 and August 2015 enrolled in the parent study and the comparator cohort (HIV-uninfected) will be included.

Inclusion Criteria

- Aged 18 years or older
- Enrolled into parent study
- Confirmed pregnancy according to urine pregnancy test, ultrasound or clinical assessment

3.4 Data Collection

Data collected during the parent study will be used for this proposed study. This data was collected using standardized questionnaires as well as the review of medical and laboratory records.

3.4.1 Enrolment Questionnaires

In the parent study, the standardized questionnaires completed by all enrolled women, included maternal demographics and medical history (Appendix 1A). For the enrolled HIV-infected women, additional data was collected on current ART use based on self-report and previous antiretroviral exposure (Appendix 1B).

3.4.2 Medical Record Review

Data abstracted, during the parent study, from clinical and obstetric records of enrolled women following their first antenatal visit and discharge from the postnatal ward will also be used for the proposed study (Appendices 1C and 1D). Information abstracted includes maternal physical examination data (height and weight), results of routine blood tests (Hb, syphilis screening, ABO blood group), HIV status and maternal diagnoses during pregnancy and delivery. For the enrolled HIV-infected women additional data abstracted from PMTCT records includes date of diagnosis, CD4 cell count and viral load (VL) enumeration, dates and

types of antiretroviral drugs received. Antiretroviral regimen data used in the proposed study will be a combination of the self-reported ART use and abstracted information. Infant data abstracted from infant medical records will also be used for the proposed study and this includes birth outcome, gender, birthweight and any delivery complications.

3.4.3 Gestational Age Measurement

To determine gestational age (GA), all enrolled participants had an obstetric ultrasound (US) conducted by an experienced research sonographer using standardized assessment protocols. In most cases, the estimated GA was calculated based on this ultrasound determined estimated delivery date (EDD), however in cases where the GA seemed implausible and last menstrual period (LMP) was known, LMP EDD was used.

Table 1. Variables to be included in the analysis

Variable	Scale	Categories
Maternal Characteristics		
Age (years)	Numerical - Continuous	*Quartile Category Proportions*
	Categorical - Ordinal	<24, 25-29, >30
Education	Categorical - Binary	Finished high school, Did not finish high school
Employment Status	Categorical - Binary	Employed, Not Employed
Socio-economic Status	Categorical - Ordinal	Lowest, Medium, Highest
Obstetric Characteristics		
Gestation at Booking (weeks)	Numerical - Continuous	*Quartile Category Proportions*
Maternal Height (cm)	Numerical - Continuous	*Quartile Category Proportions*
	Categorical - Ordinal	<155, 156-161, >162
Gravidity	Numerical - Discrete	*Quartile Category Proportions*
	Categorical - Ordinal	1, 2, >3
Parity	Numerical - Discrete	*Quartile Category Proportions*
	Categorical - Ordinal	0, 1, >2
Previous Miscarriage	Numerical - Discrete	*Quartile Category Proportions*
Previous Preterm	Numerical - Discrete	*Quartile Category Proportions*
HIV		
ART Regimen	Categorical - Nominal	TDF+3TC+EFV, TDF+3TC+NVP, Other NNRTI-based, PI-based regimen
CD4 (cells/µl)	Numerical - Continuous	*Quartile Category Proportions*
	Categorical - Ordinal	<200, 201-350, 351-500, >500
Viral Load (log10 copies/ml)	Numerical – continuous log (10)	*Quartile Category Proportions*
HIV Status	Categorical - Binary	HIV-infected, HIV-uninfected
ART Initiation Status	Categorical - Binary	Initiated before conception, initiated during pregnancy
Obstetric Outcomes		
Gestational Age at delivery (weeks)	Categorical - Ordinal	Term (>37), Preterm (<37) Late Preterm (34-37), Moderately Preterm (32-34), Very Preterm (28-32)
Birthweight (grams)	Numerical - Continuous	*Quartile Category Proportions*
	Categorical - Ordinal	Normal (>2500), Low Birthweight (1500-2500) Very Low Birthweight (<1500)
Size for Gestational Age	Categorical - Ordinal	Large (LGA), Appropriate (AGA), Small (SGA)

3.5 Outcomes of Interest

The main outcomes of interest are adverse birth outcomes, and this will include pregnancy loss, PTD, LBW and SGA. These outcomes will be estimated within each stratum of the exposure variable and compared using odds ratios obtained from regression modelling. Definitions and classifications of outcome variables will be as follows:

3.5.1 Pregnancy Loss

These will include ectopic pregnancies, miscarriages and stillbirths. Ectopic pregnancies will be determined by the research sonographer. Miscarriages will be defined as pregnancy loss <28 weeks and stillbirths will be defined as fetal death occurring before/during labour and birth based on a 1 minute APGAR score of 0 (17).

3.5.2 Preterm Delivery (PTD)

Preterm delivery will be defined as delivery <37 weeks' gestation. Preterm infants will be categorized as late preterm (34-37 weeks), moderately preterm (32-34 weeks) and very preterm (<32 weeks).

3.5.3 Low Birth Weight (LBW)

Low birthweight will be defined as infants with a birth weight <2500g and very low birthweight (VLBW) as <1500g.

3.5.4 Small for Gestational Age (SGA)

Size for gestational age will be based on INTERGROWTH-21st Project Standards. Infants with birthweights <10th percentile for their gestational age will be classified SGA and infants between 10th – 90th percentile, appropriate for gestational age (AGA).

3.6 Exposure of Interest

The exposure of interest is HIV/ART status and this will be categorized as:

- No ART (HIV-uninfected women)
- ART initiated before conception
- ART initiated during pregnancy

Among the women who initiated ART during pregnancy there will be a further subdivision according to the gestational age at ART initiation

- First trimester (<14 weeks)
- First half of second trimester (14-20 weeks)
- Second half of the second trimester (21-27 weeks)
- Third trimester (≥28 weeks)

ART regimens used by enrolled women will be categorized according to regimen classes as either PI or NNRTI. NNRTI regimens will be categorized as EFV-based, nevirapine-based (NVP) or other NNRTIs.

3.7 Data Management and Analysis Plan

3.7.1 Data Management

Data collected during the course of the parent study has been entered into a customized study Microsoft Access database, which is maintained in a firewall-protected UCT server with nightly backups. This database is password-protected following standard password safety procedures. All study records contain anonymous participant identification numbers, and no participant names or identifiers are recorded. The data used for this analysis will be stored on a password protected personal computer that can only be accessed by the researcher.

3.7.2 Data Analysis

All statistical analyses will be conducted using STATA Version 14 (Stata Corporation, College Station, Texas USA). Continuous variables will be summarized using either the mean and standard deviation (SD) for normal distributed variables; or the median and the interquartile range (IQR) for non-normal distributed variables. Categorical variables will be described using proportions.

Analyses will focus on three exposure comparisons: HIV-infected versus HIV-uninfected (Comparison A); among HIV-infected women, those initiating ART before conception versus those initiating ART during pregnancy (Comparison B); and among women initiating ART during pregnancy across gestational ages at ART initiation (Comparison C).
Descriptive statistics will be used to describe the overall prevalence of the adverse birth outcomes (PTD, LBW and SGA) across the exposure groups. For continuous variables either parametric (t-test or ANOVA) or non-parametric tests (Wilcoxon Sign Rank or Kruskal Wallis) will be used to test for associations; while chi-squared and rank-sum tests will be used to test for associations between categorical variables. Regression modelling will be used to estimate the association between HIV/ART status and the adverse birth outcomes of interest. *A priori* confounders will include age, maternal height, parity and previous PTD; and among the HIV-infected women, CD4 cell count and VL at first ANC visit.

4. ETHICAL CONSIDERATIONS

The University of Cape Town Faculty of Health Sciences Research Ethics Committee (UCT-HREC; REC REF: 451/2012) (Appendices 2A and 2B); and the Columbia University Medical Center Institutional Review Board (CUMC-IRB) (Appendix 2C) approved the parent study. Additionally, permission to conduct the parent study was granted by the research oversight body of the Provincial Government of the Western Cape Department of Health (Appendix 2D). Ethical approval for this proposed study will be sought from the UCT-HREC.

4.1 Informed Consent

All women deemed eligible and who agreed to participate in Phase 1 of the parent study completed a written informed consent form (Appendix 3A). In consenting to participate in the study, participants gave permission for the abstraction of data from their routine clinical records through the pregnancy and post-partum period. As part of this proposed study, pre-existing data collected from the enrolment questionnaires and abstraction clinical and obstetric records will be accessed and utilized in accordance with the consent received from phase 1 participants. Given that no direct contact with participants will be required for this study, we will not obtain informed consent from individual participants.

4.2 Privacy and Confidentiality

The following provisions were made to minimize the risk of loss of confidentiality during the course of the parent study:

- All staff involved in the collection and management of data underwent training on their ethical obligations to ensure participant confidentiality
- As per standard practice, participants were identified by anonymous identifiers used on all study documents. Participant names only appear on the informed consent and locator tracer documents and these documents were kept separate from participant study documents.

- All study related documents were kept in a locked cabinet at UCT
- All databases were password protected and maintained in a firewall protected UCT server

During the proposed study no personal identifiers will be present in the data used for analysis, participants will be identified by the anonymous identifiers assigned in the parent study. Additionally, the results of the proposed study will not report on individual participants ensuring confidentiality.

4.3 Risks and Benefits

A description of risks and benefits, reimbursement details of the parent study have been provided and approved previously (HREC REF: 451/2012).

4.3.1 Risks

Participants are considered to be at minimal risk in this proposed study, with the only potential risk being the loss of confidentiality. Measures have previously been implemented to minimize the possibility of these risks as noted above.

4.3.2 Benefits

Participants will not derive any direct benefit from this proposed study as it is a retrospective analysis of previously collected data. There will however be considerable indirect benefit to the community of HIV-infected pregnant women in Cape Town, South Africa and other LMIC. Current HIV treatment guidelines recommend lifelong ART for all HIV-infected pregnant women, and understanding the long term impact of this *in vitro* ART exposure on infants and children of exposure to HIV and ART during pregnancy and breastfeeding will be beneficial to health care providers and maternal and child health.

4.4 Reporting and Implementation

Upon completion of the analysis, the results of this proposed study will be submitted to an appropriate peer-reviewed journal agreed upon in collaboration with the relevant stakeholders. These results will also be presented at appropriate local and international conferences, workshops or meetings as well as to the staff at the Gugulethu MOU.

4.5 Logistics

Table 2. Study time frame

Task	**Duration**			
	Dec 16	**Jan 17**	**Feb 17**	**Mar 17**
Merge, clean and check data sets				
Analysis				
Prepare draft manuscript				
Prepare final manuscript and submit for publication				

4.6 Budget

Ms Malaba will be conducting this analysis as part of her MPH degree and will not require any payment.

5. REFERENCES

1. WHO. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf?ua=1 (accessed 20 November 2016)
2. Rollins NC, Coovadia HM, Bland RM, et al. Pregnancy outcomes in HIV-infected and uninfected women in rural and urban South Africa. J Acquir Immune Defic Syndr. 2007;44(3):321-8.
3. Brocklehurst P, French R. The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis. BJOG. 1998;105(8):836-48.
4. Thorne C, Patel D, Newell ML. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. AIDS. 2004;18(7):2337-9.
5. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. AIDS. 2007;21(8):1019-26.
6. Tuomala RE, Shapiro DE, Mofenson LM, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. N Engl J Med. 2002;364(24):1863-70.
7. Tuomala RE, Watts DH, Li D, et al. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. J Acquir Immune Defic Syndr. 2005;38(4):449-73.
8. Powis KM, Kitch D, Ogwu A, et al. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based ART during pregnancy. J Infect Dis. 2011;204(4):506-14.
9. Ekouevi DK, Coffie P, Becquet R, et al. Antiretroviral therapy in pregnant women with advanced HIV disease and pregnancy outcomes in Abidjan, Cote d'Ivoire. AIDS. 2008;22(14):1815–20.
10. Chen JY, Ribaudo HJ, Souda S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. J Infect Dis. 2012;206(11):1695-705.

11. Zash R, Souda S, Chen JY, et al. Reassuring Birth Outcomes with Tenofovir/Emtricitabine/Efavirenz used for Prevention of Mother to Child Transmission of HIV in Botswana. J Acquir Immune Defic Syndr. 2016;71(4):428-36.

12. Fowler MG, Qin M, Fiscus SA, et al. Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention. N Engl J Med. 2016;375(18):1726-1737.

13. ARASA. HIV, TB and Human Rights in Southern and East Africa: 2016 Report. http://www.arasa.info/files/3314/8119/1044/ARASA_2016_Human_Rights_report.pdf (accessed 18 June 2017)

14. Williams BL, Dunlop AL, Kramer MS, et al. Perinatal origins of first-grade academic failure: Role of prematurity and maternal factors. Pediatrics. 2013;131(4): 693-700.

15. Watts DH, Mofenson LM. Antiretrovirals in pregnancy: a note of caution. J Infect Dis. 2012;206(11):1639-41.15.

16. Myer L, Phillips TK, Zerbe A, et al. Optimizing Antiretroviral Therapy (ART) for Maternal and Child Health (MCH): Rationale and Design of the MCH-ART Study. J Acquir Immune Defic Syndr. 2016;72(Suppl 2):S189-S96.

17. Myer L, Phillips TK, Manuelli V, et al. Evolution of antiretroviral therapy services for HIV-infected pregnant women in Cape Town, South Africa. J Acquir Immune Defic Syndr. 2015;69(2):e57–e65.

18. WHO. Neonatal and perinatal mortality: country, regional and global estimates http://apps.who.int/iris/handle/10665/43444 (accessed 10 February 2017)

SECTION B: LITERATURE REVIEW

1. INTRODUCTION

Significant progress has been made globally in the reduction of child mortality since 1990. There has been a global decline in under-5 deaths from 12.7million in 1990 to 5.9 million in 2015 (1). Preterm delivery (PTD) is the second major cause of these under-5 deaths, and the single most important direct cause of death in the critical neonatal period (2). Low birth weight (LBW), which is generally recognized as having short- and long-term consequences, is also an indirect cause of neonatal deaths. The global prevalence of LBW is estimated to be 15.5%, which translates into 20 million LBW infants born each year (3).

Birthweight is a function of the duration of gestation and rate of fetal growth, or a combination of both (4). Accordingly, a LBW infant could be result of either an early delivery (PTD) or being born small-for-gestational age (SGA), which is commonly used as a measurable proxy for intrauterine grown restriction (IUGR) (5). PTD and SGA are distinct but related outcomes, with different etiologies and consequences (short and long term). In 2010, out of all the 135 million infants born in low- and middle-income countries (LMIC) an estimated 43.3 million were born either preterm and/or SGA; and the highest prevalence's were in South Asia and sub-Saharan Africa (SSA) (2). Infants who are preterm-SGA have a 10 to 39 times increased risk of neonatal death compared to otherwise normal infants (6, 7). Even if these infants do survive, they still have to deal with long term consequences for child development, educational attainment (8), and quality of life.

Many of the countries where these adverse birth outcomes are common also have the added disadvantage of being high HIV prevalence settings. In particular, the vast majority of infants born to HIV-infected women reside in SSA; where the antenatal prevalence exceeds 30% in some areas of southern Africa (9). The management of HIV-infected pregnant women has evolved significantly due to advancements in antiretroviral (ARV) drug development and better understanding of mother-to-child transmission (MTCT). As ARVs have gotten more efficacious over time, recommended

regimens for use during pregnancy have also changed progressively from short course prophylaxis for prevention of mother-to-child transmission (PMTCT) to lifelong antiretroviral therapy (ART).

During the last five years, there has been a substantial increase in the number of HIV-infected pregnant using ART around the world, and particularly in SSA. While increased ART access has been invaluable for promoting the health of HIV-infected women and their infants, there are ongoing concerns surrounding the effects of this *in utero* ART exposure, with some evidence of increased risk of adverse birth (PTD, LBW, and SGA). Adverse birth outcomes among HIV-infected pregnant women on ART were first reported in Europe (10, 11); although this was less clear in Latin and North American studies where no associations were observed (12-15). This raised concern because while the majority of this early data came from cohorts in high income countries (10, 16-19); most women requiring ART during pregnancy reside in LMIC where neonatal care services are limited, magnifying the effects of any increase in adverse birth outcomes.

With more than 1 million pregnancies exposed to ART annually (20), any putative association between ART use and birth outcomes has major public health implications. Additionally, given the long term consequences of adverse birth outcomes it is essential to quantify their associations with ART use in high prevalence settings in order to facilitate risk-benefit assessment of ART and the different regimens.

2. OBJECTIVES

This literature review seeks to appraise published data on adverse birth outcomes associated with ART exposure during pregnancy and to identify knowledge gaps and further research needs.
This review focuses on ART use during pregnancy in SSA, the region with the highest HIV burden; however since adverse birth outcomes associated with ART use in pregnancy cut across settings, this review will selectively draw on studies from high income countries. For this review ART will refer to

triple drug fixed dose combination, which has been implicated in increased adverse birth outcomes compared to prophylaxis.

3. METHODS

3.1 Search Strategy

A search of the Medline bibliographic database through the PubMed interface (National Center for Biotechnology Information, Bethesda, MD) was performed using the search terms antiretroviral therapy, pregnancy outcomes as well as their variations:

- *ART* or *Antiretroviral Therapy* or *Triple Drug Antiretroviral* or *HAART*

AND

- *Pregnant* or *Pregnancy* or *Maternal* or *Maternity*

AND

- *Birth Outcomes or Pregnancy Outcomes*

(Antiretroviral[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) AND (adverse[All Fields] AND ("pregnancy outcome"[MeSH Terms] OR ("pregnancy"[All Fields] AND "outcome"[All Fields]) OR "pregnancy outcome"[All Fields] OR ("pregnancy"[All Fields] AND "outcomes"[All Fields]) OR "pregnancy outcomes"[All Fields])) AND ("0001/01/01"[PDAT] : "2016/12/31"[PDAT])

The search was restricted to English language publications. Publications were included in this review if the study was conducted in SSA, the population of interest included HIV-infected pregnant women on ART during pregnancy and if at least one adverse birth outcome (PTD, LBW, SGA) was an outcome of the study.

The titles and abstracts of the publications the search yielded were reviewed, as well as reference sections of the studies meeting the inclusion criteria. Additionally, the reference sections of review

articles covering antiretroviral therapy in pregnancy and birth outcomes were reviewed and additional publications were identified. All publications available through 31 December 2016 were included in this review. The included studies are summarized in Tables 1a and 1b.

4. QUALITY AND COMPARABILITY OF STUDIES

The PubMed search returned 279 publications of which only 10 met the inclusion criteria. The main reasons for exclusion were that the study was conducted outside of SSA, pregnant women were treated with <3 antiretroviral drugs without an ART comparator group, and/or study outcomes did not include any of the outcomes of interest. Following the review of the reference sections of the included studies and review articles (21-28) an additional 10 studies were identified.

The included studies were conducted between 2001 (29) and 2014 (30-32); and they represent 16 countries across SSA. Countries that had more than one study include South Africa (30, 31, 33-36), Botswana (32, 37, 38), Zambia (30, 39), Tanzania (30, 40), Malawi (30, 41) and Cote d'Ivoire (29, 42). Tables 2a and 2b summarize the key features reflecting study quality and comparability. Quality criteria were based on study design, sample size and methods of assessing outcomes (primarily gestation).

4.1 Study Design

Sixteen out of the 20 included studies were observational, enabling the researchers to observe diverse populations in a range of different settings with the exposure (HIV status or timing of ART initiation) determined before the ascertainment of the adverse birth outcomes of interest. The three types of observational studies employed were retrospective and prospective cohort (32, 33, 36, 37, 39, 41, 43, 44), case-control (45) and cross-sectional (29, 31, 42, 46, 47) studies. All of the retrospective cohort studies (32, 33, 36, 39, 41, 43, 44) identified participants after delivery, collected data through data abstraction of routinely recorded clinical information from the antenatal and postpartum period. The two prospective cohorts collected data at various time points at study

visits which included questionnaires, anthropometric measurements and sample collection (35, 40). The study conducted in Tanzania enrolled women at their first postnatal visit at the designated HIV care and treatment centres (40), while the study conducted in South Africa and Zambia enrolled women antenatally either at the antenatal clinic or HIV care clinic (35). A prospective matched case-control study was conducted in Nigeria with HIV-infected women matched to HIV-uninfected controls who were women presenting for antenatal booking who delivered in the hospital (45). The four cross-sectional studies were conducted in Côte d'Ivoire (46, 47), Cameroon (29, 42) and South Africa (31). In these studies, exposures and outcomes were either assessed during one time period (29, 47) or were comparative and assessed across several time periods (29, 31, 46). The studies investigating one time period compared women on different ART regimens (efavirenz (EFV)-based vs nevirapine (NVP)-based) (42) or women who initiating ART at different time points relative to pregnancy (ART initiated before conception vs ART initiated during pregnancy) (47). The comparative cross-sectional studies aimed to determine the association between adverse birth outcomes and the different ARV treatment guidelines at the different time points assessed (31, 46). In contrast to the observational studies, the four randomized control trials (RCT) (30, 34, 38, 48) by nature of their design had highly selected populations with strict inclusion and exclusion criteria. The Mma Bana study conducted in Botswana enrolled ART naïve women with CD4 cell count ≥200cells/µl, randomized to either protease inhibitor (PI)-based or nucleoside reverse transcriptase inhibitor (NRTI)-based ART arms between 26 to 34 weeks gestation (38); whereas the PROMOTE-Pregnant Women and Infants Study in Uganda which also enrolled ART naïve women/ARV-unexposed women (in last 24 months) had no CD4 cell count restrictions, and randomized women to either lopinavir/ritonavir (LPV/r)-based or EFV-based ART arms between 12 to 28 weeks gestation (48). The multicentre studies PROMISE (30) and Kesho Bora (34), both compared single course Zidovudine prophylaxis (scZDV) to ART for PMTCT. The PROMISE study inclusion criteria was ART naïve women with CD4 ≥350cells/ µl, randomized to either scZDV, ZDV-based ART or tenofovir (TDF)-based ART arms at ≥14 weeks gestation. Kesho Bora study enrolled women with CD4 200-500 cells/µl, randomized to either scZDV or ART arms.

4.2 Sample Size

The total sample sizes of the included studies ranged from n=188 in a study conducted in Congo (43) to n=33 148 in a surveillance study conducted in Botswana (37). The majority of the studies (12) had <1000 participants, 2 studies had >10 000 participants.

4.3 Outcome Assessment

For the birthweight outcome, birthweight was abstracted from clinical records in all the studies which reported their birthweight assessment method (39, 41, 47), one of the studies conducted a study measurement of birthweight within 1 week of delivery (41). Based on the study design (retrospective) it can be assumed the other studies also abstracted birthweight from clinical records. Across the studies, gestational age (GA) was determined using either last menstrual period (LMP), symphysis fundal height (SFH) and/or ultrasound scans (US). The majority of studies estimated GA based on the obstetric records, which was primarily based on LMP and SFH (29, 30, 32, 37, 39, 41, 43, 44, 47); while the prospective studies measured GA at enrolment using a combination of estimation methods (34, 38, 40, 48). Problems of availability mean ultrasonography is not routinely used for GA estimation in LMIC, consequently few of the study populations had US-based GA. In the studies that had US available (32, 34-38, 42-44, 46, 48), this was principally used as part of an algorithm for when there was discordancy between measures or unknown LMP. Four studies did not report how they determined their GA (29, 31, 33, 45).

4.4 Summary of Study Quality Appraisal

For the purposes of this review, ideally studies of good quality would have adequate sample size, designed to avoid selection bias, have high quality measures for outcome assessment, use ART regimens widely available in SSA, and have comparison groups of participants who initiated ART before conception and those who initiated at different time points during pregnancy. None of the studies fulfilled all these criteria, however Zash et al. (32), Chen et al. (37) and Fowler et al. (30) were the closest.

5. RESULTS FROM STUDIES REVIEWED

The results of the review of the included studies will be presented in terms of the exposures (HIV and ART status) and the outcomes. The key findings from the included studies are summarized in Tables 3a and 3b.

5.1 Outcome Definitions

Different combinations of adverse birth outcomes were reported by the included studies. PTD and LBW were reported by the majority of studies however SGA was only reported in few studies. Only two studies reported all three outcomes (40, 43).

5.1.1 Preterm Delivery

Eighteen out of the 20 studies reported PTD as an outcome, with eight of the studies also reporting a PTD sub-category(30, 32, 34, 36, 38, 40, 47, 48). The standard definition of PTD promulgated by the WHO and International Federation of Gynaecology and Obstetrics (FIGO), is birth at <37 completed weeks (259 days) weeks of gestational age (GA) (49). WHO has also defined sub-categories of PTD based on GA and these are moderate to late PTD (32 to <37 weeks); very preterm (28 to <32 weeks) and extremely PTD (<28) (50). The sub-categories reflect the differences in the survival probabilities and the long term health consequences.

The WHO definition of PTD was used in all 18 studies that reported PTD as an outcome; however there were differences in the definition of the PTD sub-categories used by the 8 studies which reported PTD and a PTD sub-category. The PTD sub-categories were named either very PTD, extremely PTD or severely PTD. Three studies defined the PTD sub-category as birth at <34 weeks GA (30, 36, 40), one study defined it as <33 weeks GA (32) while four studies defined it as <32 weeks GA (34, 38, 46, 48).

5.1.2 Low Birth Weight

Fifteen out of the 20 studies reported LBW as an outcome, with six studies also reporting a LBW sub-category. The standard WHO definition of LBW is birth weight <2500g, a cut-off based on epidemiological observations that these infants are at increased risk of mortality compared to normal weight infants; sub-categories of LBW include very LBW (VLBW) defined as <1500g and extremely LBW (ELBW) defined as <1000g (51).

Fourteen studies used the standard WHO definition for LBW, one study defined LBW based on birthweight (<2500g) and GA at delivery (≥37) (43). Five studies used the WHO definition for VLBW, while one study defined VLBW as <2000g (29).

5.1.3 Small for Gestational Age

Only four of the 20 reported SGA as an outcome with one study reporting a SGA sub-category. SGA is generally defined as a birth weight < 10^{th} percentile of a reference distribution of birth weights specific to gestation age. The definition of SGA is challenging in populations worldwide and no global reference exists because of differences in population characteristics which may affect fetal growth patterns and differences in methods used in the measurement of gestational age. Consequently several references exist however there are problems associated with them, those based on birthweight tend to be deficient for preterm deliveries, unisex references do not account or the known difference in birthweights between male and female infants and the individualized references tend to be too complicated for use in resource limited settings. Accordingly difference reference standards were used in the studies, of the four studies investigating SGA as an outcome the following references standards were used: Botswana norms (32, 37), US standards (40) and Fenton Growth Standards (36). One study did not report which reference standard was used (31).

5.2 Associations between ART and Adverse Birth Outcomes

5.2.1 Adverse Birth Outcomes – pre-ART era data

In the absence of ART (either for treatment or for PMTCT), maternal HIV infection has been associated with adverse birth outcomes (52-57) and increased neonatal mortality. In these early studies, the strongest associations were among women in LMIC and those with lower CD4 cell counts. The proposed mechanisms for these adverse birth outcomes were poor maternal health, increased risk factors for coinfections and the acute HIV infection of the fetus.

5.2.2 Adverse Birth Outcomes –ART era data

ART use introduces complexity to interpreting associations with adverse birth outcomes. ART may decrease some adverse birth outcomes by improving maternal health and reducing acute retroviral infection of the fetus, it would therefore appear to be logical that healthier women have better birth outcomes. However ART may also increase adverse birth outcomes through other mechanisms. This complicates the understanding these competing forces and makes the epidemiology of this challenging.

In 2010 WHO treatment guidelines recommended two treatment options based on a CD4 cell count: Option A (maternal scZDV and infant NVP during pregnancy and breastfeeding) and Option B (ART for pregnancy and breastfeeding if >350cells/µl; or lifelong ART if ≤350cells/µl) (58). Several studies in high income countries showed increased risk of adverse birth outcomes among pregnant women on ART in comparison to those on mono or dual therapy (11, 12, 59). Nine of the included studies evaluated the comparison between scZDV and ART, these include observational and randomized studies (29, 30, 32, 34, 37, 39, 40, 44, 46).

Between 2009 - 2011, the largest birth surveillance study in Africa (total births n=33 148) conducted in Botswana found that, when compared to scZDV, ART (initiated during

pregnancy) was found to be associated with an increased rate of PTD (adjusted odds ratio (AOR) 1.4, 95% confidence interval (CI) 1.2 - 1.8) and SGA (AOR 1.5, 95% CI 1.2 - 1.9) (37). Similarly, findings from a prospective cohort in Tanzania, found that ART (initiated before conception), when compared to scZDV, was associated with higher risks of PTD (adjusted relative risk (ARR) 1.24, 95% CI 1.05 – 1.47) and VPTD (ARR 1.42, 95% CI 1.02 – 1.91) (40). In this cohort ART (initiated during pregnancy) was also associated with higher risk of severe SGA (RR 1.47, 95% CI 1.09 – 1.98). A comparative cross-sectional study in Cameroon which compared outcomes over two time periods found that ART (initiated during pregnancy), when compared to scZDV, had an increased risk of LBW (AOR 1.7, 95% CI 1.0 - 2.9) but not PTD (AOR 1.9, 95% CI 0.9 - 3.7) (46). Recent findings from the PROMISE study, appear to mirror the observational studies, with ART (initiated in pregnancy) associated with increased rate of PTD (25% vs 12%) and LBW (21% vs 13%) compared to scZDV (30). Data from the Kesho Bora study, showed similar rates of PTD in the ART and scZDV arms, while LBW was slightly higher in the ART arm (34).

These results appear to suggest the adverse effect of ART, however in contrast to these findings a recent study in Botswana evaluating the current recommended WHO first-line regimen (TDF+FTC+EFV) found that ART (initiated during pregnancy), when compared to scZDV/other ART had lower odds of any adverse birth outcome (AOR 0.4, 95% CI 0.3 - 0.6) and SGA (AOR 0.4, 95% CI 0.2 - 0.7), while there was no difference in PTD (AOR 0.7, 95% CI 0.5 - 1.1) (32). The difference in conclusions about the effects of ART use in pregnancy between the previous studies and this study could be attributed differences in regimens used: these were primarily NVP-based in the previous studies and EFV-based in this study. This could suggest that EFV-based regimens have fewer adverse effects than other regimens (NVP-based and PI-based) (32).

Additionally, the lack of association with adverse birth outcomes when TDF was used with EFV, suggests that the PROMISE findings of increased birth outcomes in the ART arms could have been a result of drug interactions between TDF and LPV/r.

In LMIC, ART was previously reserved for women who had advanced disease (low CD4 cell count), suggesting that the adverse effects seen in earlier studies could have been subject to confounding by indication. However, studies have shown that even among women receiving ART solely for PMTCT (10, 60), suggesting that ART itself could be the problem.

In 2013, WHO guidelines changed to recommend that all HIV-infected pregnant and breastfeeding women should initiate ART regardless of clinical or immune status, which would be continued for the duration of the MTCT risk period (Option B), with an option for continuing lifelong ART (Option B+) (61). These guidelines were updated in 2015 to recommend Option B+ for all pregnant women, which has led to a rapid increase in the number of women initiating ART during pregnancy (62), it is therefore important to understand the effects of ART in these women. Three studies evaluated adverse birth outcomes among women who initiated ART during pregnancy, and these were either comparisons of the effect of different durations of ART (before delivery) or the effect different regimens (38, 41, 48). A retrospective cohort study in Malawi and Mozambique comparing ART duration prior to delivery found that there was a significant association between PTD and duration of ART with longer duration proving to be protective, this effect was however not replicated with LBW(41). Based on studies conducted in high income countries, uncertainties exist regarding the potential adverse effects of PI-based ART regimen which suggestions that PI-based regimens could play a significant in increasing the risk of adverse birth outcomes. Two randomized trials Mma Bana (Botswana) and PROMOTE (Uganda) investigated the PI effect by comparing PI-based regimens to other non PI-based regimens. In the Mma Bana trial the comparison between PI-based and NRTI-based regimens initiated between 26 and 34 weeks gestation, found that the PI arm had higher

rates of PTD and that PI regimen was the most significant risk factor for PTD (OR 2.03, 95% CI 1.26 – 3.27) (38). These results could help to clarify findings from previous observational studies in high income countries that had conflicting results (12, 13, 59) or were underpowered to detect differences (63). However in contrast, another randomized trial comparing PI-based (LPV/r) and EFV-based regimens among women initiating between 12 and 28 weeks gestation, did not find increased risk in the PI arm (OR 1.12, 95% CI 0.63 – 2.00) (48). It should however be noted that these two studies had very different gestational ages at ART initiation as well as different comparison regimens which could explain the different conclusions.

The number of women in LMIC who initiated ART before conception, is relatively low however as a result of the recent guideline changes, these numbers will dramatically increase due to the growing number of HIV-infected women already on lifelong ART and the newly initiating pregnant women who will have subsequent pregnancies. Few studies have evaluated risks associated with ART initiated before conception, and those that have usually have small sample sizes, however as the numbers of women in this group rapidly increases it will be crucial to monitor potential adverse birth outcomes.

Following recommendations by WHO for the use of EFV-based regimens, concerns were raised regarding congenital abnormalities associated with first trimester EFV exposure. The two studies that evaluated adverse birth outcomes among women ART initiated before conception (42, 43), were focused primarily on the effects EFV exposure. Retrospective studies were conducted in Côte d'Ivoire (42) and Congo (43) to compare EFV-based to other non EFV-based ART. The study in Côte d'Ivoire found that there was no significant increased risk of PTD and LBW in women on EFV-based ART compared to those on NVP-based ART in the first trimester. In contrast, the study in Congo which compared EFV-based ART to non-EFV-based ART (primarily but not exclusively NVP-based), found that there was an increased risk of LBW but not PTD.

Timing of ART initiation with respect to gestation appears to be critical, however there is limited data available to allow comparisons of adverse birth outcomes in women on ART initiated before conception with outcomes in women on ART initiated during pregnancy. In some studies women on ART initiated before conception were compared to women with other regimens during pregnancy, including scZDV; whereas in other studies women on ART initiated before conception were combined with women who initiated ART in the first trimester use, without accounting for timing of initiation. Previous studies in high income countries demonstrated an increased risk of PTD and/or LBW either in women on ART initiated before conception (64, 65) or in women on ART initiated during pregnancy (17, 66). Five of the included studies evaluated the comparison of adverse birth outcomes according to timing of ART initiation (ART initiated before conception vs ART initiated during pregnancy) all of these studies were observational (29, 33, 37, 40, 47).

A South African cohort study which investigated the impact of ART on birth outcomes according to timing of ART initiation found that there was no difference in the rate of PTD and LBW between women on NNRTI-based ART initiated before conception and those on ART initiated after the first trimester (33). Similarly, findings from cross-sectional studies in Cameroon and Côte d'Ivoire also found that when women on ART initiated before conception were compared to those who on ART initiated during pregnancy, the rates of adverse birth outcomes (PTD and/or LBW) were also comparable (29, 47).

Results from these studies are however in contrast to findings from larger studies conducted in Botswana and Tanzania, which demonstrated increased risk in the women on ART initiated before conception when compared to those on ART initiated during pregnancy. In the Botswana birth surveillance study this comparison was only conducted for the SGA outcome, since women in both groups had equal chances of experiencing the outcome (37). In this study, women on ART initiated before conception had higher odds of SGA deliveries

compared to those who initiated ART before 34 weeks (AOR 1.3, 95% CI 1.0 – 15). In Tanzania the women on ART initiated before conception were at increased risk of PTD (RR 1.37, 95% CI 1.13 – 1.67) and VPTD (RR 1.65, 95% CI 1.12 – 2.43) but not SGA (40).

5.3 Major methodological concerns in the literature

Similar to studies conducted in high income countries there are different conclusions reached among the studies included in the review, which can be attributed in part to the different methodologies used which complicate comparisons of individual studies. The drivers of the different conclusions reached between the studies could be related to the heterogeneous populations studied, varying study designs and selection of exposure categories.

5.3.1 Different study populations

The difficulty in comparing studies from high income countries and those in LMIC is not surprising given the stark health and health-care disparities that exist. However, within SSA multiple disparities also exist—across regions, within countries, and between different segments of the population. The regional prevalence is 4.7%, however this varies considerably between regions within SSA as well as within individual countries. Southern Africa, which is considered the epicentre of the global epidemic, has the country with the highest prevalence (Swaziland) and the country with the largest epidemic (South Africa) (67). In contrast, HIV prevalences in East and West Africa are low to moderate ranging from 0.5% to 6% (67). As a result of these differences in the epidemiology of HIV in SSA, differences exist between HIV-infected pregnant women populations, in terms of the characteristics of the women (demographics, differences in risk of exposure to and transmission of HIV, and the prevalence of coinfections); and characteristics of their antenatal and therapeutic management. All these factors complicate study comparisons. Additionally, over the time period that the studies were conducted (2001 – 2014) the profile of HIV-infected women

regionally and within countries has changed drastically, as a result of improvements in PMTCT programmes.

Similar to HIV-related factors, differences also exist in SSA in terms of background rates of adverse birth outcomes. Women in SSA are exposed to numerous risk factors for adverse birth outcomes and these include anaemia, untreated hypertension (68), poor nutritional status (69), and other factors related to HIV and low socioeconomic status (SES). While these individual level factors are often considered in studies investigating the association between ART and adverse birth outcomes, health system factors which have also been shown to influence adverse birth outcomes are not always considered. Population level characteristics, treatment guidelines and polices vary within SSA and this may impact the incidence of adverse birth outcomes (35). This is demonstrated in the study conducted by Lui et al, a comparison of two health care systems in Zambia and South Africa, where adverse birth outcomes differed significantly between the two cohorts (35). The authors concluded that while differences in maternal characteristics in the two cohorts contributed to the differences in rates of adverse birth outcomes, the disparity in the health care systems also played a part with fewer adverse birth outcomes in South Africa where women received hospital based ANC compared to the primary health care facility based ANC in Zambia (35). These individual and population level differences in SSA are likely to contribute to the differences in conclusions reached in the various studies conducted in this region and internationally.

5.3.2 Different study designs

The varying study designs used in studies investigating the association between ART and adverse birth outcomes could also contribute to different conclusions reached. In order to understand the antecedents and predictors of adverse birth outcomes and any related biological mechanisms, investigation of representative populations of HIV-infected

pregnant women with high quality measures of study procedures are required. Unfortunately this is not always possible, with compromises often having to be made in design choices; foregoing strength in some areas for strength in others. This is demonstrated in the studies conducted in Botswana, the two retrospective cohort studies were able to evaluate outcomes in approximately 10 000 HIV-infected women (32, 37) compared to the RCT which only evaluated outcomes 560 HIV-infected women (38). Different study designs provide different data quality because of the compromises are made with respect to measurement quality and generalizability of the results.

Observational studies and RCTs are the main study types used to evaluate the association between ART and adverse birth outcomes. They do not always have same conclusions with observational studies tending to overestimate effects and have more variable estimates of effects because of residual confounding in comparison to RCTs. Observational studies draw inferences about the effect of the exposure on much wider populations and are often population-based. There may however be large observed and unobserved differences in the characteristics of pregnant women in the different treatment groups, leading to biased estimates (70). When information on participant characteristics is missing/unavailable, as is common in observational studies, this impacts the ability to adjust for important confounders such as demographics, substance use, HIV factors (degree of immunosuppression, indication for treatment) and coinfections. Several of the observational studies in this review had these limitations. The two retrospective cohort studies conducted in Botswana (32, 37), had large sample sizes, however because routine laboratory tests were inconsistently performed and/or recorded, they had missing CD4 cell count and VL data. Similarly, the retrospective cohort studies in South Africa and Cameroon had missing data on coinfections (33, 36), nutritional status (36, 46) and SES (33). Studies conducted in multiple countries or facilities, are also subject to problems of

inconsistent data – this was demonstrated in the South African study conducted within routine clinical settings had two sites which collected different data (36).

In contrast, this selection bias tends to be absent in RCTs because of the randomization which is why these trials are considered to have greater internal validity and provide the strongest evidence for concluding causality. However there are concerns about the generalizability of results of these clinical trials, which is influenced by the inclusion and exclusion criteria and participant self-selection (71).

All four RCTs had stringent inclusion and exclusion criteria based primarily on CD4 cell count and GA at enrolment. In the studies that had CD4 cell count inclusion criteria these were ≥200 cells/µl for Mma Bana (38); ≥350 cells/µl for PROMISE (30) and between 200-500cells/µl for Kesho Bora (34). There were also differences in the GA at enrolment criteria, PROMOTE (12-28 weeks), PROMISE (>14 weeks) and Kesho Bora (<32 weeks) enrolled women early in pregnancy which enabled evaluation of early events such as VPTD, unlike Mma Bana which only enrolled women later in pregnancy (26-36 weeks)

Because of these inclusion criteria, study populations of RCTs do not tend to mirror the population characteristics of the target population (72) and could explain the different conclusions reached on observational studies and RCTs.

5.3.3 Measurement of gestation

Associations of ART and adverse birth outcomes in SSA are greatly affected by the inability to obtain precise information on pregnancy duration. Accurate GA assessment is of critical importance for the correct diagnosis of adverse birth outcomes, particularly in these high HIV prevalence areas, where ultrasonography is usually unavailable. It should be noted that even when US facilities are available, women in this region tend to seek antenatal services later in the pregnancy when biologic variations and effects of growth restriction have occurred which affects the precision (73, 74). Consequently, GA assessment is routinely

based on clinical assessment including dating the LMP and measurement of SFH. However, LMP-based GA may be unreliable with recall issues and use of injectable hormonal contraception (with lack of, or irregular, periods after cessation), while SFH-based GA assessment is affected by poor reproducibility and difficult in women early in pregnancy (<12 weeks), and in women with high BMI.

Measurement error in GA assessment may introduce bias where an imprecise GA can result in the misclassification of preterm versus term deliveries and preterm versus SGA infants. This warrants cautious interpretation of GA at delivery as predicted by either of menstrual history or clinical examination, particularly outside the range of term deliveries.

Since the majority of studies in this review used a combination of LMP and/or SFH for GA assessment, misclassification of outcomes is a possibility, which could have substantial effects on the inference made from the study findings. Limiting measurement error in epidemiological studies through the use of robust measures with fewer errors will result in sounder and more interpretable scientific findings. These different methods of outcome assessments used in the studies are summarized in Tables 2a and 2b.

5.3.4 Different exposure groups

The different exposures or comparison groups in studies investigating the associations between ART and adverse birth outcomes impacts the comparability of these studies and can explain some of the differences in study conclusions. There were three major groups of comparisons in the studies: HIV-infected (on ART) women compared to HIV-infected women; HIV-infected women only and HIV-infected women on ART only. These different exposure groups are summarized in Table 4.

When the exposure groups were HIV-infected (on ART) and HIV-uninfected women, results were consistent with higher rates of adverse birth outcomes in HIV-infected women (31, 32,

37, 45). In the comparisons among the 'HIV-infected women only' there were many different groups of women compared to the women on ART. These included women who were untreated (no ARVs in pregnancy) and women on PMTCT regimens. In the comparisons with untreated women, there were no associations between ART and adverse birth outcomes, with higher rates seen in the untreated women (31, 40, 41).

Among the women on short-course PMTCT regimens, the comparator groups were either women on monotherapy only (31, 44) or a combination of women on mono and dual therapy (29, 36). The women on ART were not a homogenous group, in some studies these were women who were initiating on ART (30, 37, 40, 46), while it others it was women on ART initiated before conception (40).

In the comparisons among the women on 'ART only', the women were either compared according to timing of initiation or regimen types. Comparisons of timing of ART initiation were between women on ART initiated before conception and those who on ART initiated during pregnancy. Among the women who initiated ART during pregnancy some were either restricted i.e. only those who initiated after 1st trimester (33) or categorized as late or early (47). Regimen comparisons among women on 'ART initiated before conception only' included TDF+3TC+EFV versus any other ART (32), EFV-based versus non EFV-based (43) and EFV-based versus NVP-based (42). Among those on 'ART initiated during pregnancy', the regimen comparisons were PI-based versus NRTI-based (38), LPV/r-based versus EFV-based (48) and ZDV-based versus TDF-based (30).

5.3.5 Different ART regimens

ART regimens used during pregnancy in SSA consist primarily of reverse transcriptase inhibitors, which are drugs with reduced antenatal impairments compared to PI-based regimens commonly used in high income countries. National guidelines on which regimens to use during pregnancy have varied across SSA and have changed over time. Consequently

regimens used in studies in SSA are not always widely used within the region. The studies that included details of regimens had the following comparisons: NNRTI-based vs PI-based (36, 48); NNRTI-based (TDF+3TC+EFV) vs Other (32, 45), NRTI-based vs PI-based (38), NNRTI-based only (29, 31, 39, 42, 43) and PI-based only (30, 34). This wide range of regimen comparisons may also contribute to the different conclusions reached by studies, particularly since there is uncertainty about whether any observed associations are drug specific, with some but not all reports suggesting that the relationship may be driven in part by PI-based regimens (24, 75). Randomized data from Mma Bana study (38) was similar to observational studies that associated PI-based regimens with PTD (36, 60), these results were however different from results from the PROMOTE study which found no association between PI-based regimens and PTD (48). The PROMISE study results also showed differences by regimens, although it was the NRTI backbone (TDF+FTC) that was of concern with considerably more severe adverse birth outcomes (VPTD and VLBW) with the TDF+FTC backbone compared to the ZDV+3TC backbone (30). This has raised concerns that TDF+FTC backbone when used in combination with LPV/r may contribute to adverse birth outcomes particularly since TDF was not associated with adverse birth outcomes when combined with EFV in a recent study in Botswana (32).

WHO currently recommends TDF+FTC+EFV as the first-line regimen – however few studies have evaluated adverse birth outcomes associated with this regimen. Results from a birth outcomes surveillance in Botswana, found that there was no increased risk of adverse birth outcomes with this regimen regardless of timing of ART initiation (32).

6. SUMMARY

This review shows that in the last five years there has been an increase in larger studies being conducted in SSA to examine the associations between ART use and birth outcomes, however the current state of epidemiologic knowledge still remains limited because of the limited number of high quality prospective studies from the region. One major factor influencing the study quality in studies conducted in SSA is that they rely heavily on LMP and SFH as measures of gestation even though it is known that these methods are subject to considerable error. Additionally, as in studies conducted in high income countries, study comparability is limited by the different population characteristics and the wide range of exposure groups and ART regimens used. The majority of the studies reviewed were based on regimens not widely used in SSA; and very few studies examined the first-line regimen (TDF+3TC+EFV) currently recommended by WHO, which is the most commonly used combination of antiretroviral drugs.

7. RECOMMENDATIONS

Although there is an unquestionable benefit of ART use in pregnancy to both HIV-infected mother and her infant, it is clear from the studies included in this review and in studies conducted in other settings that there is some link between ART use in pregnancy and adverse birth outcomes. What remains unclear is whether the associations observed between ART and adverse birth outcomes are a result of the class of ARV drug used or timing of ART initiation. One of the problems that exists is that in the majority of studies investigating this association, birth outcomes analyses tend to be planned or unplanned secondary analyses. Consequently, data collection procedures are not designed to examine this association and so the best high quality measures and procedures are not always utilised. This is predominantly the case with GA assessment and given that adverse birth outcomes, notably PTD, are defined by their timing, it is critical that in future studies high quality measures of GA assessment are used to ensure an accurate degree of exposure ascertainment. This

will substantially strengthens results and allow inferences into how the timing of ART initiation in pregnancy may or may not be associated with adverse birth outcomes.

Another problem that exists is that there is still limited evidence about the risks of fetal exposure to different ART regimens. Recent observational data from Botswana, evaluating adverse birth outcomes with *in utero* exposure to different ART regimens initiated before conception has shown that there are differences (in birth outcomes) between regimens (76). Women on NVP-based and LPV/r-based regimens had significantly worse outcomes than those on TDF+FTC+EFV. This raises the question of whether we should be concerned about the continued use of certain older regimens in pregnancy. Regimens used by women initiating ART during pregnancy have changed over time to safer regimens, in line with changes in treatment guideline; however women who initiated before conception tend to continue using the regimens they were initiated on in the past despite some of these regimens being implicated in increasing the risk of adverse birth outcomes. Further research is required on the birth and long term outcomes associated with the use of different regimens in pregnancy, which includes the current recommended regimens and any new antiretroviral agents. This literature review underscores the need for the examination of representative cohorts that provide unique "real world" insights into the potential adverse effects of ART in pregnancy according to regimens used and timing of ART initiation.

8. REFERENCES

1. You D, Hug L, Ejdemyr S, et al. Global, regional, and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Inter-agency Group for Child Mortality Estimation. Lancet. 2015;386(10010):2275-86.
2. Katz J, Lee AC, Kozuki N, et al. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. Lancet. 2013;382(9890):417-25.
3. Wardlaw TM. Low birthweight: country, regional and global estimates: UNICEF; 2004.
4. Kramer MS. The epidemiology of low birthweight. Maternal and Child Nutrition: The First 1,000 Days. 74: Karger Publishers; 2013. p. 1-10.
5. Kramer MS. The Epidemiology of Adverse Pregnancy Outcomes: An Overview. J Nutr. 2003;133(5 Supplement 2):1592S-6S.
6. Katz J, Lee AC, Kozuki N, et al. Mortality risk in preterm and small-for-gestational age infants in low-income and middle-income countries: a pooled country analysis. Lancet. 2013;382(9890):417–25.
7. Blencowe H, Cousens C, Chou D, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health. 2013;10(1):1.
8. Williams BL, Dunlop AL, Kramer MS, et al. Perinatal origins of first-grade academic failure: Role of prematurity and maternal factors. Pediatrics. 2013;131(4): 693-700.
9. Myer L, Phillips TK, Manuelli V, McIntyre J, Bekker L-G, Abrams EJ. Evolution of antiretroviral therapy services for HIV-infected pregnant women in Cape Town, South Africa. J Acquir Immune Defic Syndr. 2015;69(2):e57–e65.
10. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. AIDS. 2007;21(8):1019-26.
11. Thorne C, Patel D, Newell ML. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. AIDS. 2004;18(7):2337-9.

12. Cotter AM, Garcia AG, Duthely ML, Luke B, O'Sullivan MJ. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? J Infect Dis. 2006;193(9):1195-201.
13. Szyld EG, Warley EM, Freimanis L, et al. Maternal antiretroviral drugs during pregnancy and infant low birth weight and preterm birth. AIDS. 2006;20(18):2345-53.
14. Tuomala RE, Shapiro DE, Mofenson LM, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. N Engl J Med. 2002;346(24):1863-70.
15. Tuomala RE, Watts DH, Li D, et al. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. J Acquir Immune Defic Syndr. 2005;38(4):449-73
16. Boer K, Nellen JF, Patel D, et al. The AmRo study: pregnancy outcome in HIV-1-infected women under effective highly active antiretroviral therapy and a policy of vaginal delivery. BJOG. 2007;114(2):148-55.
17. Martin F, Taylor GP. Increased rates of pre-term delivery are associated with the initiation of highly active antiretroviral therapy during pregnancy: a single centre cohort study. J Infect Dis. 2007;196(4):558–61.
18. Sibiude J, Warszawski J, Tubiana R, et al. Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost? Clin Infect Dis. 2012;54(9):1348-60.
19. Lopez M, Figueras F, Hernandez S, et al. Association of HIV infection with spontaneous and iatrogenic preterm delivery: effect of HAART. AIDS. 2012;26(1):37-43.
20. Fact Sheet: HIV/AIDS [press release]. WHO Media Centre 2016.
21. Alemu FM, Yalew AW, Fantahun M, Ashu EE. Antiretroviral Therapy and Pregnancy Outcomes in Developing Countries: A Systematic Review. Int J MCH AIDS. 2015;3(1):31-43.
22. Kourtis AP. Antiretroviral drug use during pregnancy and risk of premature delivery: is there a connection? J Infect Dis. 2010;201(7):978-80.
23. Mofenson LM. Antiretroviral therapy and adverse pregnancy outcome: the elephant in the room? J Infect Dis. 2016;213(7):1051-4.

24. Powis KM, Shapiro RL. Protease inhibitors and adverse birth outcomes: is progesterone the missing piece to the puzzle? J Infect Dis. 2015;211(1):4-7.

25. Short CE, Taylor GP. Antiretroviral therapy and preterm birth in HIV-infected women. Expert Rev Anti Infect Ther. 2014;12(3):293-306.

26. Thorne C, Townsend CL. A new piece in the puzzle of antiretroviral therapy in pregnancy and preterm delivery risk. Clin Infect Dis. 2012;54(9):1361-3.

27. Uthman OA, Nachega JB, Anderson J, et al. Timing of initiation of antiretroviral therapy and adverse pregnancy outcomes: a systematic review and meta-analysis. Lancet HIV. 2017;4(1):e21-e30.

28. Watts DH, Mofenson LM. Antiretrovirals in pregnancy: a note of caution. J Infect Dis. 2012;206(11):1639-41.

29. Ekouevi DK, Coffie P, Becquet R, et al. Antiretroviral therapy in pregnant women with advanced HIV disease and pregnancy outcomes in Abidjan, Cote d'Ivoire. AIDS. 2008;22(14):1815.

30. Fowler MG, Qin M, Fiscus SA, et al. Benefits and risks of antiretroviral therapy for perinatal HIV prevention. N Engl J Med. 2016;375(18):1726-37.

31. Moodley T, Moodley D, Sebitloane M, Maharaj N, Sartorius B. Improved pregnancy outcomes with increasing antiretroviral coverage in South Africa. BMC Pregnancy Childbirth. 2016;16(1):35.

32. Zash R, Souda S, Chen JY, et al. Reassuring birth outcomes with tenofovir/emtricitabine/efavirenz used for prevention of mother-to-child transmission of HIV in Botswana. J Acquir Immune Defic Syndr. 2016;71(4):428-36.

33. Aniji C, Towobola OA, Mashamba T, Monokoane S, Hoque M. Impact of antiretroviral therapy on pregnancy outcomes: original article. SAMJ. 2013;14(4):176-8.

34. Kesho Bora Study Group. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. Lancet Infect Dis. 2011;11(3):171-80.

35. Liu KC, Farahani M, Mashamba T, et al. Pregnancy outcomes and birth defects from an antiretroviral drug safety study of women in South Africa and Zambia. AIDS. 2014;28(15):2259-68.

36. van der Merwe K, Hoffman R, Black V, Chersich M, Coovadia A, Rees H. Birth outcomes in South African women receiving highly active antiretroviral therapy: a retrospective observational study. J Int AIDS Soc. 2011;14(1):42.

37. Chen JY, Ribaudo HJ, Souda S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. J Infect Dis. 2012;206(11):1695-705.

38. Powis KM, Kitch D, Ogwu A, et al. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. J Infect Dis. 2011;204(4):506-514.

39. Bengtson AM, Chibwesha CJ, Westreich D, et al. Duration of cART Before Delivery and Low Infant Birthweight Among HIV-Infected Women in Lusaka, Zambia. J Acquir Immune Defic Syndr. 2016;71(5):563-569

40. Li N, Sando MM, Spiegelman D, et al. Antiretroviral therapy in relation to birth outcomes among HIV-infected women: a cohort study. J Infect Dis. 2016;213:1057–64.

41. Marazzi MC, Palombi L, Nielsen-Saines K, et al. Extended antenatal use of triple antiretroviral therapy for prevention of mother-to-child transmission of HIV-1 correlates with favorable pregnancy outcomes. AIDS. 2011;25(13):1611-8.

42. Ekouevi DK, Coffie PA, Ouattara E, et al. Pregnancy outcomes in women exposed to efavirenz and nevirapine: an appraisal of the IeDEA West Africa and ANRS Databases, Abidjan, Côte d'Ivoire. J Acquir Immune Defic Syndr. 2011;56(2):183.

43. Bisio F, Nicco E, Calzi A, et al. Pregnancy outcomes following exposure to efavirenz-based antiretroviral therapy in the Republic of Congo. New Microbiol. 2015;38(2):185-92.

44. Kebede B, Andargie G, Gebeyehu A. Birth outcome and correlates of low birth weight and preterm delivery among infants born to HIV-infected women in public hospitals of Northwest Ethiopia. Health. 2013;5:25-34

45. Olagbuji BN, Ezeanochie MC, Ande AB, Oboro VO. Obstetric and perinatal outcome in HIV positive women receiving HAART in urban Nigeria. Arch Gynecol Obstet. 2010;281(6):991-4.

46. Njom Nlend A, Nga Motazé A, Moyo Tetang S, Zeudja C, Ngantcha M, Tejiokem M. Preterm Birth and Low Birth Weight after In Utero Exposure to Antiretrovirals Initiated during Pregnancy in Yaoundé, Cameroon. PLoS One. 2016;11(3):e0150565.

47. Njom Nlend A, Zeudja C, Moyo Tetang S, Nga Motazé A, The Therapeutic Committee of Centre Hospitalier d'ESSOS Djoungolo. Birth Outcomes in HIV-1-Infected Women Receiving Highly Active Antiretroviral Therapy (HAART) Prior to Conception versus During Pregnancy in Yaounde, Cameroon. J Antivir Antiretrovir. 2014;6(3):135-8.

48. Koss CA, Natureeba P, Plenty A, et al. Risk factors for preterm birth among HIV-infected pregnant Ugandan women randomized to lopinavir/ritonavir-or efavirenz-based antiretroviral therapy. J Acquir Immune Defic Syndr. 2014;67(2):128.

49. WHO. WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. Acta Obstet Gynecol Scand. 1977;56(3):247-53.

50. WHO. Fact Sheet 363: Preterm Birth. WHO Media Centre 2013.

51. WHO. International statistical classification of diseases and related health problems. World Health Organization 1992.

52. Temmerman M, Plummer FA, Mirza NB, et al. Infection with HIV as a risk factor for adverse obstetrical outcome. AIDS. 1990;4(11):1087-94.

53. Brocklehurst P, French R. The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis. BJOG. 1998;105(8):836-48.

54. Taha TE, Dallabetta GA, Canner JK, et al. The effect of human immunodeficiency virus infection on birthweight, and infant and child mortality in urban Malawi. Int J Epid. 1995;24(5):1022-9.

55. Bulterys M, Chao A, Munyemana S, et al. Maternal human immunodeficiency virus 1 infection and intrauterine growth: a prospective cohort study in Butare, Rwanda. Pediatr Infect Dis J. 1994;13(2):94-9.

56. Parekh N, Ribaudo H, Souda S, et al. Risk factors for very preterm delivery and delivery of very-small-for-gestational-age infants among HIV-exposed and HIV-unexposed infants in Botswana. Int J Gynaecol Obstet. 2011;115(1):20-5.

57. Rollins NC, Coovadia HM, Bland RM, et al. Pregnancy outcomes in HIV-infected and uninfected women in rural and urban South Africa. J Acquir Immune Defic Syndr. 2007;44(3):321-8

58. WHO. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach: 2010 revision: World Health Organization. 2010.

59. Kourtis AP, Schmid CH, Jamieson DJ, Lau J. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. AIDS. 2007;21(5):607-15.

60. Grosch-Woerner I, Puch K, Maier RF, et al. Increased rate of prematurity associated with antenatal antiretroviral therapy in a German/Austrian cohort of HIV-1-infected women. HIV Med. 2008;9(1):6-13.

61. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. World Health Organization. 2013.

62. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. World Health Organization. 2016(Ed. 2).

63. Patel K, Shapiro DE, Brogly SB, et al. Prenatal Protease Inhibitor Use and Risk of Peterm Birth among HIV-Infected Women Initiating Antiretroviral Drugs during Pregnancy. J Infect Dis. 2010;201(7):1035-44.

64. Machado ES, Hofer CB, Costa TT, et al. Pregnancy outcome in women infected with HIV-1 receiving combination antiretroviral therapy before versus after conception. Sex Transm Infect. 2009;85(2):82-7.

65. Mandelbrot L, Tubiana R, Le Chenadec J, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. Clin Infect Dis. 2015;61(11):1715-25.

66. Short CE, Douglas M, Smith JH, Taylor GP. Preterm delivery risk in women initiating antiretroviral therapy to prevent HIV mother-to-child transmission. HIV Med. 2014;15(4):233-8.

67. UNAIDS. The gap report. 2014.

68. Traisathit P, Mary JY, Le Cœur S, et al. Risk factors of preterm delivery in HIV-infected pregnant women receiving zidovudine for the prevention of perinatal HIV. J Obstet Gynaecol. 2009;35(2):225-33.

69. Young S, Murray K, Mwesigwa J, et al. Maternal nutritional status predicts adverse birth outcomes among HIV-infected rural Ugandan women receiving combination antiretroviral therapy. PLoS One. 2012;7(8):e41934.

70. Black N. Why we need observational studies to evaluate the effectiveness of health care. BMJ. 1996;312(7040):1215-8.

71. Moore D, Goodall R, Ives N, Hooker M, Gazzard B, Easterbrook P. How generalizable are the results of large randomized controlled trials of antiretroviral therapy? HIV Med. 2000;1(3):149-54.

72. Hannan EL. Randomized clinical trials and observational studies: guidelines for assessing respective strengths and limitations. JACC: Cardiovasc Interv. 2008;1(3):211-7.

73. Gebremeskel F, Dibaba Y, Admassu B. Timing of first antenatal care attendance and associated factors among pregnant women in Arba Minch Town and Arba Minch District, Gamo Gofa Zone, south Ethiopia. J Environ and Public Health. 2015;2015:971506

74. Gross K, Alba S, Glass TR, Schellenberg JA, Obrist B. Timing of antenatal care for adolescent and adult pregnant women in south-eastern Tanzania. BMC Pregnancy Childbirth. 2012;12(1):16.

75. Watts D, Mofenson LM. Antiretrovirals in pregnancy: a note of caution. J Infect Dis. 2012;206(11):1639-41.

76. Zash R, Jacobson D, Diseko M, et al. Adverse birth outcomes differ by ART regimen from conception in Botswana. Conference on Retroviruses and Opportunistic Infections (CROI); February 2017; Seattle, WA 2017.

Table 1a. Summary of included studies (2008-2013)

Study	Year Published	Region	Time Period	Setting	Study Population	Sample Size (HIV+)	Outcomes (Definition)
Ekouevi	2008	Côte d'Ivoire	2001 - 2003 2003 - 2007	PMTCT Programmes (ANC Clinics)	ART eligible HIV+ pregnant women	358	LBW (<2500g); VLBW (<2000g)
Olabuji	2010	Nigeria	2007 - 2008	Teaching Hospital	ART eligible HIV+ pregnant women referred to PMTCT services and delivered at hospital Matched HIV- women, booked for ANC and delivered at hospital	406* (203)	PTD (<37 weeks) LBW (<2500g)
Kesho Bora	2011	Burkina Faso, Kenya, South Africa	2005 - 2008	5 Research Sites (ANC Clinics)	HIV+ pregnant women, <32 weeks GA, CD4 200-500, WHO clinical stage 1-3	824	PTD (<37 weeks); VPTD (<32 weeks) LBW (<2500g); VLBW (<1500g)
Van der Merwe	2011	South Africa	2004 - 2007	Integrated ANC-ARV Clinics (2 Referral Centres)	HIV+ pregnant women, CD4 <250, singleton birth	1630	PTD (<37 weeks); EPTD (<34 weeks) LBW (<2500g); VLBW (<1500g) SGA (<10th percentile – Fenton Standard)
Powis	2011	Botswana	2006 - 2008	4 Research Sites	ART naïve HIV+ pregnant women CD4 ≥200, 26 -34 weeks GA	560	PTD (<37 weeks); VPTD (<32 weeks)
Marazzi	2011	Mozambique, Malawi	2005 - 2009	Project ANC Centres	Birth outcome data available, intends to follow-up at study centres pp	3273	PTD (<37 weeks) LBW (<2500g)
Ekouevi	2011	Côte d'Ivoire	2003 - 2009	4 HIV Care Centres	HIV+ pregnant women preconception ART (EFV-based or NVP-based)	344	PTD (<37 weeks) LBW (<2500g)
Chen	2012	Botswana	2009 - 2011	6 Government Hospitals	HIV+ and HIV- pregnant women, delivered live-born or stillborn infants ≥20 weeks GA	33148* (9504)	PTD (<37 weeks) SGA (<10th percentile - Botswana Norms)
Anji	2013	South Africa	2008 - 2009	Large Academic Hospital	HIV+ pregnant women, booked ANC and delivered at study hospital	245	PTD (<37 weeks) LBW (<2500g)
Kebede	2013	Ethiopia	2009 - 2012	2 District Hospitals 1 Referral Hospital	All infants born to HIV+ women	416	PTD (<37 weeks) LBW (<2500g)

*total population includes both HIV-infected (HIV+) and HIV-uninfected women (HIV-)

Preconception ART – ART initiated before conception; Initiating ART – initiated ART during pregnancy, PHC – primary health care, pp – postpartum, HEU – HIV exposed uninfected infant, VPTD – very PTD, EPTD – extremely, VLBW – very LBW, SSGA – severe SGA, mod SGA – moderate to severe SGA

Table 1b. Summary of included studies (2014-2016)

Study	Year Published	Region	Time Period	Setting	Study Population	Sample Size (HIV+)	Outcomes (Definition)
Koss	2014	Uganda	2009 - 2012	District Hospital	ART naïve (or no ARV in 24mo) HIV+ pregnant women, 12-28 weeks GA	389	PTD (<37 weeks); VPTD (<32 weeks) Composite (PTD, SB and Miscarriage)
Nlend	2014	Cameroon	2008 - 2013	ARV Treatment Referral Centre	ART exposed HIV+ women with live births	617	PTD (<37 weeks); SPTD (<32 weeks) LBW (<2500g)
Lui	2014	South Africa, Zambia	2010 - 2011	SA: 1 Referral Hospital Zambia: 5 PHC Clinics	Preconception ART HIV+ pregnant women	600	PTD (<37 weeks)
Li	2015	Tanzania	2004 - 2011	10 HIV Care and Treatment Centres	Postpartum HIV+ women with HEU infant	3314	PTD (<37 weeks); VPTD (<34 weeks) LBW (<2500g); VLBW (<1500g) SGA (<10^{th} percentile - US standards) SSGA (<3^{rd} percentile - US standards)
Bisio	2015	Congo	2005 - 2012	Research Sites (ANC Clinics)	All women enrolled in PMTCT projects over2 time periods 2005-2008; 2009-2012	188	PTD (<37 weeks) LBW (≥37 weeks GA and BW <2500)
Bengtson	2016	Zambia	2009 - 2013	ANC Clinics	HIV+ women, Initiating ART CD4 ≤350 (restricted to singleton births >37 weeks)	4474	LBW (<2500g)
Fowler	2016	India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe	2011 - 2014	Research Sites	ART naïve HIV+ pregnant women, CD4 ≥350 (or country specific threshold), ≥14 weeks GA	3490	PTD (<37 weeks); VPTD (<34 weeks) LBW (<2500g); VLBW (<1500g)
Zash	2016	Botswana	2009 - 2011 2013 - 2014	2 Maternity Hospitals	HIV+ and HIV- pregnant women, delivered live-born or stillborn infants	31463* (9445)	PTD (<37 weeks); VPTD (<33 weeks) SGA (<10^{th} percentile - Botswana Norms) Any ABO (any SB, PTD or SGA)
Moodley	2016	South Africa	2011 2014	Regional Hospital	HIV+ and HIV- women with birth outcomes recorded, delivering a neonate >500g	9847	PTD (<37 weeks); mod PTD (<34 week) LBW (<2500g); VLBW (<1500g) SGA (definition NR)
Nlend	2016	Cameroon	2008 - 2011	PMTCT Programme (Referral Hospital)	HIV+ women, initiating ART, singleton birth	760	PTD (<37 weeks) LBW (<2500g)

*total population includes both HIV-infected (HIV+) and HIV-uninfected women (HIV-)

Preconception ART – ART initiated before conception, Initiating ART – initiated ART during pregnancy, PHC – primary health care, pp – postpartum, HEU – HIV exposed uninfected infant, VPTD – very PTD, EPTD – extremely PTD, VLBW – very LBW, SSGA – severe SGA, mod SGA – moderate to severe SGA

Table 2a. Key features of quality of included studies (2008-2013)

Study	Study Design	Data Collection	Comparison Groups	Regimen/Exposure	Outcomes Assessment
Ekouevi	Repeated Cross-sectional	NR	▪ PMTCT group vs ART group ▪ PMTCT group: Monotherapy vs Dual Therapy ▪ ART group: Preconception vs Initiating	▪ *ART group:* 87% ZDV+3TC+NVP ▪ *PMTCT group:* 54% scZDV; %NR sc(ZDV+3TC)	NR
Olabuji	Matched Case-Control	NR	▪ HIV+ (on ART) vs HIV-	▪ NR	NR
Kesho Bora	RCT	Study Measures (visits every 2 weeks until delivery)	▪ ART Group vs Monotherapy Group	▪ *ART group:* ZDV+3TC+LPV/r ▪ *Monotherapy group:* scZDV	SFH and LMP, US (when available) (Study Clinicians)
Van der Merwe	Retrospective Observational Cohort	Data Abstraction	▪ ART unexposed (no antenatal ARVs) ▪ ART exposed: Initiated <28 weeks (early) vs Initiated ≥28 weeks (late)	▪ *Clinic 1:* d4T +3TC+ LPV/r ▪ *Clinic 2:* d4T+3TC+ NVP ▪ Preconception ART regimen continued; EFV-based switched to PI-based if <1st trimester	US (when available), LMP and SFH (Obstetric Record)
Powis	RCT (Retrospective Analysis)	Study Measures	▪ Initiated ART (regimens compared)	▪ 51% ABC+ZDV+3TC; 49% ZDV+3TC+LPV/r	LMP and US (Study Clinicians)
Marazzi	Retrospective Observational Cohort	Data Abstraction	▪ ART duration (None vs 0-30days vs 31-90days vs >90days)	▪ *Lifelong ART:* d4T-based/ZDV based ▪ *Stopped 6mo pp*: d4T-based/ZDV based	SFH and LMP (Obstetric Record)
Ekouevi	Retrospective Observational Cohort	Data Abstraction	▪ Preconception ART: EFV-based vs NVP-based	*2 drugs associated with EFV or NVP:* ▪ 60% ZDV+3TC; 37% d4T+3TC; 2% TDF+FTC; 1% DDI+d4T	LMP or US (when available) (Obstetric Record)
Chen	Retrospective Observational Cohort	Data Abstraction	▪ HIV + vs HIV- ▪ Preconception ART vs ALL other HIV+ ▪ Initiated ART vs scZDV (≤34 weeks) ▪ Preconception ART vs Initiated ART	▪ 87% ZDV+3TC+NVP; 9% ZDV+3TC+LPV/r; 4% Other (NR)	LMP - if unknown/discordant with SFH, US used (Obstetric Record)
Anji	Retrospective Observational Cohort	Data Abstraction	▪ Preconception ART ▪ Initiated ART (<1st trimester)	▪ *Preconception:* 96% NNRTI-based; 4% PI-based ▪ *Initiated:* 95% NNRTI-based; 5% PI based	NR
Kebede	Retrospective Observational Cohort	Data Abstraction (Delivery Record and PMTCT Record)	▪ No ARVs ▪ PMTCT Group ▪ ART Group	▪ NR	LMP, SFH and US (when available) (Obstetric Record)
Koss	RCT (Secondary Analysis)	Study Measures	▪ *Initiated ART:* LPV/r based vs EFV-based	▪ 50% ZDV+3TC+LPV/r; 50% ZDV+3TC+EFV	LMP GA used if concordant with US GA. US used if LMP and US discordant (Study Staff)

Study Measures – study visits with questionnaires, anthropometric measurements and specimen collection
Preconception ART – ART initiated before conception, Initiating ART – initiated ART during pregnancy, ART group - >3 antiretroviral drugs, PMTCT - <3 antiretroviral drugs, pp – postpartum, NR - not reported

Table 2b. Key features of quality of included studies (2014-2016)

Study	Study Design	Data Collection	Comparison Groups	Regimen/Exposure	Outcomes Assessment
Nlend	Nested Cross-sectional	Data Abstraction (PMTCT Registers)	▪ Preconception ART vs Initiated ART ▪ *Initiated ART:* <28 weeks (early) vs ≥28 weeks (late)	▪ *Preconception group:* 68% ZDV+3TC+NVP; 14% ZDV+3TC+EFV; 10% TDF+3TC+NVP; 4% TDF+3TC+EFV; 4% PI-based ▪ *Initiated group:* 64% ZDV+3TC+NVP; 26% ZDV+3TC+EFV; 4% TDF+3TC+NVP; 4% PI-based	LMP (Obstetric Record)
Lui	Prospective Cohort	Study Measures and Data Abstraction	▪ South African women (high risk) ▪ Zambian women (low risk)	▪ d4T+3TC+NVP (56% SA; 30% Zam); TDF-based (25% SA; 44% Zam); EFV-based (53% SA; 26% Zam); PI-based (8% SA; 2% Zam)	LMP (Zambia); US (South Africa)
Li	Prospective Observational Cohort	Study Measures	▪ ZDV vs Preconception ART ▪ ZDV vs Initiated ART ▪ ZDV vs Preconception ART vs Initiated ART	▪ 80% ZDV+3TC+NVP; 11% d4T+3TC+NVP; 3% ZDV+3TC+EFV; 6% Other (NR)	LMP and SFH (Study Clinician)
Bisio	Retrospective Observational Cohort	Data Abstraction	▪ *Preconception ART:* EFV-based vs non-EFV based	▪ 81% non EFV-based (ZDV+3TC+NVP and d4T+3TC+NVP); 19% EFV-based (ZDV+3TC+EFV and d4T+3TC+EFV)	LMP and US (when available) (Obstetric Record)
Bengtson	Retrospective Observational Cohort	Data Abstraction (Zambia Electronic Perinatal Record System and Maternity Registers)	▪ *Duration of ART (Initiated):* Never Initiated vs ≤8 weeks vs 9-20 weeks vs 21-36 weeks	▪ Regimen data not available (recommended 1st line NNRTI-based ▪ *Never Initiated:* ZDV (with or without sdNVP)	<20 weeks: LMP >20 weeks: both LMP and SFH
Fowler	Open label RCT	Study Measures (antenatal visits 2, 4, 8, 12 weeks and then every 4 weeks till delivery)	▪ Initiated scZDV vs ZDV-based ART vs TDF-based ART ▪ ZDV-based ART vs TDF-based ART	▪ ZDV + sdNVP + (TDF+FTC) ▪ ZDV +3TC + LPV/r ▪ TDF + FTC + LPV/r	Ballard Score or Obstetric Estimate (Obstetric Record)
Zash	Retrospective Observational Cohort	Data Abstraction	▪ *Initiated:* TDF+3TC+EFV vs scZDV vs Other ART ▪ *Initiated:* TDF+3TC+EFV vs Other ART ▪ *Preconception:* TDF+3TC+EFV vs Other ART	▪ *ARVs initiated:* ZDV+3TC+NVP; ZDV+3TC+LPV/r; TDF+FTC+NVP	LMP, SFH and US (occasionally used if LMP unknown)
Moodley	Cross-sectional	Data Abstraction	▪ HIV+ vs HIV- ▪ No ARV vs Monotherapy vs ART	▪ ZDV + sdNVP ▪ *ART:* d4T+3TC+NVP; TDF+FTC+EFV	NR
Nlend	Comparative Cross-sectional	Data Abstraction (PMTCT Registers)	▪ ART group ▪ Monotherapy group	▪ *ART group:* 98% NNRTI-based; 2% PI-based	LMP and SFH, and US (when necessary) (Obstetric Record)

Study Measures – study visits with questionnaires, anthropometric measurements and specimen collection
Preconception ART – ART initiated before conception, Initiating ART – initiated ART during pregnancy, ART group - >3 antiretroviral drugs, PMTCT - <3 antiretroviral drugs, pp – postpartum, NR - not reported

Table 3a. Key findings from included studies (2008–2013)

Study	Key Finding
Ekouevi	▪ ART (vs scZDV/ZDV+3TC) had a higher proportion of LBW (22% vs 12%). This did not vary by PMTCT subgroup or by timing of ART initiation ▪ ART (vs scZDV/ZDV+3TC) had similar rates of VLBW ▪ Preconception ART (vs Initiated ART) had similar rates of LBW (20.5% vs 21.5%) and VLBW
Olabuji	▪ HIV+ on ART (vs HIV-) had increased risk of PTD (OR 2.89, 95% CI 1.2 – 7.0) and LBW (OR 5.43, 95% CI 2.4 – 12.0)
Kesho Bora	▪ ART (vs scZDV) no difference in prevalence of PTD (13% vs 11%) ▪ ART (vs scZDV) slight difference in prevalence of LBW (11% vs 7%)
Van der Merwe	▪ ART-unexposed (vs early ART-exposed vs late ART-exposed) (27% vs 23% vs 19%) ▪ ART exposure (vs ART-unexposed) had increased risk of PTD (15% vs 5%) ▪ Early NVP-based and EFV-based (vs ART-unexposed) had increased risk of PTD (AOR 5.4, 95% CI 2.1 - 13.7 and AOR 5.6, 95% CI 2.1 - 15.2 respectively)
Powis	▪ PI group (ZDV+3TC+LPV/r) (vs NRTI group (ABC+ZDV+3TC)) rates of PTD (21.4% vs 11.8%) ▪ PI group (ZDV+3TC+LPV/r) (vs NRTI group (ABC+ZDV+3TC)) increased risk of PTD (OR 2.03, 95% 1.26 - 3.27)
Marazzi	▪ At least 90days ART (vs No ART) was protective of PTD (OR 0.15, 95% CI 0.14 – 0.19) ▪ LBW not associated with ART duration
Ekouevi	▪ EFV-based ART (vs NVP-based ART) had no increased risk of PTD (9.5% vs 12.7%) ▪ EFV-based ART (vs NVP-based ART) had no increased risk of LBW (17.2% vs 24.2%) ▪ EFV-based ART (vs NVP-based ART) similar proportion of miscarriages and stillbirths
Chen	▪ Maternal HIV was significantly associated with PTD and SGA ▪ Preconception ART (vs other HIV+ women) had higher odds of PTD (AOR 1.2, 95% CI 1.1 - 1.4) and SGA (AOR 1.8, 95% CI 1.6 - 2.1) ▪ ART initiated during pregnancy (vs scZDV) had higher odds of PTD (AOR 1.4, 95% CI 1.2 - 1.8) and SGA (AOR 1.5, 95% CI, 1.2 - 1.9) ▪ Preconception ART (vs Initiated ART <34v, no events before 34wks) had higher odds of SGA (AOR 1.3, 95% CI 1.0 - 15)
Anji	▪ Preconception ART (vs Initiated ART) PTD rates did not differ significantly (21% vs 24%) ▪ Preconception ART (vs Initiated ART) LBW rates did not differ significantly (21% vs 24%)
Kebede	▪ ARV exposed (ART and scZDV) (vs untreated) had lower risk of PTD (12% vs 24%) ▪ ART initiated during pregnancy (vs preconception ART) increased risk of PTD (AOR 1.82, 95% 1.02 - 3.81) ▪ ART exposed (vs ART-unexposed) had higher prevalence of LBW (39% vs 6%) ▪ ART exposed (vs ART-unexposed) increased risk of LBW (AOR 8.24, 95% CI 2.53 - 14.34)
Koss	▪ LPV/r-based ART (vs EFV-based ART) had similar rates of PTD (14.7% vs 16.2%) ▪ LPV/r-based ART (vs EFV-based ART) had no increased risk of PTD (OR 1.12, 95% CI 0.63 – 2.0)

Preconception ART – ART initiated before conception, Initiating ART – initiated ART during pregnancy

Table 3b. Key findings from included studies (2014–2016)

Study	Key Finding
Nlend	▪ Preconception ART (vs Initiated ART) similar rates of PTD (8.1% vs 10.1%) ▪ Among initiated ART: early ART (vs late ART) had similar rates of PTD (10.9% vs 9%) ▪ Preconception ART (vs Initiated ART) similar rates of LBW (11.7% vs 11.6%) ▪ Among initiated ART: early ART (vs late ART) had higher odds of LBW (AOR 1.87, 95% CI 1.02 - 3.44)
Lui	▪ Zambian women (vs South African women) had higher rates of PTD (29.7% vs 18.4%) ▪ Zambian women (vs South African women) had higher rates of LBW (18.1% vs 15.5%)
Li	▪ Preconception ART (vs ZDV) higher risks of PTD (ARR 1.24, 95% CI 1.05 – 1.47) and VPTD (ARR 1.42, 95% CI 1.02 – 1.919) ▪ ART initiated during pregnancy (vs ZDV) associated with higher risk of SSGA (RR 1.47, 95% CI 1.09 – 1.98) ▪ ART initiated during pregnancy (RR 1.31, 95% CI 1.04 – 1.65) and preconception ART (RR 1.34, 95% CI 1.05 – 1.71) (vs ZDV) higher risk of LBW ▪ Preconception ART (vs ART initiated during pregnancy) associated with higher risks of PTD (RR 1.37, 95% CI 1.13 – 1.67) and VPTD (RR 1.65, 95% CI 1.12 – 2.43) but not SGA
Bisio	▪ EFV-based ART (vs non EFV-based ART) had no increased risk of PTD (13% vs 10%) ▪ EFV-based ART (vs non EFV-based ART) had increased risk of LBW in term deliveries (33% vs 16%) ▪ EFV-based ART (vs non EFV-based ART) had increased risk of composite adverse birth outcomes (49% vs 28%)
Bengtson	▪ Initiated ART (different durations) (vs never initiated (ZDV (with or without sdNVP)/sdNVP/unknown)) no increased risk of LBW among term infants. ▪ Initiated ART 1-8 weeks (vs never initiated) (RR 1.22, 95% CI 0.77 - 0.91) ▪ Initiated ART 9-20 weeks (vs never initiated) (RR 1.23, 95% CI 0.82 - 1.83) ▪ Initiated ART 21-36 weeks (vs never initiated) (RR 0.87, 95% CI 0.22 - 3.46)
Fowler	▪ Both ART arms (vs scZDV) had higher prevalence of composite adverse birth outcomes: ZDV-based ART (40% vs 28%) and TDF-based ART (35% vs 27%) ▪ ZDV-based ART (vs scZDV) had higher prevalence of PTD (20.5% vs 13.1%) and TDF-based ART had higher prevalence of VPTD (6.0% vs 2.6%) ▪ Both ART arms (vs scZDV) had higher prevalence of LBW: ZDV-based ART (23.0% vs 12.0%) and TDF-based ART (16.9% vs 8.9%) ▪ ZDV-based ART (vs TDF-based ART) no differences in adverse events
Zash	▪ Initiated ART (TDF+FTC+EFV) (vs ZDV/other ART) had decreased risk of any adverse birth outcome (AOR 0.4, 95% CI 0.3 - 0.6) ▪ Initiated ART (TDF+FTC+EFV) (vs ZDV/other ART) had decreased odds of SGA infants (AOR 0.4, 95% CI 0.2 - 0.7) and no increased risk of PTD (AOR 0.7, 95% CI 0.5 - 1.1) ▪ Preconception ART (TDF+FTC+EFV) (vs Other ART) reduced overall adverse birth outcomes (33% vs 51%) and SGA (8% vs 24%)
Moodley	▪ HIV+ on ART (vs HIV-) had increased risk of PTD (AOR 1.26, 95% CI 1.14 - 1.4), LBW (AOR 1.26, 95% CI 1.11 - 1.43) and SGA (AOR 1.15, 95% CI 0.98 - 1.35) ▪ ART (TDF+FTC+EFV) (vs no ARVs) had decreased risk of PTD (OR 0.31, 95% CI 0.11 - 0.9) and LBW (OR 0.12, 95% CI 0.04 - 0.37)
Nlend	▪ Initiated ART (vs ZDV) had no increased risk of PTD (AOR 1.9, 95% CI 0.9 - 3.7) ▪ Initiated ART (vs ZDV) had increased risk of LBW (AOR 1.7, 95% CI 1.0 - 2.9)

Preconception ART – ART initiated before conception; Initiating ART – initiated ART during pregnancy

Table 4. Summary of exposure groups of the included studies

Study	HIV-infected vs HIV-uninfected	HIV-infected women Only							
		ART vs Other (Mono and/or Dual Therapy)					ART only		
		Untreated vs ART	Untreated vs Monotherapy /ART	Untreated vs Monotherapy vs ART	Monotherapy vs ART	Mono/Dual Therapy vs ART	Preconception ART	Initiated ART	Preconception ART vs Initiated ART
Ekouevi						✓			✓
Olabuji	✓								
Kesho Bora					✓				
Van der Merwe						✓			
Powis								✓	
Marazzi		✓							
Ekouevi								✓	✓
Chen	✓				✓				
Anji									✓
Kebede				✓					✓
Koss								✓	
Nlend									✓
Lui							✓		
Li			✓		✓				
Bisio							✓		
Bengtson					✓				
Fowler					✓			✓	
Zash	✓				✓		✓		
Moodley	✓			✓	✓				
Nlend					✓				

SECTION C: MANUSCRIPT

Title

Antiretroviral therapy use during pregnancy and adverse birth outcomes in South African women

Authors

Thokozile R Malaba[1,2] *§

Affiliations

1. Division of Epidemiology and Biostatistics, School of Public Health and Family Medicine, University of Cape Town, South Africa
2. Centre for Infectious Disease Epidemiology and Research, School of Public Health and Family Medicine, University of Cape Town, South Africa

Corresponding Author (*)

Thokozile R Malaba, Division of Epidemiology & Biostatistics, School of Public Health & Family Medicine, Falmouth Building, University of Cape Town Faculty of Health Sciences, Anzio Road, Observatory, Cape Town, South Africa, 7925; Tel: +27 21 406 6713; Email: thoko.malaba@uct.ac.za

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ABSTRACT

Background

Studies of antiretroviral therapy (ART) use during pregnancy in HIV-infected women have suggested that ART exposure may be associated with adverse birth outcomes. However there are few data from sub-Saharan Africa where HIV is most common, and few studies involving the World Health Organization's (WHO) recommended first-line regimens.

Methods

We enrolled consecutive HIV-infected pregnant women and a comparator cohort of uninfected women at a primary-level antenatal care facility in Cape Town, South Africa. Gestational assessment combined clinical history, examination and ultrasonography; outcomes included preterm (PTD), low birthweight (LBW) and small for gestational age (SGA) deliveries. In analysis we compared birth outcomes between HIV-infected and -uninfected women, and HIV-infected women who initiated ART before versus during pregnancy.

Results

In 1554 women (mean age 29 years) with live singleton births at time of analysis, 82% were HIV-infected, 92% of received first-line regimen of tenofovir, emtricitabine and efavirenz. Overall, higher levels of PTD (22% vs 13%; odds ratio (OR) 1.94, 95% CI: 1.34, 2.82) and LBW (14% vs 9%; OR 1.62, 95% CI: 1.05, 2.29) were observed in HIV-infected versus uninfected women although SGA deliveries were similar (9% vs 11%; OR 1.06, 95% CI: 0.71, 1.61. Adjusting for demographic characteristics and HIV disease measures, HIV-infected (versus HIV-uninfected) women had persistently increased odds of PTD [adjusted odds ratio (AOR) 2.03; CI 1.33, 3.10]; associations with LBW were reduced (AOR 1.47; CI 0.90, 2.40). Among all HIV-infected women, there appeared to be no association between the timing of ART initiation (before or during pregnancy) and adverse birth outcomes.

Conclusions

These findings suggest that current WHO-recommended ART regimens appear relatively safe in pregnancy, although more data are required to understand the aetiology of preterm delivery in HIV-infected women using ART.

1. BACKGROUND

Use of triple-drug antiretroviral therapy (ART) during pregnancy is the central intervention to promote the health of HIV-infected women and their children. Widespread ART access has significantly reduced the number of new pediatric HIV infections and improved the long-term health of HIV-infected mothers, representing one of the greatest successes of the public health response to the HIV epidemic (1).

However there are persistent questions regarding the potential effects of *in utero* ART exposure. While the association between untreated, advanced HIV disease and adverse birth outcomes is well documented (2, 3), a number of studies have suggested increased levels of preterm delivery (PTD) (4-7), low birthweight (LBW) (8-10), and/or small for gestational age (SGA) (4, 11) deliveries among women receiving ART. Findings vary by the class of antiretroviral agents (ARVs) used with protease inhibitors (PIs) more commonly implicated than nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs respectively) (12-15). However, overall findings for the putative association between antenatal ART use and adverse birth outcomes are highly mixed, with many studies finding no evidence of associations with PTD, LBW and/or SGA (11, 16-21).

With approximately 1.4 million HIV-infected women becoming pregnant annually (22), the possibility of an increased risk of adverse birth outcomes has generated considerable concern. The current evidence base is subject to several notable limitations. Few studies have focused on African populations where most pregnant women using ART live and where rates of PTD are often high (23, 24). In addition most studies investigate ARVs not widely used in low- and middle- income countries (LMIC), and there are few data examining the World Health Organization (WHO) recommended regimen of two NRTIs [tenofovir (TDF) and emtricitabine

(FTC)], with the NNRTI efavirenz (EFV). And while accurate pregnancy dating is critical for defining adverse outcomes in perinatal epidemiology, the quality of gestational dating in the existing literature is variable, and subsequent potential for bias poorly understood. Finally, the choice of comparison groups varies between studies, and in studies without HIV-negative or HIV-infected, ART-unexposed comparator groups it can be difficult to attribute adverse effects to ART exposure rather than HIV disease (8).

Given the large numbers of ART-exposed pregnancies around the world and the conflicting evidence to date, better understandings of the potential associations between commonly used ART regimens, and adverse birth outcomes are critical (25). In particular, with national treatment programmes in high-burden countries implementing a first-line regimen of TDF+FTC+EFV for all HIV-infected women regardless of disease status or CD4 cell count, data on how this regimen may affect major birth outcomes are urgently required. Therefore, we examined the associations between ART use and birth outcomes in a well-characterised cohort of women seeking routine public sector antenatal care Cape Town, South Africa.

2. METHODS

Study Setting

This prospective cohort study was conducted among consecutive HIV-infected and HIV-uninfected women seeking antenatal care (ANC) at a large, community-based public sector primary care facility in Cape Town, South Africa enrolled between April 2013 and August 2015. The facility serves a catchment population of approximately 350,000 where ANC uptake is high (95%); in 2014 the antenatal HIV seroprevalence was estimated at 30% (26).

All women in this setting have gestational age estimated based on last menstrual period (LMP) and symphysis-fundal height (SFH) at the first ANC visit as part of routine clinical care at their first ANC visit.

All women without a previous HIV diagnosis underwent HIV testing, with ART eligibility based on CD4 cell count <350 cells/µl or WHO stage III/IV disease (from April to June 2013) or universal ART eligibility, regardless of CD4 cell count or disease stage (July 2013 onwards). HIV-infected women conceiving while on ART continued their current regimen throughout pregnancy; regimens included PIs (used in this setting predominantly after failure of first-line therapy) or NNRTIs such as EFV or nevirapine (NVP, used in previous first-line regimens). For women initiating ART in pregnancy, a fixed-dose combination of TDF+FTC+EFV was used throughout. Following ART initiation, clinical follow-up was through an integrated primary care service providing antenatal and HIV care.

2.1 Study Procedures

This analysis draws on data from a larger multicomponent study of antiretroviral services for HIV-infected women during pregnancy and postpartum (https://clinicaltrials.gov/ct2/show/NCT01933477) (27). HIV-uninfected women were enrolled consecutively into a separate comparator cohort with identical study procedures. The parent study was reviewed and approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee and Columbia University Medical Center Institutional Review Board. Written informed consent was obtained from all participants at their first ANC visit and this consent included access to their clinical records for this birth outcomes analysis.

Inclusion and Exclusion Criteria

Consecutive women (≥18 years) attending their first antenatal care visit, who were identified as HIV-infected through routine rapid antibody tests were eligible for enrolment into the HIV-infected cohort. Women not eligible for ART at their first ANC visit (receiving ZDV prophylaxis) were excluded from this analysis. For the comparator HIV-uninfected cohort, women were eligible for enrolment based on the same criteria provided a negative test on the same routine rapid antibody test.

Data Collection

All women (HIV-infected and HIV-uninfected) completed questionnaires including demographics, obstetric and medical history. HIV-infected women provided 5mL of blood for viral load (VL) testing using Abbot Realtime HIV-1 assay (Abbot Laboratories, Waltham, MA). At their first visit, an obstetric ultrasound (US) was performed on all women by an experienced research sonographer using a standardised assessment protocol and blinded to other clinical details. Follow-up study interviews, separate from routine clinical care, were scheduled around the second ANC visit, late 3rd trimester and within 7 days postpartum. Obstetric outcomes, including date and mode of delivery and birthweight, were abstracted from obstetric records at delivery facilities.

2.2 Data Analysis

In analysis, gestation was based on completed weeks using the best available measure (US or combination of LMP/SFH at later gestations). HIV/ART status (the exposure of interest) was categorized as (i) HIV-uninfected; (ii) ART initiated before pregnancy; and ART initiated during pregnancy in the (iii) first trimester (<14 weeks), (iv) first half of the second trimester (14-20 weeks), (v) second half of the second trimester (21-27 weeks) or (vi) third trimester (≥28 weeks). Regimens were categorized as either PI or NNRTI;

NNRTI regimens were either EFV-based (TDF+3TC+EFV), NVP-based (TDF+3TC+NVP) or involving other NNRTIs.

All deliveries before September 2015 were included in analysis. PTD was defined as delivery at <37 weeks' gestation, categorized as late preterm (34–37 weeks), moderately preterm (32-34 weeks) or very preterm (<32weeks). LBW was defined as birthweight <2500g and very low birth weight (VLBW) as <1500g. Using the INTERGROWTH-21st Project Standards, infants with birthweights <10^{th} percentile for gestational age were classified SGA; those between 10^{th} - 90^{th} percentile were classified appropriate for gestational age (AGA); and >90^{th} percentile were classified large for gestational age (LGA) (28, 29). Composite pregnancy loss was defined as any loss before delivery, and included ectopic pregnancies as determined by the research sonographer; miscarriages defined as pregnancy loss <28 weeks (30); and stillbirths defined as fetal death occurring before/during labour and delivery (based on a 1-minute APGAR score of 0).

Statistical analyses (STATA 14.0, Stata Corporation, College Station, TX, USA) focused on three exposure comparisons: HIV-infected versus HIV-uninfected women (Comparison A); among HIV-infected women, those initiating ART before pregnancy versus those initiating during pregnancy (Comparison B); and among women initiating ART during pregnancy, comparisons across gestational ages at ART initiation (Comparison C). Pregnancy outcome analyses were restricted to live singleton births. In bivariable analyses, proportions were compared using chi-squared and rank-sum tests. Birth outcomes (PTD, LBW and SGA) were compared using unadjusted and adjusted logistic regression; results are presented as odds ratios (OR) with 95% confidence intervals (CI). Confounders identified *a priori* included age, maternal height, parity and previous PTD; and among HIV-infected women, pre-ART CD4 count and pre-ART VL. Subgroup

analyses involved restrictions by EFV or PI use, and by gestation at first ANC visit. Model fit was assessed using likelihood ratio tests and Akaike's Information Criterion; throughout, statistical tests were 2-sided (alpha=0.05).

3. RESULTS

A total of 1793 women who had delivered at the time of analysis were included: 1494 (83%) HIV-infected and 299 (17%) HIV-uninfected. Among HIV-infected women, 572 (38%) initiated ART before the current pregnancy and 922 (62%) initiated during pregnancy: 186 during the first trimester, 289 during the first half and 256 during the second half of the second trimester, and 191 during the third trimester (Figure 1). TDF+FTC+EFV was the most commonly used regimen and 6% reported PI use.

Table 1 compares demographic and clinical characteristics of women at their first ANC visit. Compared to HIV-uninfected women, women who were HIV-infected were older, less educated, more likely to be unemployed and more likely to have previous adverse birth outcomes, but gestation at first ANC visit did not vary systematically between these groups. Among HIV-infected women, those initiating ART before pregnancy were older and less educated than women initiating during pregnancy. Neither pre-ART CD4 cell count nor pre-ART HIV VL appeared associated with timing of ART initiation in pregnancy among women newly initiating ART.

Figure 1 shows the cohort disposition through delivery. Overall 121 pregnancies (7%) were missing outcome data, principally among those on ART before pregnancy. Following exclusion of 40 twin deliveries and 77 pregnancy losses (4%), 1554 live singleton births were available for analysis. No difference was observed in the composite pregnancy loss outcome by HIV status or timing of ART initiation. HIV-uninfected women experienced a higher proportion of

miscarriages (n=13; 4%) compared to their HIV-infected counterparts (n=25; 2%); while the opposite was observed with stillbirths with HIV-infected women experiencing a higher proportion (n=34; 2%) compared to HIV-uninfected women (n=1; 0.3%) (Figure 1).

3.1 Birth outcomes by HIV/ART status

Comparing outcomes overall between HIV-infected (n=1276) and uninfected (n=278) women (Comparison A), a higher incidence of any PTD (OR 1.94, 95% CI: 1.34, 2.82; 22% vs 13%) and any LBW (OR 1.62, 95% CI: 1.05, 2.29; 14% vs 9%) was observed among the HIV-infected women. SGA deliveries were similar (OR 1.06, 95% CI: 0.71, 1.61; 9% vs 11%) (Figure 2). In both groups, most preterm deliveries were either late (59% and 58%) or moderately preterm (32% and 36%); similarly, most newborns were LBW (87% and 88%) rather than VLBW (Table 2). Following adjustment for age, parity, height and previous PTD, HIV infection was associated with an increased odds of PTD [adjusted odds ratio (AOR) 2.03; 95% CI: 1.33, 3.10] but not LBW (AOR 1.47; 95% CI: 0.90, 2.40) (Table 3).

Among HIV-infected women (comparisons B and C), there was a similar distribution of gestational age and birthweight subgroups, with most being late or moderately preterm and/or LBW (Table 2). Birth outcomes did not vary appreciably in comparison B (initiating ART before pregnancy, n=477 vs. initiating in pregnancy, n=799): PTD (AOR 0.70; 95% CI: 0.45, 1.07); LBW (AOR 0.72; 95% CI: 0.43, 1.21); SGA (AOR 1.05; 95% CI: 0.58, 1.91) (Figure 2; Table 3). Results were similar for comparison C (Figure 2; Table 3). In addition, the findings did not change appreciably when those comparisons were restricted to women who initiated ART after the July 2013 ART eligibility guideline changes.

Among term infants, similar proportions were AGA (87% vs 88%) and SGA (13% vs 12%), comparing those born to HIV-infected and HIV-uninfected women. Likewise, the preterm infants the proportion who were AGA (87% vs 84%) and SGA (13% vs 16%) was similar in the HIV-infected and HIV-uninfected women.

Among normal birthweight infants, the proportions of term SGA were similar in HIV-infected and HIV-uninfected women (6% vs 8%), while differences were observed in the proportions of term AGA (69% vs 76%) and preterm AGA (10% vs 5%). Among the LBW infants, the proportions of term SGA (4% vs 3%), preterm SGA (3% vs 2%) and preterm AGA (8% vs 6%) were similar in the HIV-infected and HIV-uninfected women (Supplemental Figure 1).

Subgroups of antiretroviral agents

Because the associations between ART and birth outcomes may depend on choice of ARV, we carried out the same comparisons restricted to subgroups by antiretroviral agents. The incidence of PTD, LBW and SGA were not appreciably different among women on EFV-based regimens compared to the total HIV-infected sample (Supplemental Table 1). Following adjustment for age, parity, height and previous PTD, HIV infection was associated with an increased odds of PTD (AOR 1.97; 95% CI: 1.27, 3.04) but not LBW (AOR 1.51; 95% CI: 0.91, 2.48). Among HIV-infected women (comparison B), a higher incidence of PTD was observed among women conceiving on EFV-containing regimens (29%) compared to those initiating EFV-containing regimens during pregnancy (21%). This difference in PTD persisted following adjustment for confounders (AOR 0.60; 95% CI: 0.39, 0.94) (Supplemental Table 2). When comparisons were restricted to women initiating ART in pregnancy (comparison C), no differences were observed.

When analysis was restricted to women on PI-based regimens, a higher incidence of PTD (34% vs 13%) was observed in the HIV-infected (n=29) compared to HIV-uninfected women (n=278) (Supplemental Table 3). This incidence in women on PI-based regimens (34%) was higher than that observed in HIV-infected women in the unrestricted (22%) and EFV-based analyses (23%). In multivariable analysis, HIV infection was associated with an increased odds of PTD (AOR 4.46; 95% CI: 1.55, 12.83) but not LBW or SGA (Supplemental Table 4). When women on PI-based regimens were compared to women on any NNRTI regimens, a higher incidence of PTD in women on PI-based regimens was noted (36% vs 24%) (Supplemental Table 5).

Subgroups by gestation at first ANC visit

When analysis was restricted to women who entered ANC before 20 weeks gestation in whom gestational estimation is likely to be most accurate, results for each comparison mirrored those of the main analysis. A higher incidence of PTD (22% vs 9%) and LBW (15% vs 7%) was observed in HIV-infected (n=582) compared to HIV-uninfected women (n=128) while the frequency of SGA deliveries (12% vs 11%) was similar (Supplemental Table 6). In multivariable analysis, HIV infection was associated with an increased odds of PTD (AOR 2.75; 95% CI: 1.38, 5.48) (Supplemental Table 7), however the association with LBW (AOR 2.19; 95% CI: 0.97, 4.94) did not persist. Among HIV-infected women there were no differences observed between women initiating ART before pregnancy compared to those initiating during pregnancy (comparison B). Similarly when comparisons were restricted to women initiating ART in pregnancy (comparison C), no differences were observed between groups.

4. DISCUSSION

In this cohort of HIV-infected and -uninfected pregnant women seeking ANC at a large South African public sector primary care facility, PTD appeared consistently associated with HIV infection and ART use, with HIV-infected women receiving ART approximately twice as likely to deliver preterm compared to HIV-uninfected women. We found few appreciable differences in adverse birth outcomes between women initiating ART during pregnancy versus those initiating ART before pregnancy , though in subgroup analyses restricted to EFV-based regimens PTD appeared to be more likely in women conceiving on ART compared to those initiating during pregnancy.

Our finding for a higher frequency of PTD in HIV-infected women regardless of timing of ART use is consistent with several previous studies from African populations as well as from high-income countries (4, 17, 20). However the PTD incidence among both HIV-infected (22%) and HIV-uninfected (13%) women observed here is higher than previous estimates for South Africa (approximately 10%) (31). These results raise concern as PTD is the most common cause of neonatal morbidity and mortality globally (32), particularly in LMICs (4, 33). Nonetheless, a larger proportion of our PTDs occurred later in gestation (>32weeks), which is somewhat reassuring (24, 34).

We did not observe any differences in the proportions of term or preterm SGA or any significant associations with SGA across any of the three major analytic comparisons. The lack of association between HIV status and SGA is different from a study in Botswana during the NVP-based ART era (4); however our findings were similar to those from another recent study in Botswana which evaluated TDF+FTC+EFV (11). In LMIC, SGA is usually a result of intrauterine growth restriction (IUGR) which leads to LBW as opposed to being normally grown but small

because of PTD (constitutionally small) (35). IUGR in these settings tends to be caused by extrinsic factors and is late onset (>32 weeks) (36); given our higher frequency of late PTD (34-37 weeks), our SGA findings could be a result of a reduction in the time for the effects of late onset growth restriction to take place because of earlier delivery. Consequently any reductions in birthweight would be insufficient to achieve the definition of SGA.

Overall among all HIV-infected women, we found that timing of initiation of widely used NNRTI-based regimens, before or during pregnancy, was not associated with adverse birth outcomes (PTD, LBW and SGA). A study in Cameroon came to similar conclusions in terms of PTD (19), however our overall results differ from a number of previous studies that have demonstrated an increased risk of PTD and/or LBW either in women initiating ART before pregnancy (9, 37); or in women initiating during pregnancy (5). There are concerns that previous studies comparing timing of ART initiation and adverse birth outcomes did not take into account gestational age at ART initiation, as women initiating ART later in pregnancy do not have equal opportunity to experience different outcome compared to those who initiated earlier or before pregnancy. As part of our subgroup analyses we restricted the analysis to women who initiated before 26 weeks and those who experienced an outcome after 26 weeks; these results were similar to the results of the overall analysis.

One explanation for the lack of associations observed in our study could be the relatively high overall incidence of PTD (22%), possibly obscuring a weak signal for increased adverse birth outcomes among the women who initiated ART earlier during pregnancy. It should be noted that in subgroup analyses, when restricted to EFV-based regimens women who initiated ART before pregnancy were at increased risk of PTD compared to those initiating during pregnancy which is consistent with previous studies which demonstrated an increased risk of PTD and/or LBW in women on ART initiated before pregnancy (9, 37). Given missing regimen data,

particularly among younger women, this subgroup analysis requires cautious interpretation given that previous studies have shown that differences in birth outcomes between initiating ART before pregnancy compared to those initiating during pregnancy may be largely attributable to differences in other risk factors for adverse outcomes such as gravidity (4) and maternal age.

Despite the global use of TDF+FTC+EFV, few studies to date have investigated the effect of this regimen in pregnancy on birth outcomes. Our results are consistent with a recent study of a national program using this regimen in Botswana (11) suggesting this regimen is unlikely to worsen rates of adverse birth outcomes. Despite observing no overall differences in adverse birth outcomes by timing of ART initiation or with NNRTI use, there is some suggestion in these results of increased risk linked to the use of PI-based regimens consistent with previous studies (14, 38). PIs may cause increased adverse birth outcomes via mechanisms related to interference with the adrenal system, implicated in the spontaneous onset of labor (15), and/or reductions in progesterone levels during pregnancy which could affect fetal growth (39). To investigate this potential effect here, we compared women using PI-based to those using NNTRI-based regimens and found a similarly increased risk of PTD among women using PI-based regimens, albeit with limited precision.

We found notable differences in miscarriages and stillbirths between HIV-infected and HIV-uninfected women. Stillbirths appeared more likely among HIV-infected women, consistent with a meta-analysis demonstrating a nearly fourfold increase in stillbirths among HIV-exposed pregnancies (3). Conversely, miscarriage appeared more likely in the HIV-uninfected women than HIV-infected women, a finding that is unexpected given that HIV status is often associated with early pregnancy loss (3). In considering the latter finding, it is critical to note that these data – with enrolment of women as they present for routine care at a range of gestations – are

not ideal for examining early pregnancy loss, and in turn, this finding should be approached with caution.

Interpretation of these data requires consideration of several strengths and limitations. This study of a public sector primary care population allowed examination of the impact of ART initiation across a range of gestations, compared to clinical trials where gestation at ART initiation is often fixed. Furthermore, the observational nature of our study provides good external validity of experiences in pregnancy. These results are also substantially strengthened by the use of high quality measures of gestation (40), which contrasts with the reliance on SFH and/or LMP throughout previous analyses. Ultrasonography for gestational age determination has been shown to be highly reproducible up to early second trimester (40). Since we enrolled women entering ANC throughout pregnancy we conducted sub analyses restricted to women entering ANC <20 weeks which did not affect our findings. A major limitation of our study is that our sample size is limited for certain subgroup analyses (including by ART regimen). We were also unable to directly measure birthweight and relied on data abstraction from routine records; although this approach is widely used in research, it may contribute to random measurement error, potentially attenuating findings for LBW and SGA outcomes. In addition, we had missing regimen data for women initiating ART before pregnancy; this is a result of the design of the parent study that collected less information on these women compared to those initiating during pregnancy.

This research focuses on widely used NNRTI-based regimens which include TDF+FTC+EFV, the first-line regimen currently recommended by the WHO and the most commonly used combination of antiretroviral drugs globally. However as new antiretroviral agents become more widely available it will be critical to continue to evaluate birth and long term outcomes associated with *in utero* ART exposure. This includes both ongoing epidemiological research as

well as investigations of the pathophysiologic mechanisms that may lead HIV infection and/or antiretroviral use to cause prematurity and/or growth restriction.

In summary, with the large and rapidly increasing number of HIV-infected taking ART during pregnancy around the world, our study suggests that current NNRTI-based regimens are unlikely to further increase adverse birth outcomes. However, given the limited data on TDF+FTC+EFV, and the results of the EFV-based subgroup analyses, more studies investigating this regimen according to timing of ART initiation is required in representative cohorts. These data highlight the high incidence of PTD among HIV-infected women on ART, pointing to a significant public health problem and an important consideration for the long-term health of HIV-exposed infants and children globally.

Acknowledgements

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Key Messages

- Several studies have suggested that antiretroviral therapy (ART) use in pregnancy may contribute to adverse birth outcomes but there are few data from sub-Saharan Africa where HIV is most prevalent.
- In this cohort of 1554 women enrolled in routine public sector care in Cape Town, HIV-infected women had higher incidence of adverse birth outcomes (preterm and low birth weight delivery) compared to HIV-uninfected women. There appeared to be no associations between the timing of antiretroviral initiation before or during pregnancy and birth outcomes, although some of the comparisons may have been limited by lack of power.
- While these data suggest that first-line ART regimens (TDF+FTC+EFV) appear to be safe during pregnancy, the high incidence of preterm delivery among HIV-infected women on ART remains a significant public health problem.

6. REFERENCES

1. Abrams EJ, Myer L. Can we achieve an AIDS-free generation? Perspectives on the global campaign to eliminate new pediatric HIV infections. J Acquir Immune Defic Syndr. 2013;63(Suppl 2):S208-12.
2. Rollins NC, Coovadia HM, Bland RM, et al. Pregnancy outcomes in HIV-infected and uninfected women in rural and urban South Africa. J Acquir Immune Defic Syndr. 2007;44(3):321-8.
3. Brocklehurst P, French R. The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis. BJOG. 1998;105(8):836-48.
4. Chen JY, Ribaudo HJ, Souda S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. J Infect Dis. 2012;206(11):1695-705.
5. Short CE, Douglas M, Smith JH, Taylor GP. Preterm delivery risk in women initiating antiretroviral therapy to prevent HIV mother-to-child transmission. HIV Med. 2014;15(4):233-8.
6. Thorne C, Patel D, Newell ML. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. AIDS. 2004;18(7):2337-9.
7. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. AIDS. 2007;21(8):1019-26.
8. Ekouevi DK, Coffie P, Becquet R, et al. Antiretroviral therapy in pregnant women with advanced HIV disease and pregnancy outcomes in Abidjan, Cote d'Ivoire. AIDS. 2008;22(14):1815–20.
9. Li N, Sando MM, Spiegelman D, et al. Antiretroviral therapy in relation to birth outcomes among HIV-infected women: a cohort study. J Infect Dis. 2016;213:1057–64.
10. Tuomala RE, Shapiro DE, Mofenson LM, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. N Engl J Med. 2002;364(24):1863-70.

11. Zash R, Souda S, Chen JY, et al. Reassuring Birth Outcomes with Tenofovir/Emtricitabine/Efavirenz used for Prevention of Mother to Child Transmission of HIV in Botswana. J Acquir Immune Defic Syndr. 2016;71(4):428-36.

12. Grosch-Woerner I, Puch K, Maier RF, et al. Increased rate of prematurity associated with antenatal antiretroviral therapy in a German/Austrian cohort of HIV-1-infected women. HIV Med. 2008;9(1):6-13.

13. Martin F, Taylor GP. Increased rates of pre-term delivery are associated with the initiation of highly active antiretroviral therapy during pregnancy: a single centre cohort study. J Infect Dis. 2007;196(4):558–61.

14. Powis KM, Kitch D, Ogwu A, et al. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based ART during pregnancy. J Infect Dis. 2011;204(4):506-14.

15. Sibiude J, Warszawski J, Tubiana R, et al. Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost? Clin Infect Dis. 2012;54(9):1348-60.

16. Bengtson AM, Chibwesha CJ, Westreich D, et al. Duration of cART Before Delivery and Low Infant Birthweight Among HIV-Infected Women in Lusaka, Zambia. J Acquir Immune Defic Syndr. 2016;71(5):563-9.

17. Boer K, Nellen JF, Patel D, et al. The AmRo study: pregnancy outcome in HIV-1-infected women under effective highly active antiretroviral therapy and a policy of vaginal delivery. BJOG. 2007;114(2):148-55.

18. Kesho Bora Study Group. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. Lancet Infect Dis. 2011;11(3):171-80.

19. Njom Nlend A, Nga Motazé A, Moyo Tetang S, Zeudja C, Ngantcha M, Tejiokem M. Preterm Birth and Low Birth Weight after In Utero Exposure to Antiretrovirals Initiated during Pregnancy in Yaoundé, Cameroon. PLoS One. 2016;11(3):e0150565.

20. Olagbuji BN, Ezeanochie MC, Ande AB, Oboro VO. Obstetric and perinatal outcome in HIV positive women receiving HAART in urban Nigeria. Arch Gynecol Obstet. 2010;281(6):991-4.

21. Tuomala RE, Watts DH, Li D, et al. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. J Acquir Immune Defic Syndr. 2005;38(4):449-73.

22. WHO. Prevent HIV, test and treat all - WHO support for country impact. Progress Report 2016. http://apps.who.int/iris/bitstream/10665/251713/1/WHO-HIV-2016.24-eng.pdf?ua=1 (accessed 30 November 2016)

23. Beck S, Wojdyla D, Say L, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ. 2010;88:31-8.

24. Blencowe H, Cousens C, Chou D, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health. 2013;10(1):1.

25. Watts DH, Mofenson LM. Antiretrovirals in pregnancy: a note of caution. J Infect Dis. 2012;206(11):1639-41.

26. Myer L, Phillips TK, Manuelli V, et al. Evolution of antiretroviral therapy services for HIV-infected pregnant women in Cape Town, South Africa. J Acquir Immune Defic Syndr. 2015;69(2):e57–e65.

27. Myer L, Phillips TK, Zerbe A, et al. Optimizing Antiretroviral Therapy (ART) for Maternal and Child Health (MCH): Rationale and Design of the MCH-ART Study. J Acquir Immune Defic Syndr. 2016;72(Suppl 2):S189-S96.

28. Villar J, Ismail LC, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet. 2014;384(9946):857-68.

29. Villar J, Giuliani F, Bhutta ZA, et al. Postnatal growth standards for preterm infants: the Preterm Postnatal Follow-up Study of the INTERGROWTH-21st Project. Lancet Glob Health. 2015;3(11):e681-e91.

30. WHO. Neonatal and perinatal mortality: country, regional and global estimates http://apps.who.int/iris/handle/10665/43444 (accessed 10 February 2017)

31. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832):2162-72.

32. WHO. WHO recommendations on interventions to improve preterm birth outcomes. http://apps.who.int/iris/bitstream/10665/183037/1/9789241508988_eng.pdf (accessed Oct 14, 2016).

33. Katz J, Lee AC, Kozuki N, et al. Mortality risk in preterm and small-for-gestational age infants in low-income and middle-income countries: a pooled country analysis. Lancet. 2013;382(9890):417–25.

34. Howson C, Kinney MV, McDougall L, Lawn JE. Born too soon: preterm birth matters. Reprod Health. 2013;10(1):1.

35. Villar J, Belizán J. The relative contribution of prematurity and fetal growth retardation to low birth weight in developing and developed societies. Am J Obstet Gynecol. 1982;143(7):793-8.

36. Faraci M, Renda E, Monte S, et al. Fetal growth restriction: current perspectives. J Prenat Med. 2011;5(2):31-3.

37. Machado E, Hofer C, Nogueira S, Costa T, Lambert J. Pregnancy outcome in HIV-1-infected women receiving combination therapy prior to conception. Sex Transm Infect. 2009;85(2):82-7.

38. Fowler MG, Qin M, Fiscus SA, et al. Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention. N Engl J Med. 2016;375(18):1726-1737.

39. Papp E, Mohammadi H, Loutfy MR, et al. HIV protease inhibitor use during pregnancy is associated with decreased progesterone levels; a potential mechanism contributing to fetal growth restriction. J Infect Dis. 2015;211(1):10-8.

40. Butt K, Lim K, Bly S, et al. Determination of gestational age by ultrasound. J Obstet Gynaecol. 2014;36(2):171-81.

Figure 1. Birth outcomes by HIV/ART exposure status among women in the cohort

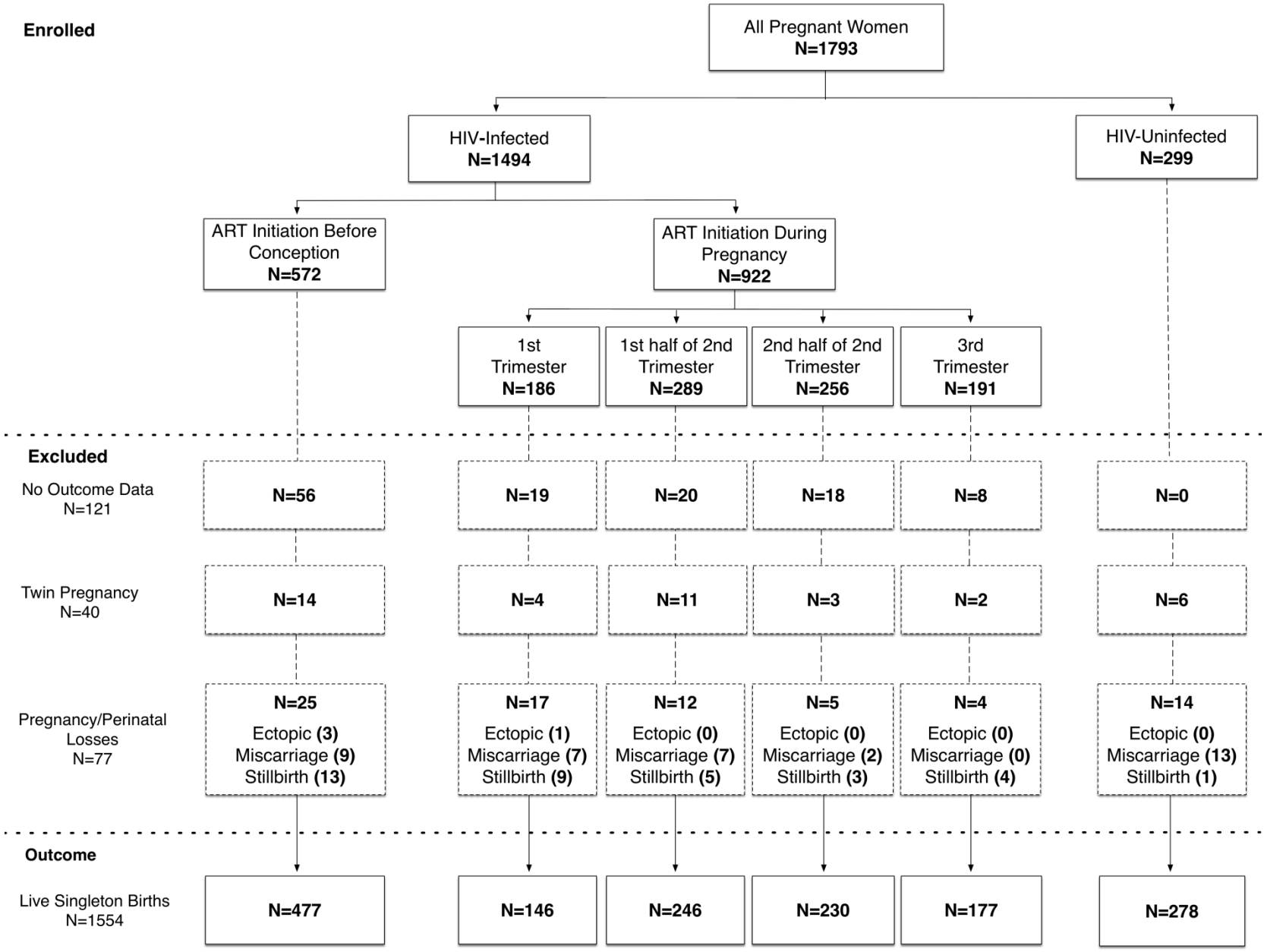


Table 1. Characteristics of pregnant women at 1st antenatal visit stratified by HIV/ART status

	HIV-uninfected N=299	HIV-infected N=1494	HIV-infected					*p-value***
			Initiation before pregnancy N=572	Initiation during pregnancy N=922				
				1st Trimester N=186	1st half of 2nd Trimester N=289	2nd half of 2nd Trimester N=256	3rd Trimester N=191	
Maternal Characteristics								
Age, years								<0.001
≤24	103 (34)	285 (19)	55 (10)	51 (27)	69 (24)	62 (24)	48 (25)	
25-29	84 (28)	472 (32)	152 (27)	72 (39)	107 (37)	72 (28)	69 (36)	
≥30	110 (37)	720 (48)	358 (63)	63 (34)	110 (38)	116 (45)	73 (38)	
Median (IQR)	27 (23-32)	29 (26-34)	31 (28-35)	27 (24-31)	28 (25-32)	29 (25-32)	29 (25-33)	
Education (Finished High School)	119 (40)	402 (27)	127 (22)	60 (32)	90 (31)	78 (30)	47 (25)	<0.001
Employment Status								0.002
Employed	139 (46)	557 (37)	214 (37)	88 (47)	118 (41)	89 (35)	48 (25)	
SES								0.66
Lowest	91 (30)	451 (30)	180 (31)	50 (27)	73 (25)	80 (31)	68 (36)	
Medium	94 (31)	539 (36)	216 (38)	65 (35)	99 (34)	89 (35)	70 (37)	
Highest	95 (32)	504 (34)	176 (31)	71 (38)	117 (40)	87 (34)	53 (28)	
Obstetric Characteristics								
Gestation, weeks								
Median (IQR)	21 (16 – 27)	21 (15-27)	21 (15 – 28)	10 (8-12)	18 (16-19)	24 (22-25)	32 (26-35)	-
Height, cm								0.9
≤155	85 (28)	444 (30)	163 (29)	60 (32)	92 (32)	79 (31)	50 (26)	
156-161	90 (30)	464 (31)	170 (30)	72 (39)	89 (31)	69 (27)	64 (34)	
≥162	73 (24)	353 (24)	142 (25)	33 (18)	68 (24)	59 (23)	51 (27)	
Mean (SD)	158 (8)	158 (7)	158 (7)	158 (7)	157 (7)	158 (7)	158 (6)	
Gravidity								0.005
1	72 (24)	244 (16)	63 (11)	38 (20)	64 (22)	48 (19)	31 (16)	
2	101 (34)	544 (36)	196 (34)	81 (44)	109 (38)	90 (35)	68 (36)	
≥3	14 (47)	706 (47)	313 (55)	67 (36)	116 (40)	118 (46)	92 (48)	
Median (IQR)	2 (2-3)	2 (2-3)	3 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)	
Parity								0.006
0	75 (25)	259 (17)	68 (12)	43 (23)	65 (22)	50 (20)	33 (17)	
1	100 (33)	558 (37)	202 (35)	79 (42)	117 (40)	94 (37)	66 (35)	
≥2	122 (41)	677 (45)	302 (53)	64 (34)	107 (37)	112(44)	92 (48)	
Median (IQR)	1 (0-2)	1 (1-2)	2 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	
Previous Miscarriage*	8 (3)	204 (14)	104 (18)	36 (19)	34 (12)	20 (8)	10 (5)	<0.001
Previous Preterm*	6 (2)	107 (7)	47 (7)	11 (6)	21 (7)	8 (3)	20 (10)	0.001
HIV								
Current ART regimen, self-report								<0.001
TDF-3TC-EFV		1116 (87)	197 (34)	186 (100)	288 (99)	256 (100)	189 (99)	
TDF-3TC-NVP		57 (4)	56 (10)	0	0	0	1 (0.5)	
Other NNRTI-based regimen		72 (6)	71 (12)	0	1 (0.4)	0	0	
PI-based regimen		33 (3)	32 (6)	0	0	0	1 (0.5)	
CD4 cell count, (cells/µL)								0.38
≤ 200		213 (14)	65 (12)	29 (16)	44 (16)	47 (19)	28 (15)	
201-350		426 (29)	167 (30)	52 (29)	90 (32)	70 (28)	47 (26)	
351-500		384 (26)	154 (28)	42 (23)	75 (27)	65 (26)	48 (26)	
>500		423 (28)	167 (30)	58 (32)	72 (25)	67 (26)	59 (31)	
Median (IQR)			396 (271-524)	379 (256 – 552)	361 (246 – 504)	357 (235 – 506)	397 (258-576)	
Median HIV RNA Viral Load (log_{10} copies/ml)		3.35 (1.59-4.25)	1.59 (1.59-1.6)	3.97 (3.41-4.49)	4.12 (3.44-4.12)	3.99 (3.41-4.64)	3.79 (3.18-4.42)	<0.001

*among women with a previous pregnancy

**P values refer to the comparisons across exposure categories: HIV-uninfected, Initiation before pregnancy, Initiation during pregnancy (all four time periods)

All variables, with the exception of height and ART regimen, had <3% missing data. For height, 16% (n=284) of data was missing with similar proportions of missing data across all comparison groups. For ART regimen, 14% (n=216) of data was missing and this was among the women who initiated ART before pregnancy

Table 2. Birth outcomes by HIV/ART status among women with live singleton births (n=1554)

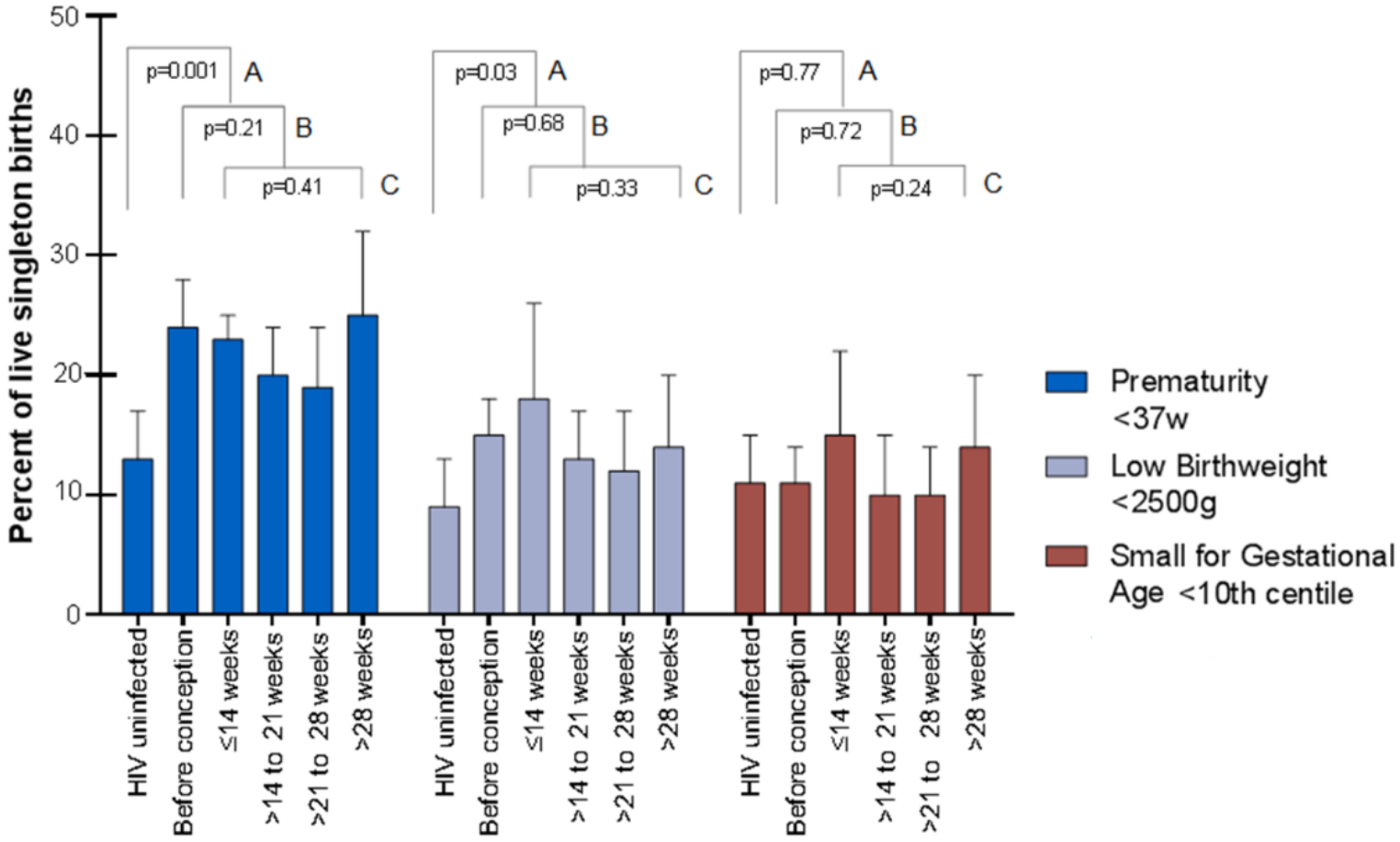
	HIV-uninfected N=278	HIV-infected N= 1276	HIV-infected vs uninfected *p-value*	HIV-infected				ART Initiation Before vs During* *p-value*
				Initiation before pregnancy N=477	ART Initiation during pregnancy N=799			
					1st Trimester N=146	1st half of 2nd Trimester N=246	2nd half of 2nd Trimester N=230	3rd Trimester N=177	
Gestational Age (weeks)			<0.0001						0.001
Term (≥ 37)	242 (87)	986 (78)		358 (75)	111 (76)	197 (80)	187 (81)	133 (75)	
Any Preterm (< 37)	36 (13)	285 (22)		115 (24)	34 (23)	49 (20)	43 (19)	44 (25)	
Late Preterm (34-37)	21 (8)	167 (13)		69 (14)	19 (13)	29 (12)	24 (10)	26 (15)	
Moderately Preterm (32-34)	13 (5)	91 (7)		37 (8)	9 (6)	16 (7)	11 (5)	18 (10)	
Very Preterm (28-32)	2 (0.7)	27 (2)		9 (2)	6 (4)	4 (2)	8 (3)	0	
Birthweight (grams)			0.03						0.68
Normal (≥2500)	252 (91)	1085 (85)		402 (84)	118 (81)	214 (87)	199 (87)	152 (86)	
Any LBW (<2500)	26 (9)	181 (14)		70 (15)	27 (18)	31 (13)	28 (12)	25 (14)	
LBW (2500-1500)	23 (8)	157 (12)		61 (13)	23 (16)	27 (11)	21 (9)	25 (14)	
Very LBW (<1500)	3 (1)	24 (2)		9 (2)	4 (3)	4 (2)	7 (3)	0	
Mean (SD)	3199 (548)	3052 (580)	0.003	3090 (602)	3080 (641)	3120 (533)	3130 (574)	3150 (531)	0.63
Size for Gestational Age (centile)			0.013						0.011
LGA (>90th)	35 (13)	112 (9)		56 (12)	13 (9)	13 (5)	11 (5)	19 (11)	
AGA (10th – 90th)	211 (76)	984 (77)		356 (75)	105 (72)	202 (82)	190 (83)	131 (74)	
SGA (<10th)	31 (11)	112 (9)		53 (11)	22 (15)	25 (10)	22 (10)	25 (14)	

LBW – Low Birthweight, LGA – Large for Gestational Age, AGA – Appropriate for Gestational Age, SGA – Small for Gestational Age

*P values refer to comparisons between women who initiated ART before pregnancy vs during pregnancy (not expanded into the 4 time periods)

All the variables had <4% missing data, with similar proportions of missing data across the comparison groups

Figure 2. Incidence of preterm, low birth weight and small for gestational age deliveries by HIV status and timing of ART initiation before and during pregnancy among 1554 women who had live singleton deliveries



***unadjusted p-values reported**

Table 3. Adjusted associations between HIV/ART status and adverse birth outcomes

Outcome Measure	Comparison A* (Ref category: HIV-uninfected)			Comparison B** (Ref category: Before pregnancy)			Comparison C** (Ref Category: P1: <14weeks)		
		AOR [95% CI]	**P value**		**AOR [95% CI]**	**P value**		**AOR [95% CI]**	**P value**
Preterm Delivery (<37 weeks)	HIV-infected	2.03 (1.33–3.10)	0.001	During pregnancy	0.70 (0.45–1.07)	0.102	P2	0.91 (0.52–1.60)	0.75
							P3	0.79 (0.44–1.42)	0.442
							P4	1.41 (0.79–2.51)	0.244
Low Birth Weight (<2500g)	HIV-infected	1.47 (0.90–2.40)	0.124	During pregnancy	0.72 (0.43–1.21)	0.217	P2	0.70 (0.36–1.35)	0.283
							P3	0.68 (0.34–1.34)	0.264
							P4	1.15 (0.59–2.28)	0.669
Small for Gestational Age(<10th centile)	HIV-infected	0.91 (0.58–1.43)	0.695	During pregnancy	1.05 (0.58–1.91)	0.861	P2	0.77 (0.38–1.56)	0.461
							P3	0.74 (0.35–1.54)	0.414
							P4	1.62 (0.79–3.30)	0.184

Comparison A (HIV-infected vs HIV-uninfected), Comparison B (ART initiated before pregnancy vs ART initiated during pregnancy), Comparison C (ART initiated during pregnancy at 4 time points: P1 (<14 weeks), P2 (14-20 weeks), P3 (21-27 weeks), P4 (>28weeks)

* adjusted for age, maternal height, parity and previous PTD

** adjusted for age, maternal height, parity and previous PTD, CD4 count and VL

SECTION D: APPENDICES

1 QUESTIONNAIRES AND DATA ABSTRACTION FORMS

1A MCH-ART Demographics and Medical History Questionnaire

MCH-ART: Demographics & Medical History, Phase 1
Xhosa-English of Version 3.0, 15 October2013

PID: 1 - __ __ __ __ - __ __

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

Initials of counsellor: _____

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

Initials of counsellor: _____

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

Initials of counsellor: _____

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

Initials of counsellor: _____

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

Initials of counsellor: _____

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

Initials of counsellor: _____

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

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

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

Initials of counsellor: _____

MCH-ART: Maternal adherence Phase 1(women on ART) PID: 1 - __ __ __ __ - __ __
X-E Version 1.0 13 May2013

This CRF is to be completed by women on ART only

		Visit Date: __ __/__ __ __/__ __ __ __
1.	Yintoni igama lamachiza owatyayo? *What are the names of the ARVs you are taking?*	
2.	Ukususela ukuqala kwakho ukutya amachiza, wawuke wawayeka na? *Since you first started taking ART, have you ever stopped?*	Hayi *No* –> SKIP to Q5 Ewe *Yes*
3.	Mangaphi amaxesha uyeka uphinde uqalele ukutya amachiza? *How many times have you stopped and restarted ART?*	Amaxesha: _____ *# times*
4.	Bekunini ukugqibela kwakho ukuqalela amachiza? *When did you restart ART the last time?*	Umhla:___ Inyanga:_____ Unyaka:_____ *Day Month Year*
5.	iART uzithatha kangaphi ngemini? *How many times a day do you take your ART pills?*	Amaxesha: _____ *# of times*
6.	Zingaphi ipilisi ozityayo ngexesha? *How many pills do you take each time?*	# Iipilisi:_____ *# of pills*
7.	Mangaphi amachiza entsholongwane ohlukeneyo owatyayo? *How many different HIV medicines do you take?*	# amchiza:_____ *# of medicines*
8.	Oko waqala ukuwatya,ungazibeka kweliphi inqanaba lokutya ngendlela owawuyibonisiwe yokutya amachiza akho? *Since you started taking them, how would you rate how well you usually do taking your HIV medicines in the way you are supposed to?*	Kakubi kakhulu=1 *Very poor* Kakubi=2 *Poor* Ndiphakathi=3 *Fair* Kakuhle=4 *Good* Kakuhle kakhulu=5 *Very good* Kakuhle okugqithisileyo=6 *Excellent*
9.	Ngoku cinga ngentsuku ezi-30 ezidlulileyo.yeyiphi kwezi zilandelayo echaza eyona ndlela otya ngayo amachiza akho? *Now think about the last 30 days. How would you rate how well you did taking your HIV medicines?*	Kakubi kunakuqala=1 *Worse than usual* Kakuhle kunakuqala=2 *Better than usual* Kuyafana njengesiqhelo=3 *About the same as usual*
10.	Kwintsuku ezi-30 ezidlulileyo,zimini ezingaphi okhe walibala ukutya amchiza akho entsholongwana? *In the last 30 days, on how many days did you miss at least one dose of any of your HIV medicines?*	Intsuku*: _____ (0-30)* *# of days*
11.	Kwezi ntsuku zi-30 zidlulileyo uwatye kakuhle kanjani amachiza akho entsholongwane njengohlobo omele ukuwatya ngalo? *In the last 30 days, how good a job did you do at taking your HIV medicines in the way that you were supposed to?*	Kakubi kakhulu=1 *Very poor* Kakubi=2 *Poor* Ndiphakathi=3 *Fair* Kakuhle=4 *Good* Kakuhle kakhulu=5 *Very good* Kakuhle okugqithisileyo=6 *Excellent*

Initials of counsellor: ___

12.	Kwezi ntsuku zi-30 zidlulileyo,kukangaphi usitya amachiza akho entsholongwane ngendlela omele kuwatya ngayo? *In the last 30 days how often did you take your HIV medicines in the way that you were supposed to?*	Zange=1 *Never* Kumbalwa=2 *Rarely* Ngamanye amaxesha=3 *Sometimes* Ngesiqhelo = 4 *Usually* Malunga lonke ixesha=5 *Almost always* Lonke ixesha=6 *Always*
13.	Kunzima kangakanani ukutya amachiza akho entsholongwana ngendlela omele kukuwatya ngayo? *How hard is it for you to take your HIV medicines in a way you are supposed to?*	Kunzima kakhulu kakhulu=1 *Extremely hard* Kunzima kakhulu=2 *Very hard* Kunzima nje=3 *Somewhat hard* Akunzimanga=4 *Not very hard* Akunzimanga kwaphela =5 *Not hard at all*
14.	Kwintsuku ezi-30 ezidlulileyo ,zeziphi izinto ezibangele ulibale, okanye ezenze kubenzima ukutya amachiza akho? *In the past 30 days which of the following things made you miss a pill or made it hard for you to take your pills?* Zifunde zonke.Urhangqe zonke ezikhe zakwehlele. *Read all. Circle as many as apply.*	a. Bendingekho ekhaya *Was away from home?* b. Zilahlekile *Lost your pills?* c. Bendixakekile ndisenza omnye umsebenzi *Was busy with other things?* d. Ndilibele *Simply forgot?* e. Bezininzi ipilisi ebekufuneka ndizitye *Had too many pills to take?* f. Bendifumana imiphumela *Was getting side effects?* g. Bendibaleka imiphumela okanye ndingaziva mnandi *Wanted to avoid side effects or were feeling bad?* h. Bendizinika ikhefu kwipilisi *Wanted to take a break from the pills?* i. Bendingafuni abanye bazi ukuba nditya ipilisi *Did not want others to notice you taking medication?* j. Kuye kwabakho utshintsho kwindlela endisebenza ngayo okanye ngendlela endiqhele *Had a change in daily routine or work schedule?* k. Bendicinga ukuba ipilisi ziyasebenza noba ezinye andizityanga *Thought that the pills would still work even if*

Initials of counsellor: ___

		a few were missed? l. Bendiba amachiza ayingozi *Felt the drugs were toxic/ harmful?* m. Bendilele ngexesha lokutya ipilisi *Slept through dose time?* n. Ndizive ndingaphilanga *Felt sick or ill?* o. Ziye zandongamela *Felt overwhelmed?* p. Ndive ndino xinezelelo *Felt depressed?*

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

Date of QC: _ _ /_ _ _ / _ _ _ _ Signed Measurement Nurse: _____

Initials of counsellor: ___

MCH-ART data abstraction: Maternity Case records Version 2.0
1 September 2013

Please circle and/complete answers for all questions NR = not recorded NA = not applicable

Demography	
Initials of data abstractor	
Date of data abstraction	*(dd/mm/yyyy*)
MCH-ART number	
Mothers surname	
Mothers date of birth	*(dd/mm/yyyy)*
Mothers provincial folder number	
Gravidity	
Parity	

Previous Pregnancies (per maternity chart)						
Year	**Gestation**	**Delivery**	**Weight**	**Sex**	**Outcome**	**Complications**

Medical & General History						
Hypertension	Epilepsy	Diabetes	Cardiac	TB	Other	Healthy
Details of history:						
Other						

Screening CD4 date - NHLS	
Screening CD4 result - NHLS	
Screening CD4 date – PIMA	
Screening CD4 result - PIMA	
Patient on ART already?	Yes=1 No=0

Details of Booking Examination	
Date of booking examination	*dd/mm/yyyy)*
BP	Systolic: Diastolic:
Height	cm:
Weight	kg:
MUAC	cm:
SFH	cm:
RPR result	Pos=1 Neg=0 → Titre:
Rhesus	Pos=1 Neg=0
ABO	Enter blood group

EDD Estimation		
EDD estimate #1	EDD (dd/mmm/yy)	Gestational age (weeks)
Type of assessment #1 (circle one)	Dates/ LNMP SFH USS	
Date of assessment #1 (dd/mmm/yyyy)		
EDD estimate #2	EDD (dd/mmm/yy)	Gestational age (weeks)
Type of assessment #2 (circle one)	Dates/ LNMP SFH USS	
Date of assessment #2 (dd/mmm/yyyy)		
EDD estimate #3	EDD (dd/mmm/yy)	Gestational age (weeks)
Type of assessment #3 (circle one)	Dates/ LNMP SFH USS	
Date of assessment #3 (dd/mmm/yyyy)		

MCH-ART data abstraction: OBSTETRIC records
Version 2.3 11th February 2014

Please circle and/complete answers for all questions NR = not recorded NA = not applicable

1. Demography	
Source document	
Initials of data abstractor	
Date of data abstraction	*(dd/mm/yyyy)*
MCH-ART number	
Mothers surname	
Mothers date of birth	*(dd/mm/yyyy)*
Mothers provincial folder number	
Mothers date of delivery	*(dd/mm/yyyy)*
Patient details	
Where did the patient deliver? *(Gugs MOU – Gugulethu MOU* *MMH - Mowbray maternity hospital* *GSH - Groot Schuur hospital)*	Gugs MOU=1 MMH=2 GSH=3 Other=4 if other specify
Gravida	
Para	
Blood group *(please circle one)*	A=1 B=2 AB=3 O=4 NR=9
Rhesus	Pos-1 Neg=0 NR=9
Syphilis test	Pos-1 Neg=0 NR=9
Estimated gestational age	weeks
Gestational age estimated by *(Please circle one)*	Dates=1 Palpation=2 SFH=3 USS=4
2. Labour and delivery	
Method of delivery *(C/S = caesarean section)*	NVD=1 Forceps=2 Vacuum=3 Elective C/S=4 Emergency C/S=5
Duration of rupture of membranes *(NR if not recorded)*	mins
If by C/S, indication for a C/S	Fetal distress=1 Obstructed labour=2 Twins/Triplets=3 Placenta praevia=4 Pre-eclampsia/eclampsia=5 Previous C/S=6
If by C/S, Was the C/S done after ROM?	Yes=1 No=0 NR=9
Is mother on any ARVs?	Yes=1 No=0 NR=9
If yes, describe	
Did mother receive any ARVs during labour?	Yes=1 No=0 NR=9
If yes, describe	

3. Infant details	
Was any resuscitation done to infant?	Yes=1 No=0 NR=9
Did infant have any birth injuries?	Yes=1 No=0 NR=9
Gender of infant	Male=1 Female=0
Outcome of infant	Alive=1 Stillborn=2 Dead=3 NR=9
Birth weight	g
Placental weight	g
Head circumference	cm
length	cm
Apgar scores	1 min 5 min
Did the infant receive NVP at birth?	Yes=1 No=0 NR=9
Did the infant receive polio vaccine?	Yes=1 No=0 NR=9
Did the infant receive BCG vaccine?	Yes=1 No=0 NR=9
4. Infant details of twin B. (fill only if twin pregnancy)	
Was any resuscitation done to infant?	Yes=1 No=0 NR=9
Did infant have any birth injuries?	Yes=1 No=0 NR=9
Gender of infant	Male=1 Female=0
Outcome of infant	Alive=1 Stillborn=2 Dead=3 NR=9
Birth weight	g
Placental weight	g
Head circumference	cm
length	cm
Apgar scores	1 min 5 min 10 min
Did the infant receive NVP at birth?	Yes=1 No=0 NR=9
Did the infant receive polio vaccine?	Yes=1 No=0 NR=9
Did the infant receive BCG vaccine?	Yes=1 No=0 NR=9
5. Discharge summary	
Feeding option	Breast=1 formula=2 NR=9
If breastfeeding, was breastfeeding initiated successfully?	Yes=1 No=0 NR=9
Choice of family planning *(TL –tubal ligation)*	Injectable=1 Oral=2 IUCD=3 TL=4 Other=5 If other, specify
Date of discharge	*dd/mm/yyyy*

2. ETHICS APPROVAL DOCUMENTS

2A MCH-ART UCT HREC Approval October 2012

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Faculty of Health Sciences Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: sumayah.ariefdien@uct.ac.za

24 October 2012

HREC REF: 451/2012

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

Dear A/Prof Myer

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

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

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

- Study protocol MCH-ART study: Version 1.2 (FINAL DRAFT, dated 08Oct2012)
- Phase 1 Informed Consent form: Version 2.0, 18 October 2012
- Phase 2 Informed Consent Form: Version 2.0 18 October 2012
- Phase 3 Informed Consent Form: Version 2.0 18 Oct 2012

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

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

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

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

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

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

sAricfdicn

2B MCH-ART UCT HREC Renewal 2016 -2017

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

5 OCT 2016

HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

HREC office use only (FWA00001637; IRB00001938)
This serves as notification of annual approval, including any documentation described below

☑ Approved	Annual progress report	Approved until/next renewal date	30.10.2017
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	7/10/16

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	03 Oct 2016		
HREC REF Number	451/2012	Current Ethics Approval was granted until	30 OCT 2016
Protocol title	Strategies to optimize antiretroviral therapy services for maternal & child health: the MCH-ART study		
Protocol number (if applicable)	N/A		
Are there any sub-studies linked to this study?	✓ YES		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.	**HREC REF 194/2013** Estimation of delivery dates using obstetric ultrasound in the MCH-ART study **HREC REF 550/2015** Childbearing, family planning and relationships among women living with HIV in Gugulethu, Cape Town.		
Principal Investigator	Prof Landon Myer		
Department / Office Internal Mail Address	CIDER, School of Public Health and Family Medicine, Faculty of Health Sciences		

1.1 Does this protocol receive US Federal funding?	✓ Yes	☐ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	✓ No

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

2C MCH-ART ICAP IRB Approval

COLUMBIA UNIVERSITY MEDICAL CENTER
Institutional Review Board
154 Haven Avenue, 1st Floor
New York, NY 10032
212.305.5883 Tel
212.305.1316 Fax

November 1, 2015

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

Protocol Number: IRB-AAAK8059
Title: Strategies to optimize antiretroviral therapy services for maternal & child health: the MCH-ART study
Approval Date: 10/06/2015 Expiration Date: 10/05/2016

Grant #: 1R01HD074558-01

Dear Dr. Abrams,

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

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

The following study-related materials were approved:
- MCH-ART MICS indicators Version 1_23April 2015_tp, attached 5/12/2015
- CBCL_pid- English, attached 5/12/2015
- CBCL Xhosa final sent ASEBA May 2008_pid, attached 5/12/2015
- Infant Dem and MH - Phase 3_18 months pp_V1.0 X-E_clean, attached 5/12/2015
- Qualitative Interview guide, 01October2014- Xhosa, attached 10/16/2014
- Qualitative Interview guide, 01October2014- English, attached 10/16/2014
- Phase 3 Maternal demo & Med hx, 12mo pp, 04August2014- Xhos, attached 9/9/2014
- In-depth interview ICF, 16May2014- Xhosa, attached 9/9/2014
- In-depth interview ICF, 16May2014- English, attached 9/9/2014
- Neurodevelopmental feedback form, 02July2014- Xhosa, attached 9/9/2014
- Neurodevelopmental ICF, 18July2014- Xhosa, attached 9/9/2014
- Neurodevelopmental ICF, 18July2014- English, attached 9/9/2014
- Infant Adherence, Phase 3 6-12 mo, Xhosa, attached 5/1/2014
- Infant Adherence, Phase 3 6wk&3mo, Xhosa- clean, attached 5/1/2014
- Infant Adherence, Phase 2 <7dayspp, Xhosa-clean, attached 5/1/2014
- Infant Demo & Med Hx, Phase 3 6wks, Xhosa- clean, attached 5/1/2014
- Infant Feeding, Phase 3 3mo-12mo, Xhosa- clean, attached 5/1/2014
- Infant Feeding, Phase 3 6wk, Xhosa-clean, attached 5/1/2014
- Infant Feeding, Phase 2 <7dayspp, Xhosa- clean, attached 5/1/2014
- Infant Demo & Med Hx, Phase 3 12mo, Xhosa- clean, attached 5/1/2014
- Infant Demo & Med Hx, Phase 3 9mo, Xhosa- clean, attached 5/1/2014
- Infant Demo & Med Hx, Phase 3 6mo, Xhosa- clean, attached 5/1/2014
- Infant Demo & Med Hx, Phase 3 3mo, Xhosa- clean, attached 5/1/2014
- Infant Demo & Med Hx, Phase 2 <7dayspp, Xhosa- clean, attached 5/1/2014
- Verbal Autopsy Tool, attached 5/1/2014
- Telephone Follow-up CRF, 09April2014, attached 5/1/2014
- Home Visit CRF, 24 April2014, attached 5/1/2014
- Food Security questionnaire- Xhosa, 25April2014, attached 5/1/2014
- Food Security questionnaire- English, 02April2014, attached 5/1/2014
- Resource Interview questionnaire- Xhosa, 25April2014, attached 5/1/2014
- Resource Interview questionnaire- English, 14April2014, attached 5/1/2014

COLUMBIA UNIVERSITY MEDICAL CENTER
Institutional Review Board
154 Haven Avenue, 1st Floor
New York, NY 10032
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212.305.1316 Fax

- Pt-provider relationship scale, Phase 2 (late 3rd)- Xhosa, attached 12/16/2013
- Pt-provider relationship scale, Phase 2 (late 3rd)- English, attached 12/16/2013
- Pt-provider relationship scale, Phase 2 (<7days)- Xhosa, attached 12/16/2013
- Infant Adherence, Phase 2 <7dayspp, 29Sept13-clean, attached 11/6/2013
- Anthropometry CRF, Phase 3 visits, 29Oct2013, attached 11/6/2013
- Anthropometry CRF, Phase 2, <7 days pp, 29Oct 2013, attached 11/6/2013
- Demo & Medical Hx, Phase 2, <7days pp, Xhosa, attached 7/3/2013
- Demo & Medical Hx, Phase 2, <7days pp, attached 7/3/2013
- Demo & Medical Hx, Phase 2, 3rd trimester, Xhosa, attached 7/3/2013
- Demo & Medical Hx, Phase 2, 3rd trimester, attached 7/3/2013
- Trauma & Abuse Assessment, Phase2, <7days pp, Xhosa, attached 7/3/2013
- Trauma & Abuse Assessment, Phase 2, <7 days pp, attached 7/3/2013
- Maternal Adherence, Phase 3, attached 7/3/2013
- Maternal Adherence, Phase 3, Xhosa, attached 7/3/2013
- DUDIT, Phase 3, 12PP, 21May2013, Xhosa, attached 7/2/2013
- DUDIT, Phase 3, 12PP, 12May2013- clean, attached 7/2/2013
- DUDIT, Phase 3, 6PP, 21May2013, Xhosa, attached 7/2/2013
- DUDIT, Phase 3, 6PP, 12May2013- clean, attached 7/2/2013
- DUDIT, Phase 2, 21May2013, Xhosa, attached 7/2/2013
- DUDIT, Phase 2, 12May2013-clean, attached 7/2/2013
- AUDIT, Phase 3, 6PP, 21May2013, Xhosa, attached 7/2/2013
- AUDIT, Phase 3, 12PP, 21May2013, Xhosa, attached 7/2/2013
- AUDIT, Phase 2, 21May2013, Xhosa, attached 7/2/2013
- AUDIT, Phase 3, 12PP, 12May2013- clean, attached 7/2/2013
- AUDIT, Phase 3, 6PP, 12May2013-clean, attached 7/2/2013
- AUDIT, Phase 2, 12May2013-clean, attached 7/2/2013
- Maternal Adherence & ART History, 13May2013, Xhosa, attached 7/2/2013
- Maternal Adherence & ART History, 13May2013- clean, attached 7/2/2013
- London Measure of Unplanned Pregnancy, 17May2013, Xhosa, attached 7/2/2013
- London Measure of Unplanned Pregnancy, dated 17May2013, attached 7/2/2013

The following changes included with the renewal were also approved:
- MCH-ART Unanticipated Problems September 2015.pdf
- Annual Review Approval Oct 2014.pdf

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

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

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

Sincerely,

Yaritza Collazo, CIP
Manager, IRB #3

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 6857: fax: +27 21 483 9895
5th Floor, Norton Rose House,, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: RP 167/2012
ENQUIRIES: Ms Charlene Roderick

School of Public Health & Family Medicine
University of Cape Town
Faculty of Health Sciences
Falmouth Building
Anzio Road
Observatory

For attention: **Prof Landon Myer**

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

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.
Please contact the following people to assist you with any further enquiries in accessing the following sites:

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

Kindly ensure that the following are adhered to:

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

Yours sincerely

DR NT Naledi
DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE: 20/5/2013
CC **MS P OLCKERS** **DIRECTOR: KLIPFONTEIN / MITCHELLS PLAIN**

Phase Informed Consent Form

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

WHAT IS THE PURPOSE OF THIS STUDY?

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

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

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

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

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

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

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

Review of medical records

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

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

Contact for future study

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

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

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

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

WHAT ARE THE ALTERNATIVES TO TAKING PART?
The alternative to taking part in this study is to continue with your usual care at the MOU.

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

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

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

WILL I BE GIVEN ANYTHING FOR TAKING PART?
No, there is no compensation for taking part in the study today.

ARE THERE ANY COSTS?
There is no cost for being in this study.

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

FUTURE USE OF SPECIMENS:

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

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

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

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

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

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

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

DO YOU HAVE ANY QUESTIONS?

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

Do you have any questions?

FOR ADDITIONAL INFORMATION:

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

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

Dr Elaine Abrams
ICAP, Columbia University
Mailman School of Public Health
College of Physicians and Surgeons
Tel: +1 212 342 0543
Email: eja1@columbia.edu

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

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

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

Town
Tel: 021 406 6338

CONSENT STATEMENT:

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

Please indicate your consent with your signature.

Volunteer's name _____

_____ _____

Signature of Volunteer Date

Staff member's name_____

_____ _____

Signature of study staff Date

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

Fingerprint of volunteer:

Witness:

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

Witness's name_____

_____ _____

Signature of witness Date

Thank you.

4. SUPPLEMENTAL MATERIAL

SUBGROUP ANALYSES

Regimen Groups

Table 1. Birth outcomes by HIV/ART status among women using EFV-based regimen (TDF+FTC+EFV) with live singleton births (n=961)

	HIV-uninfected N=278	HIV-infected N=961	HIV-infected vs uninfected *p-value*	HIV-infected					Before vs During* *p-value*	During (P1 vs P2 vs P3 vs P4)** *p-value*
				Initiation before pregnancy N=164	Initiation during pregnancy N=797					
					1st Trimester N=146	1st half of 2nd Trimester N=245	2nd half of 2nd Trimester N=230	3rd Trimester N=177		
Gestational Age (weeks)			<0.0001						0.03	0.36
Term (≥ 37)	242 (87)	743 (77)		116 (71)	111 (76)	197 (80)	187 (81)	132 (75)		
Any Preterm (< 37)	36 (13)	217 (23)		48 (29)	34 (23)	49 (20)	43 (19)	44 (25)		
Late Preterm (34-37)	21 (8)	124 (57)		26 (16)	19 (13)	29 (12)	24 (10)	26 (15)		
Moderately Preterm (32-34)	13 (5)	70 (32)		16 (10)	9 (6)	16 (7)	11 (5)	18 (10)		
Very Preterm (28-32)	2 (0.7)	23 (11)		6 (4)	6 (4)	3 (2)	8 (3)	0		
Birthweight (grams)			0.03						0.19	0.3
Normal (≥2500)	252 (91)	815 (85)		133 (81)	118 (81)	214 (87)	199 (87)	151 (86)		
Any LBW (<2500)	26 (9)	139 (15)		29 (18)	27 (18)	30 (12)	28 (12)	25 (14)		
LBW (<2500)	23 (8)	119 (12)		23 (14)	23 (16)	27 (11)	21 (9)	25 (14)		
Very LBW (<1500)	3 (1)	20 (2)		6 (4)	4 (3)	3 (1)	7 (3)	0		
Mean (SD)	3260 (548)	3120 (584)	0.0001	3140 (680)	3080 (641)	3120 (524)	3130 (574)	3145 (532)	0.89	0.27
Size for Gestational Age (centile)			0.06						0.14	0.05
LGA (>90th)	35 (13)	75 (8)		19 (12)	13 (9)	13 (5)	11 (5)	19 (11)		
AGA (10th – 90th)	211 (76)	750 (80)		124 (76)	105 (72)	201 (82)	190 (83)	130 (74)		
SGA (<10th)	31 (11)	111 (12)		17 (10)	22 (15)	25 (10)	22 (10)	25 (14)		

* P values refer to comparisons between women who initiated ART before pregnancy vs during pregnancy (not expanded into the 4 time periods)

** P values refer to comparisons among women who initiated during pregnancy across the 4 time periods

All the variables had <4% missing data, with similar proportions of missing data across the comparison groups

Table 2. Adjusted associations between HIV/ART status and adverse birth outcomes among women using TDF+FTC+EFV with live singleton births (n=961)

Outcome Measure	Comparison A* (Ref category: HIV-uninfected)			Comparison B** (Ref category: Before pregnancy)			Comparison C** (Ref Category: P1)		
		AOR [95% CI]	**P value**		**AOR [95% CI]**	**P value**		**AOR [95% CI]**	**P value**
Prematurity (<37 weeks)	HIV-infected	1.97 (1.28–3.04)	0.002	During pregnancy	0.60 (0.39–0.94)	0.024	P2	0.89 (0.51–1.56)	0.694
							P3	0.79 (0.44–1.43)	0.441
							P4	1.43 (0.80–2.54)	0.223
Low Birth Weight (<2500g)	HIV-infected	1.51 (0.91–2.48)	0.107	During pregnancy	0.61 (0.36–1.02)	0.06	P2	0.67 (0.35–1.31)	0.243
							P3	0.68 (0.34–1.34)	0.263
							P4	1.19 (0.60–2.33)	0.620
Small for Gestational Age(<10th centile)	HIV-infected	0.96 (0.61–1.52)	0.869	During pregnancy	1.02 (0.55–1.90)	0.956	P2	0.77 (0.38–1.56)	0.461
							P3	0.74 (0.35–1.54)	0.414
							P4	1.62 (0.79–3.30)	0.184

Comparison A (HIV-infected vs HIV-uninfected), Comparison B (ART initiated before pregnancy vs ART initiated during pregnancy), Comparison C (ART initiated during pregnancy 4 time points: P1 (<14 weeks), P2 (14-20 weeks), P3 (21-27 weeks), P4 (>28weeks)

* adjusted for age, maternal height, parity and previous PTD

** adjusted for age, maternal height, parity and previous PTD, CD4 count and VL

Table 3. Birth outcomes by HIV/ART status among women using PI-based regimen with live singleton births (n=29)

	HIV-uninfected N=278	**HIV-infected N=29**	**HIV-infected vs uninfected** *p-value*	**HIV-infected**		**Before vs After*** *p-value*
				Initiation before pregnancy N=28	**Initiation during pregnancy N=1**	
Gestational Age (weeks)			0.002			0.46
Term (≥ 37)	242 (87)	19 (66)		18 (64)	1 (100)	
Any Preterm (< 37)	36 (13)	10 (34)		10 (36)	0	
Late Preterm (34-37)	21 (8)	6 (21)		6 (21)	0	
Moderately Preterm (32-34)	13 (5)	4 (14)		4 (14)	0	
Very Preterm (28-32)	2 (0.7)	0		0	0	
Birthweight (grams)			0.18			0.642
Normal (≥2500)	252 (91)	24 (83)		23 (82)	1 (100)	
Any LBW (<2500)	26 (9)	5 (17)		5 (18)	0	
LBW (<2500)	23 (8)	5 (17)		0	0	
Very LBW (<1500)	3 (1)	0		0	0	
Mean (SD)	3260 (548)	3016 (639)	0.0001	3002 (646)	3410 (-)	-
Size for Gestational Age (centile)			0.737			0.813
LGA (>90th)	35 (13)	5 (18)		5 (18)	0	
AGA (10th – 90th)	211 (76)	20 (71)		19 (68)	1 (100)	
SGA (<10th)	31 (11)	3 (11)		3 (11)	0	

* P values refer to comparisons between women who initiated ART before pregnancy vs during pregnancy (not expanded into the 4 time periods)
All the variables had <4% missing data, with similar proportions of missing data across the comparison groups

Table 4. Adjusted associations between HIV/ART status and adverse birth outcomes among women using PI-based regimen with live singleton births (n=29)

Outcome Measure	Comparison A* (Ref category: HIV-uninfected)		
		AOR [95% CI]	**P value**
Preterm Delivery (<37 weeks)	HIV-infected	4.46 (1.55–12.83)	0.005
Low Birth Weight (<2500g)	HIV-infected	2.39 (0.67–8.57)	0.182
Small for Gestational Age (<10th centile)	HIV-infected	1.01 (0.26–3.92)	0.994

Comparison A (HIV-infected vs HIV-uninfected)

* adjusted for age, maternal height, parity and previous PTD

Table 5. Birth outcomes by HIV/ART status among women initiating before conception with live singleton births (n=477)

	NNRTI regimens N=271	**PI regimens N=28**	**Missing N=178**	*p-value**
Gestational Age (weeks)				0.35
Term (≥ 37)	205 (76)	18 (64)	135 (77)	
Any Preterm (< 37)	64 (24)	10 (36)	41 (23)	
Late Preterm (34-37)	37 (14)	6 (21)	26 (15)	
Moderately Preterm (32-34)	21 (8)	4 (14)	12 (7)	
Very Preterm (28-32)	6 (2)	0	2 (2)	
Birthweight (g)				0.85
Normal (≥2500)	230 (86)	23 (82)	149 (85)	
Any LBW (<2500)	38 (14)	5 (18)	27 (15)	
LBW (<2500)	32 (12)	5 (18)	24 (13)	
Very LBW (<1500)	6 (2)	0	3 (2)	
Mean (SD)	3135 (618)	3055 (646)	3068 (570)	0.59
Size for Gestational Age (centile)				0.88
LGA (>90th)	30 (11)	5 (19)	21 (12)	
AGA (10th – 90th)	203 (77)	19 (70)	134 (77)	
SGA (<10th)	30 (11)	2 (11)	20 (11)	

* P values refer to comparison between women conceiving on ART on NNRTI regimens, PI regimens and those with missing regimen data

All the variables had <4% missing data, with similar proportions of missing data across the comparison groups

Booking Groups

Table 6. Birth outcomes by HIV/ART status among women booking at <20 weeks with live singleton births (n=710)

	HIV uninfected N=128	HIV infected N=582	HIV Infected vs Uninfected* *p-value*	HIV infected		Before vs During** *p-value*
				Initiation before pregnancy N= 215	Initiation during pregnancy N= 367	
Gestational Age (weeks)			0.005			0.64
Term (≥ 37)	116 (91)	454 (78)		165 (77)	289 (79)	
Any Preterm (< 37)	12 (9)	127 (22)		49 (23)	78 (21)	
Late Preterm (34-37)	8 (6)	73 (13)		27 (13)	46 (13)	
Moderately Preterm (32-34)	3 (2)	41 (7)		19 (9)	22 (6)	
Very Preterm (28-32)	1 (0.8)	13 (2)		3(1)	10 (3)	
Birthweight (g)			0.05			0.85
Normal (≥2500)	119 (93)	494 (85)		181 (85)	313 (86)	
Any LBW (<2500)	9 (7)	85 (15)		32 (16)	53 (14)	
LBW (<2500)	8 (89)	73 (86)		28 (88)	45 (85)	
Very LBW (<1500)	1 (11)	12 (14)		4 (13)	8 (15)	
Mean (SD)	3208 (535)	3026 (581)	0.001	3026 (588)	3026 (579)	0.99
Size for Gestational Age			0.58			0.13
LGA	15 (12)	50 (9)		25 (12)	25 (7)	
AGA	99 (77)	447 (79)		159 (76)	288 (81)	
SGA	14 (11)	69 (12)		26 (12)	43 (12)	

*P values refer to comparison between HIV-infected and HIV-uninfected women

**P values refer to comparisons between women who initiated ART before pregnancy vs during pregnancy (not expanded into the 4 time periods)

All the variables had <4% missing data, with similar proportions of missing data across the comparison groups

Table 7. Adjusted associations between HIV/ART status and adverse birth outcomes among women booking at <20 weeks with live singleton births (n=710)

Outcome Measure	Comparison A* (Ref category: HIV-uninfected)			Comparison B** (Ref category: Before pregnancy)			Comparison C** (Ref Category: P1)		
		AOR [95% CI]	**P value**		**AOR [95% CI]**	**P value**		**AOR [95% CI]**	**P value**
Preterm Delivery (<37 weeks)	HIV-infected	2.75 (1.38–5.48)	0.004	During pregnancy	1.18 (0.57–2.43)	0.655	P2	0.9 (0.51–1.60)	0.724
Low Birth Weight (<2500g)	HIV-infected	2.19 (0.97–4.94)	0.06	During pregnancy	0.91 (0.39–2.10)	0.827	P2	0.65 (0.33–1.29)	0.214
Small for Gestational Age (<10th centile)	HIV-infected	1.05 (0.53–2.11)	0.884	During pregnancy	0.94 (0.36–2.46)	0.895	P2	0.7 (0.32–1.50)	0.357

Comparison A (HIV-infected vs HIV-uninfected), Comparison B (ART initiated before pregnancy vs ART initiated during pregnancy), Comparison C (ART initiated during pregnancy 4 time points: P1 (<14 weeks), P2 (14-20 weeks), P3 (21-27 weeks), P4 (>28weeks)

* adjusted for age, maternal height, parity and previous PTD

** adjusted for age, maternal height, parity and previous PTD, CD4 count and VL

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