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THE ASSOCIATION BETWEEN MATERNAL HIV INFECTION AND LOW BIRTH WEIGHT AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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Original published work submitted to the Faculty of Health Science, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Medicine.

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Johannesburg, 2020

DECLARATION

I, Juliette Jane Phelp, student number 1596003, declare that this dissertation is my own work and that I contributed adequately towards research findings published in the article stated below which are included in my dissertation. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Signature of Student_____ Date__03/03/2020___

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Signature of Primary Supervisor_____ Date__28/02/2020___

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her dissertation. The student wrote the paper with assistance and corrections from co-authors and all work reported in the paper was performed by the candidate.

For Praval.

ABSTRACT

Background: Maternal HIV infection has been associated with infant low birth weight (LBW), whilst highly active antiretroviral therapy (HAART) has improved maternal health and reduced rates of mother to child transmission (MTCT) of HIV. Whether there is an association between maternal HIV and LBW in the context of HAART is uncertain.

Methods: We used data from the V98_28OBTP study conducted at Chris Hani Baragwanath Academic Hospital from July 2014 to December 2016 to assess the association between maternal HIV infection, LBW and other variables.

Results: Of 36 808 study participants 10 990 (29.9%) infants were HIV exposed and 25 818 (70.1%) were HIV unexposed with a mean birth weight (BW) of 2 948g (standard deviation (SD) ± 604g) and 3 061g (SD ± 599g) respectively (P<0.001). HIV infected infants tended to be smaller than HIV exposed uninfected infants, mean BW 2 680g (SD ± 679g) and 2 917g (SD ± 622g) respectively (P=0.063). The adjusted odds ratio (OR) for LBW as related to maternal HIV infection was 1.49 (95% confidence interval (CI) 1.35-1.64). Any maternal antiretroviral treatment was associated with reduced odds of LBW (OR 0.80, 95% CI 0.647-0.995). Other variables strongly associated with LBW included, maternal hypertension, poor maternal nutrition and prior pregnancy loss.

Conclusion: Maternal HAART usage has improved LBW but a weak association between HIV exposure and LBW still exists.

Key words: maternal HIV infection, low birth weight, perinatal HIV infection.

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LIST OF ABBREVAITIONS

ART	antiretroviral therapy
BW	birth weight
CHBAH	Chris Hani Baragwanath Academic Hospital
CI	confidence interval
HAART	highly active antiretroviral therapy
HREC	Human Research Ethics Committee
HIV	human immunodeficiency virus
IUGR	intrauterine growth restriction
LBW	low birth weight
MTCT	mother to child transmission
MUAC	mid-upper arm circumference
NHLS	National Health Laboratory Service
OR	odds ratio
PCR	polymerase chain reaction
PMTCT	prevention of mother to child transmission
RMPRU	Respiratory and Meningeal Pathogens Research Unit
RR	relative risk
SD	standard deviation
SGA	small for gestational age
WHO	World Health Organisation

CHAPTER 1 – RESEARCH PROTOCOL AND EXTENDED LITERATURE REVIEW

1.1 EXTENDED LITERATURE REVIEW

THE ASSOCIATION BETWEEN MATERNAL HIV INFECTION AND LOW BIRTH WEIGHT AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

INTRODUCTION

According to the World Health Organization (WHO) in 2017 there were 7.2 million people living with HIV in South Africa. Second to this was Nigeria with 3.1 million people, making South Africa home to the largest population, globally, of HIV infected individuals (1). The prevalence of HIV rapidly increased before the national roll out of antiretroviral therapy (ART) in 2004. The first national antenatal survey in 1990 found an HIV prevalence of 0.7%, by 2004 this number had increased to 29.5%, where it plateaued and has remained (2). Prevalence of HIV varies by province, however, the rate in Gauteng matches the national prevalence of almost 30% (2).

According to the 2014 Saving Mothers report, the leading cause of maternal death in South Africa is non-pregnancy related infection, causing overall 29.5% of deaths (3). Of deaths caused by non-pregnancy related infection 89.9% were HIV infected, making HIV an important contributor to maternal mortality.

Infants born to mothers with HIV are at risk of contracting the virus either in utero, intrapartum or during breastfeeding. Mother to child transmission in an important contributor to infant mortality in Africa with an estimated 52.5% of HIV infected children dying by age 2 compared to 7.6% of HIV exposed uninfected children (4).

The History of PMTCT

The first prevention of mother to child transmission (PMTCT) programme in South Africa was rolled out in 2002 and offered single dose Nevirapine to the mother in labour and to the infant within 72 hours of birth (2). In 2004 Zidovudine from 28 weeks gestation was added to the existing PMTCT regimen. In 2010 PMTCT

recommendations changed to Zidovudine from 14 weeks gestation with Tenofovir and Lamivudine given in labour. Infants were given Nevirapine for six weeks or until cessation of breastfeeding. Concurrently ART guidelines for the non-pregnant population changed, prescribing triple agent highly active ART (HAART) for all people with a CD4+ cell count of <350cells/mm_3 and all people with tuberculosis irrespective of CD4+ cell count. In 2013 all pregnant women became eligible for HAART from first diagnosis or presentation at antenatal clinic until cessation of breastfeeding, with infants receiving 6 weeks of Nevirapine prophylaxis (2). Currently HIV testing of pregnant women in South Africa is close to 100% with 98% of health facilities offering PMTCT (5). The 2015 guidelines for PMTCT advocate WHO option B+; lifelong HAART for all pregnant or breastfeeding women, regardless of gestational age, CD4+ cell count or disease stage (5).

The Success of PMTCT

Since 2004 the number of HIV positive pregnant women in South Africa receiving ART has steadily increased (5). With this, the rate of mother to child transmission (MTCT) has decreased from estimates of 20.5% in 2004 to 1.8% in 2014 (6). There is local and global evidence to support that HAART significantly reduces MTCT compared to single or dual agent therapy (7,8). Besides the success in reducing MTCT, HAART is able to suppress viral replication to minimal levels which markedly improves the health of the mother (2,9). Saving Mothers 2014-2016 report shows a 47% drop, from 2011 to 2016, in the number of deaths as a result of non-pregnancy related infection (10). This coincides with increasing ART roll-out in South Africa. Following the success of PMTCT, elimination of mother to child transmission is the next national goal.

The Problem of Low Birth Weight

Low birth weight (LBW) is defined by the WHO as a weight at birth less than 2500g (11). This cut-off is based on observations that infants with a weight at birth below 2500g are 20 times more likely to die than infants with a weight at birth above 2500g (12). It has long since been recognised that LBW contributes to increased infant mortality and childhood morbidity (13). A meta-analysis by Risnes et al has shown that low birth weight can carry its adverse effect into adulthood; moderately

increasing the cardiovascular and all-cause mortality risk for both men and women (14). This meta-analysis showed a 6% lower risk of all-cause mortality per kg higher birth weight. The global prevalence of LBW is 15% (11). It is estimated that 2.5 million neonates died in 2017, approximately 80% of these having LBW (15). Low birth weight is a more serious problem in developing countries where access to healthcare is limited (16) and yet this is where over 95% of LBW infants are born (12). The size of the problem has prompted the WHO to include a 30% reduction in LBW as one of its 2025 Global Nutrition Targets (11).

The aetiology of LBW includes infants born preterm (<37 weeks of gestation) and those that are growth restricted or small for gestational age (SGA), with a birth weight falling below the 10th centile for gestation. Evidence indicates that the more serious problem is being born too early (13). In weight-matched categories infants that are SGA have lower mortality rates than infants that are appropriate for gestational age. In South Africa, as in other low and middle-income countries, gestational age is calculated from either last menstrual period, symphysis fundal height palpation or, if available, obstetric ultrasound. Gestational age calculation is prone to inaccuracy. Problems that arise leading to this inaccuracy include; incorrect recall of date of last menstrual period, amenorrhoea or irregular menses related to wide-spread use of injectable progesterone-containing contraceptives, obesity with subsequent inaccurate symphysis fundal height measurement, and limited access to obstetric ultrasound. Low birth weight as a measure is not prone to these inaccuracies but will include a heterogeneous group of infants who are born premature, growth restricted or both.

The Association between Maternal HIV Infection and LBW

A meta-analysis by Brocklehurst et al showed an association, although not strong, between maternal HIV infection and adverse perinatal outcome (17). The review included literature published from 1988 to 1996, in 16 countries across the world. It showed an odds ratio (OR) of 2.09 (95% confidence interval (CI): 1.86-2.35) for LBW as related to maternal HIV infection. During this time in our history ART was not widely available and it was only in 1996 that HAART was introduced (9). Although not specified, it is safe to assume that the vast majority, if not all, of those in this

study population were not on treatment. The review covered research in both developed and developing countries and found a much higher risk of infant death in developing countries associated with maternal HIV infection.

Another meta-analysis by Xiao et al included literature covering the years 1976 to 2013 in 21 countries across the world (18). It demonstrated that maternal HIV infection was significantly associated with LBW (OR 1.73, 95% CI: 1.64-1.82) and preterm delivery (PTD) (OR 1.56, 95% CI: 1.49-1.63). It also found that ART did not significantly change this association. However, any ART usage before or during pregnancy was included in this analysis and details of specific regimens were not available. This may have resulted in confounding of this result. It was also only in 2010 that WHO first recommended HAART for PMTCT (19), we can deduce from this that only a very small number of participants included in this review would have been on HAART. This analysis also showed a stronger association between maternal HIV infection and LBW in developing countries as opposed to developed countries.

A third meta-analysis by Wedi et al looked specifically at treatment naïve HIV positive mothers, 71% of which were in Sub-Saharan Africa (20). The reviewed studies were published between 1989 and 2014. The analysis included many of the studies reviewed in the above-mentioned meta-analyses but excluded those where treatment was given to mothers and those where treatment status was not available. They found maternal HIV infection was significantly associated with LBW (relative risk (RR) 1.62, 95% CI 1.41-1.86 for prospective studies and RR 1.93, 95% CI 1.48-2.52 for retrospective studies) (20).

A study conducted in Cameroon looked at the relationship between SGA (determined using gender specific charts) and HIV (21). This study categorised infants as HIV-unexposed uninfected, HIV-exposed uninfected or HIV-infected. They found a much higher incidence of SGA among those infants that were HIV-infected compared to those that were HIV-exposed but uninfected (adjusted OR 4.0, 95% CI: 2.0-8.1). Three possible causes for his association include: intra-uterine infection with HIV and the resultant disease process causes intra-uterine growth restriction

(IUGR), maternal disease processes which result in intra-uterine infection also result in placental insufficiency and IUGR, and IUGR increases foetal susceptibility to transmission of HIV. The study also showed that HIV-unexposed infants were less likely to be small for gestational age compared to HIV-exposed uninfected infants (adjusted OR 0.5, 95% CI: 0.4-0.8), although the association was not strong. This study focused on small for gestational age only, consequently excluding those infants born preterm which, as discussed above, is an important outcome to look at. Prevention of mother to child transmission in Cameroon at the time of the study was based on the 2006 WHO guidelines which advocated HAART only for those mothers with CD4+ cell counts of 200 cells/mm^3 or less, single agent Zidovudine was recommended from 28 weeks for all other HIV infected mothers (21).

Possible Causes for the Relationship between Maternal HIV Infection and LBW

A study conducted in Tanzania from 1995 to 1997 reviewed several socio-demographic, nutritional, HIV related, parasitic and infant factors and how they related to LBW and SGA in a population of HIV positive pregnant women and their infants (22). They found that WHO stage III HIV disease and lower maternal weight were significantly associated with LBW (22). The study does not report whether women received ART or not, although it is unlikely, given the study period. Another study conducted in Kenya, where mothers received short course zidovudine for PMTCT, found that maternal cervical HIV-1 RNA levels and bacterial vaginosis were significantly associated with LBW, while maternal serum and cervical HIV-1 RNA levels and CD4+<15% were associated with preterm birth (23). It is reasonable to assume that with HAART given to pregnant women the above factors may be improved upon resulting in a reduction in LBW among HIV exposed infants, provided that the ART itself does not cause LBW.

Is There Still an Association in the Context of HAART Usage

A study conducted in Bronx, New York looked at 155 HIV exposed uninfected infants and matched them to 775 HIV unexposed controls using a birth certificate database (24). They found the mean birth weight of HIV exposed infants to be lower than the unexposed controls (-101.5g [95% CI -181.4 to -21.6g]). Within the HIV exposed group 81% were documented to be on HAART with 19% having no information on

ART regimen. It is estimated that over 95% of HIV positive mothers in the United States are on some form of HAART. The OR for LBW associated with maternal HIV infection in this study was 1.4 but was not statistically significant [95% CI: 0.6 to 2.9]. The study also looked into the relationship between birth weight and HAART regimen, namely protease inhibitor (PI)-based vs non-PI-based. They found no association but as noted by the authors the majority of participants in this study were on PI-based ART which limited the power of the study to detect an association (24).

A study in Blantyre, Malawi recruited 614 healthy HIV positive mothers (CD4+ cell count ≥350cells/mm_3 and no WHO stage 3 or 4 disease) who were on HAART at least 1 week prior to delivery and 685 HIV negative controls (25). They investigated several adverse birth outcomes but did not find a statistically significant difference in incidence between HIV exposed infants and controls. The adjusted OR for LBW in HIV exposed infants was 1.62 but was not statistically significant (95% CI: 0.97 to 2.71). The study concluded that ART has reduced the high rates of adverse pregnancy outcome among HIV infected women. HIV infected women in this study were taking the national ART regimen: lamivudine, tenofovir and efavirenz (25).

South African Research Looking at Maternal HIV Infection and LBW

Local research has suggested an improvement in perinatal outcomes as ART coverage has increased (7,26). A maternity register audit conducted in Durban over 2 time periods, January-June 2011 and July-December 2014, showed higher rates of adverse birth outcomes (stillbirth, preterm delivery, LBW and SGA) in pregnancies of HIV positive women compared to HIV negative women. In the second time period they showed a statistically significant reduction in the number of stillbirths and the number of infants born preterm, this correlating with higher rates of HAART usage among mothers. They also showed a significant reduction in all adverse outcomes for HIV positive mothers on ART (either dual or triple) compared to those on no treatment (26).

An observational study conducted in Johannesburg looked at the effect of in utero exposure to HAART on adverse birth outcomes in women with advanced HIV disease (7). The Study was conducted between October 2004 and March 2007 and

included women with CD4+ cell counts of 250cells/mm^3 or less. Patients with CD4+ cell counts <200 cell/mm^3 or WHO stage 4 HIV disease received HAART, the exposure group. It is not stated whether the control group in this study received any PMTCT, it is mentioned that many of the control group were diagnosed with HIV in labour or post-delivery suggesting the majority received no ART. They found significantly lower rates of MTCT in the HAART exposed group. After adjusting for confounding variables this study showed that in utero HAART exposure was not associated with LBW. They did show that more advanced immunosuppression was a risk factor for LBW (7). All of these findings suggesting that patients with well controlled HIV on treatment may have lower rates of adverse birth outcomes.

It is only since the beginning of 2015 that lifelong HAART has been advocated as standard PMTCT among South African pregnant women (5). With this it can be expected that further improvement in adverse birth outcomes will be seen and perhaps the association between HIV and LBW will no longer be significant.

1.2 RESEARCH PROTOCOL

AIM

The aim of this study is to review the current association between maternal HIV infection and LBW in the context of widespread HAART usage in pregnant women in South Africa, a developing country with a high burden of disease.

STUDY OBJECTIVES

1) To describe the socio-demographic and clinical characteristics of the study maternal and newborn infant populations.
2) To compare the mean birth weights of HIV-exposed and HIV-unexposed infants.
3) To compare the mean birth weights of HIV-exposed infants with a positive birth HIV PCR result and those with a negative birth HIV PCR.

4) To determine the association between LBW and HIV status of mother (if any) after accounting for confounding variables.

METHODOLOGY

This study will be a retrospective cross-sectional study.

Population

The target population will be mother-infant pairs delivering at Chris Hani Baragwanath Academic Hospital (CHBAH). The sample population will be made up of mother-infant pairs who deliver at CHBAH between July 2014 and December 2016. Only singleton deliveries will be included in this analysis. CHBAH is the third largest hospital in the world with approximately 3 200 beds (27). The maternity department delivers between 50 and 70 babies daily. CHBAH is one of the Gauteng provincial hospitals and is a teaching hospital for the University of Witwatersrand. The hospital serves the community of Soweto. Soweto is located in the south of Johannesburg with a population of 1.25 million people, comprising more than 40% of the city's population (28). It is a poorer area within the city contributing only 4% of the city's total economic activity. CHBAH is a referral hospital, managing both high and low risk patients.

Data Collection

Details on study participants will be retrieved from the data base collected for the V98_28OBTP study as per the attached data sheet (appendix 1). The V98_28OBTP study is a study conducted at CHBAH between July 2014 and Dec 2016 by the Respiratory and Meningeal Pathogens Research Unit (RMPRU). The aim of the V98_28OBTP study is to determine a sero-correlate of protection against invasive Group B streptococcus disease in newborns and infants up to 90 days of age. All mothers who were 18 years and older and willing to participate in the study were included. Trained research assistants and enrolled and professional nurses recruited a cohort of 35 000 mother-infant pairs over the study period. Permission has been granted for use of this data set by RMPRU (appendix 2).

Necessary information not routinely collected as part of the V98_28OBTP study includes infant birth PCR result, maternal CD4+ cell count and maternal viral load level. This information will be retrieved from the National Health Laboratory Services (NHLS) or by review of patient records, where possible. NHLS has agreed to provide access to this information provided the review acquires ethical approval. In the interest of maintaining confidentiality where this information is linked to patient identifying information, it will be kept in a separate password-protected data sheet. All that will be imported into the study data set will be NHLS results. The consent form for the V98_28OBTP study included participation of both the mother and her infant and also included participation in further research not related to the diseases under study.

In summary, data will be retrieved from RMPRU, NHLS and patient records, consolidated into one data set, where after the data will be analysed.

Inclusion Criteria

- Mother-infant pairs delivering at CHBAH between July 2014 and December 2016.
- Enrolment into the V98_28OBTP study.

Exclusion Criteria

- Multiple pregnancy.

There will be no other exclusion criteria, potential confounders will be accounted for during statistical analysis.

Variables to be Measured

The outcome variable of this study will be infant birth weight. The primary independent variable will be maternal HIV status. Other independent variables, such as hypertension in pregnancy or smoking in pregnancy, will be considered as possible confounders of the association between maternal HIV infection and LBW.

DATA ANALYSIS

All data will be analysed using STATA statistical software (version 14.2).

For the first objective, all categorical variables will be described using frequency and percentage. All normally distributed continuous variables will be described using mean and standard deviation and any continuous variables not normally distributed will be described using median and interquartile range. Normality will be determined using histogram distribution plots and the central limit theorem.

For the second objective, all HIV-exposed infants and HIV-unexposed infants with recorded birth weight will be included. The mean birth weight for each group will be calculated along with 95% confidence. The Student's t-test will be used to determine if there is a statistically significant difference between the two means. Statistical significance will be set at a p-value < 0.05. The difference will also be quantified to determine if it is clinically significant.

For the third objective, HIV-exposed infants for whom birth HIV-PCR results are available will be included, and HIV-PCR-positive newborns will be compared to HIV-PCR-negative newborns. Analysis will be carried out as for the second objective.

For the fourth objective, the birth weight of infants in the study population will be stratified into all infants with birth weight less than 2500g (cases) and all those with birth weight of 2500g or more (controls). The characteristics of each group will be described and compared to determine if they differ significantly. Significant level will be set at a p-value < 0.05. Categorical variables will be described using frequency and percentage and will be compared using Pearson's Chi-square test. Normally distributed continuous variables will be described using mean and 95% confidence intervals and will be compared using Student's t-test. Continuous variables not normally distributed will be described using median and interquartile range and compared using the Mann-Whitney U test. Since the outcome of interest (LBW) is a binary variable, a univariate logistic regression will be individually conducted between LBW and all other variables including maternal HIV status. Variables with a

p-value < 0.2 will be sequentially added to a logistic multivariate model with maternal HIV status as the primary explanatory variable. The final multivariate model will then give the association of maternal HIV status and LBW (in terms of odds ratio) after controlling for confounding variables.

ETHICS

The V98_28OBTP study was reviewed and approved by the Human Research Ethics committee of the University of the Witwatersrand (Wits HREC) in June 2014 (Wits HREC reference #: 140203).

Ethical approval will be sought from the University of Witwatersrand's Human Research Ethics Committee. Permission will be sought from the Chris Hani Baragwanath Academic Hospital's Chief Executive Officer by registering the project on the National Health Research Database.

Protection of human research participants

As the trial is retrospective, there are no risks or benefits for participants.

Confidentiality

Participants in the V98_28OBTP study were identified for study purposes with a unique numerical identifier. Names and hospital numbers will be utilized to obtain HIV PCR results, CD4+ and viral load results, however, personal identifiers will be maintained in a separate password-protected database.

Costs to participants

None.

Disseminating results to the public

Results will be included in an MMed dissertation and submitted to the University of the Witwatersrand on completion. Summary of results will be reported to the HREC on completion of the study. Results may be presented at professional clinical meetings and national or international scientific meetings. Results will be submitted

for publication in a peer-reviewed journal, where they will also be available to the public.

TIMING

2017	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	
Literature review									
Protocol development									
Protocol assessment									
Ethics application									
Corrections									
Apply for permission									
2018	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept
Data collection									
Data analysis									
Write-up									
Marking									
Corrections									

Figure 1.1 – Gant chart describing timing of research.

FUNDING

All costs will be covered by the researcher.

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CHAPTER 2 – SUBMISSIBLE ARTICLE

The Association between Maternal HIV Infection and Low Birth Weight at Chris Hani Baragwanath Academic Hospital

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INTRODUCTION

According to the World Health Organization (WHO) in 2017 there were 7.2 million people living with HIV in South Africa. Second to this was Nigeria with 3.1 million people, making South Africa home to the largest population, globally, of HIV infected individuals (1). In the 2014-2016 Saving Mothers report, the leading cause of maternal death in South Africa was non-pregnancy related infection (2). Of these deaths 88.8% were HIV infected. The report also described a 47% reduction in the number of deaths as a result of non-pregnancy related infection from 2011 to 2016. This coincided with roll-out of highly active antiretroviral therapy (HAART) for pregnant women in South Africa. Highly active antiretroviral therapy is able to suppress viral replication to minimal levels which has markedly improved the health of HIV positive mothers (3,4).

Mother to child transmission (MTCT) in an important contributor to infant mortality in Africa with an estimated 52.5% of HIV infected children dying by age 2 compared to 7.6% of HIV exposed uninfected children (5). The rate of MTCT in South Africa has decreased from estimates of 20.5% in 2004 to 1.5% in 2016 (6,7), this success is due to increasing and evolving antiretroviral therapy (ART) use in pregnant women. There is local and global evidence to support that HAART significantly reduces MTCT compared to single or dual agent therapy (8,9).

Human immunodeficiency virus infection is not the only concern for infants born to HIV positive mothers. A meta-analysis by Brocklehurst et al calculated an odds ratio (OR) for low birth weight (LBW) of 2.09 (95% confidence interval (CI) 1.86-2.35) as related to maternal HIV infection (10). The review covered research in both low-income and high-income countries and found a much higher risk of infant death in low-income countries associated with maternal HIV infection. Another meta-analysis by Xiao et al demonstrated that maternal HIV infection was significantly associated with LBW (OR 1.73, 95% CI 1.64-1.82) (11). This analysis revealed a stronger association between maternal HIV infection and LBW in low-income countries as opposed to high-income countries. Both of these meta-analyses were conducted at a time when HAART was not the standard of care for HIV infected pregnant women. A third meta-analysis by Wedi et al included many of the studies included in the above reviews but looked specifically at treatment naïve HIV positive mothers (12). They excluded reviews in which patients received treatment or treatment status was unknown. They found maternal HIV infection was significantly associated with LBW (relative risk (RR) 1.62, 95% CI 1.41-1.86 for prospective studies and RR 1.93, 95% CI 1.48-2.52 for retrospective studies).

Low birth weight is defined by the WHO as a weight at birth less than 2500g (13). This is based on observations that infants with a weight at birth below 2500g are 20 times more likely to die than infants with a weight at birth above 2500g (14). It has long since been recognised that LBW contributes to increased infant mortality and childhood morbidity (15–17). In addition a meta-analysis by Risnes et al has shown that low birth weight can carry its adverse effect into adulthood, moderately increasing the cardiovascular and all-cause mortality risk for both men and women (18). The global prevalence of LBW is 15% (13). It is estimated that 2.5 million neonates died in 2017, approximately 80% of these having LBW (19). Low birth weight is a more serious problem in developing countries where access to healthcare is limited (20) and yet this is where over 95% of LBW infants are born (14). The size of the problem has prompted the WHO to include a 30% reduction in LBW as one of its 2025 Global Nutrition Targets (13).

An observational study conducted in Johannesburg looked at the effect of in utero exposure to HAART on adverse birth outcomes in women with advanced HIV disease (8). After adjusting for confounding variables this study showed that in utero HAART exposure was not associated with LBW. A maternity register audit conducted in Durban over 2 time periods, January-June 2011 and July-December 2014, showed a statistically significant reduction in the number of stillbirths and the number of infants born preterm in the second time period, this correlated with higher rates of HAART usage among mothers (21). A study in Blantyre, Malawi recruited healthy HIV positive mothers who were on HAART and HIV negative controls (22). The adjusted OR for LBW in HIV exposed infants was 1.62 but was not statistically significant (95% CI 0.97 to 2.71). The study concluded that ART has reduced the high rates of adverse pregnancy outcome among HIV infected women (22).

Highly active antiretroviral therapy has improved maternal health and some studies suggest that HAART has improved the rates of adverse birth outcomes among HIV exposed infants. The aim of our study was to evaluate the association between maternal HIV infection and infant LBW in the context of widespread HAART usage.

METHODS

Study Design and Participant Selection

This study was a retrospective cross-sectional study. The V98_28OBTP study was conducted by the Respiratory and Meningeal Pathogens Research Unit (RMPRU) between July 2014 and December 2016 at Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, Johannesburg. Chris Hani Baragwanath Academic Hospital is a referral hospital for 4 surrounding hospitals and 3 midwife obstetric units and delivers 50-70 babies per day (approximately 20 000 deliveries per year). Soweto is an area within Johannesburg, and is home to just under 1,7 million people (23). The V98_28OBTP study looked into Group B streptococcal disease in new-borns. Women aged at least 18 years old, who delivered at CHBAH during the study period were invited to participate. Women who consented to study participation for her and her new-born(s) were included. Trained research assistants and enrolled and professional nurses recruited a cohort of mother-infant pairs over the study

period. With permission the V98_28OBTP data set was used for this study. All participants of the V98_28OBTP study with singleton pregnancies, known infant birth weight and known maternal HIV status were included. The final data set consisted of 36 808 mother-infant pairs.

In the V98_28OBTP study maternal characteristics were retrieved through history taking and maternity case record review. Mid-upper arm circumference (MUAC) was measured by study recruiters at enrolment. Patients were enrolled in the antenatal clinic, in the labour ward and in the postnatal wards. Information not available antenatally was captured post-delivery. Maternal hypertensive disease included any form of hypertensive disease found in pregnant women, similarly with maternal diabetes. Birth weight was recorded as measured by the midwife post-delivery using the hospital scale in the area where the patient delivered. In addition to the V98_28OBTP study data, infant birth HIV polymerase chain reaction (PCR) results, maternal CD4+ cell counts and maternal viral load levels were retrieved from the National Health Laboratory Services (NHLS). These results were linked to the main data set using maternal hospital folder numbers.

Low birth weight was chosen as the outcome variable for this study. This variable includes a heterogeneous group of infants who are born premature (<37 weeks of gestation), growth restricted (small for gestational age (SGA)) or both. Research shows that infants born premature are at greater disadvantage when compared to infants who are growth restricted (ref 14). In weight-matched categories infants that are SGA have lower mortality rates than infants that are appropriate for gestational age. In South Africa, as in other low and middle-income countries, gestational age is calculated from either last menstrual period, symphysis fundal height palpation or, if available, obstetric ultrasound. Gestational age calculation is prone to inaccuracy. Problems that arise leading to this inaccuracy include; incorrect recall of date of last menstrual period, amenorrhoea or irregular menses related to wide-spread use of injectable progesterone-containing contraceptives, obesity with subsequent inaccurate symphysis fundal height measurement, and limited access to obstetric ultrasound. Low birth weight was chosen as it is not prone to these inaccuracies.

Statistical Methods

Data were analysed using STATA version 14.2 (College Station, Texas). Characteristics (including mean birth weight) of HIV negative mothers and their infants were compared to HIV positive mothers and their infants using Student's t-test for continuous, normally distributed variables and Pearson's Chi-square test for categorical variables. Normality was determined using histogram distribution plots and the central limit theorem. Similarly, mean birth weight of all birth HIV PCR positive infants was compared to PCR negative infants.

Univariate logistic regression was then individually conducted between LBW and other variables. All statistically significant and/or clinically relevant variables were sequentially added to a logistic multivariate model with maternal HIV status as the primary explanatory variable. The final multivariate model gave the association of maternal HIV status and LBW (in terms of odds ratio) after controlling for confounding variables.

Sub group analysis looking only at HIV positive mothers was done to assess the association between LBW and ART regimen.

Ethics statement

The study protocols for both the V98_28OBTP study (HREC reference number: 140203) and the sub-study (HREC reference number M171107) were reviewed and approved by the Human Research Ethics Committee (HREC) of the University of Witwatersrand. The V98_28OBTP study was registered on Clinicaltrials.gov (NCT02215226). All data with patient identifying information were kept password protected and identifiers were removed from the data set prior to data analysis.

RESULTS

From an initial cohort of 39 725 mother-infant pairs after excluding 2 917 participants (figure 2.1) from the V98_28OBTP study, a total of 36 808 mother infant pairs were included. The maternal study population had a mean age of 27.6 years (standard deviation (SD) ± 6.2 years), 35 653 (97%) were Black Africans, had a mid-upper arm

circumference (MUAC) of 29.2cm (SD ± 4.4cm) and 10 711 (29.2%) were primigravids (table 2.1). Of the 36 808 women with known HIV results, 10 990 (29.9%) mothers were HIV positive and 25 818 (70.1%) were HIV negative. There were 10 maternal deaths (27 per 100 000), 3 974 (12.3%) mothers with hypertensive disease and only 267 (0.8%) with diabetes. The rate of caesarean section was 41.3% (n=15 187). The mean birthweight of infants in the study was 3 027g (SD ± 603g) with 5 294 (14.4%) qualifying as LBW.

When comparing the maternal HIV positive and negative groups. Mothers who were HIV positive were older, more likely to be infected with syphilis and more likely to have used alcohol in pregnancy. Mothers who were HIV negative were more likely to be primigravids and more likely to have hypertension or diabetes (table 2.1).

The mean birthweight of infants born to HIV positive mothers was 2 948g (SD ± 604g) and differed significantly from HIV negative mothers 3 061g (SD ± 599g) (P<0.001) (table 2.1) difference of 113g (95% CI 99-126g).

Among the subgroup of HIV positive mothers, 884 (8.0%) had an unknown ART history (table 2.2). Of those with a known ART history, 9 564 (94.6%) were on some form of ART with 542 (5.4%) never having received any ART. Among those whose ART regimen was recorded, 8 881 (98.1%) were on the first line regimen provided in South Africa which is a fixed dose combination consisting of emtricitabine, tenofovir and efavirenz. CD4+ cell information from NHLS was successfully matched to 1 758 participants and found a mean CD4+ cell count of 453 cells/uL (SD ± 247cells/uL). Maternal viral load information from NHLS was successfully matched to 1 508 participants and found 826 (54.7%) to be virally suppressed, of those viral loads that were detectable the median viral load was 658 (interquartile range 81 – 15 200).

Of infants born to HIV positive mothers, 2 907 had a birth PCR result successfully matched. The HIV transmission rate was 0.8% with only 24 infants diagnosed as HIV positive at birth. 2 859 (98.4%) were HIV PCR negative and 24 (0.8%) had indeterminate PCR results.

The mean birthweight of infants with a positive birth HIV PCR results was 2 680g (SD ± 679g). This was lower than the mean birth weight of PCR negative infants, 2 917g (SD ± 622g) but was not statistically significant (P=0.063).

In univariate logistic regression (table 2.3) LBW was associated with increasing maternal age, Caucasian and Coloured race, positive syphilis serology, smoking and using alcohol during pregnancy, 2 or more prior pregnancies, prior stillbirth, prior miscarriage, maternal death, maternal hypertension, maternal HIV infection, caesarean section delivery and female gender. Larger MUAC was protective against LBW. The OR for LBW as related to maternal HIV infection was 1.43 (95% CI 1.35-1.52). After adjusting for confounding variables the multivariate model gave an adjusted OR for LBW as related to maternal HIV infection of 1.49 (95% CI 1.35-1.64). In this model syphilis serology, alcohol use in pregnancy and maternal death were no longer associated with LBW. Two or more prior stillbirths and 3 or more prior miscarriages were strongly associated with LBW as well as maternal hypertension.

Any ART was found to be protective of LBW with an OR of 0.80 (95% CI 0.647-0.995) (table 2.4). When comparing the different ART regimens, no statistically significance differences were found.

TABLES/FIGURES

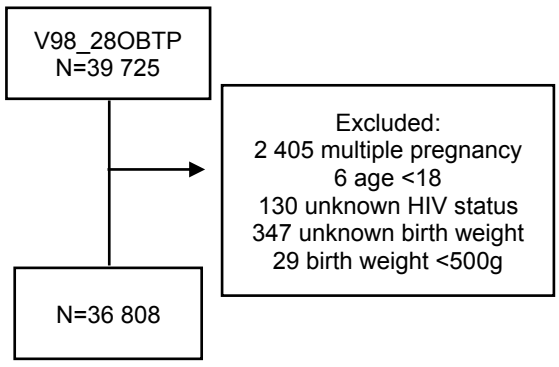


Figure 2.1 – Study population flow diagram.

Table 2.1 – Maternal and infant demographics for total, HIV negative and HIV positive study populations.

Variable	N Study participants for whom this information was available	Total Expressed as n(%) or mean(±SD)	HIV negative Expressed as n(%) or mean(±SD)	HIV positive Expressed as n(%) or mean(±SD)	P-value
Maternal					
Age (years)	36 807	27.6(±6.2)	26.7(±6.1)	30.0(±6.0)	<0.001
Race	36 755				
Black		35 653(97.0%)	24 800(96.2%)	10 853(98.9%)	
Coloured		961(2.6%)	846(3.3%)	115(1.1%)	
Caucasian		24(0.1%)	24(0.1%)	0	
Asian		69(0.2%)	66(0.3%)	3(0.03%)	
Other		48(0.13%)	45(0.2%)	3(0.03%)	<0.001
MUAC (cm)	34 614	29.2(±4.4)	29.2(±4.4)	29.1(±4.2)	0.030
Booking Hb (g/dL)	35 318	11.60(±1.69)	11.76(±1.64)	11.21(±1.73)	<0.001
Syphilis positive	33 917	324(0.96%)	149(0.62%)	175(1.75%)	<0.001
Smoked in pregnancy	29 827	1 212(4.1%)	842(4.0%)	370(4.2%)	0.583
Used alcohol in pregnancy	29 667	1 953(6.6%)	1 304(6.3%)	649(7.3%)	0.001
Number of prior pregnancies	36 725				
primigravida		10 711(29.2%)	9 135(35.5%)	1 576(14.4%)	
1		11 552(31.5%)	8 034(31.2%)	3 518(32.1%)	
2		8 375(22.8%)	5 048(19.6%)	3 327(30.4%)	
3		3 963(10.8%)	2 271(8.8%)	1 692(15.4%)	
≥4		2 124(5.8%)	1 278(5.0%)	846(7.7%)	<0.001
Prior stillbirth	25 929				
1		1 277(4.9%)	820(5.0%)	457(4.9%)	
≥2		165(0.6%)	99(0.6%)	66(0.7%)	0.571
Prior miscarriage	25 927				
1		3 921(15.1%)	2 563(15.5%)	1 358(14.5%)	
2		583(2.3%)	374(2.3%)	209(2.2%)	
≥3		250(1.0%)	177(1.1%)	73(0.8%)	0.126
Maternal death	35 411	10(0.03%)	5(0.02%)	5(0.05%)	0.166
Maternal hypertensive disease	32 383	3 974(12.3%)	2 951(13.1%)	1 023(10.5%)	<0.001
Maternal diabetes	31 777	267(0.8%)	215(1.0%)	52(0.5%)	<0.001
Foetal					
Delivery by Caesarean section	36 806	15 187(41.3%)	10 579(41.0%)	4 608(41.9%)	0.086
Elective	15 183	2 549(16.8%)	1 638(15.5%)	911(19.8%)	
Emergency		12 634(83.2%)	8 938(84.5%)	3 696(80.2%)	<0.001
5 Min apgar <8	35 562	1 003(2.8%)	693(2.8%)	310(2.9%)	0.441
Female gender	36 804	18 097(49.2%)	12 663(49.0%)	5 434(49.4%)	0.493
Birthweight (g)	36 808	3027(±603)	3061(±599)	2948(±604)	<0.001
Low birth weight (<2500g)	36 808	5 294(14.4%)	3 358(13.0%)	1 936(17.6%)	<0.001

Abbreviations: MUAC – mid upper arm circumference, SD – standard deviation, Hb – haemoglobin

Table 2.2 – HIV related demographics

Variable	N*	n(%), mean(±SD), median[IQR]
Maternal		
ARV history	10 990	
Unknown		884(8.0%)
Known ARV history	10 106	
Never received		542(5.4%)
Received		9 564(94.6%)
Received	9 564	
Regimen not specified		508(5.3%)
ARVs received known	9 056	
ETE		8 881(98.1%)
Other HAART		121(1.3%)
Other not HAART		54(0.6%)
Serum CD4+ cell count (cells/uL)	1 758	453(±247)
Serum VL (copies/ml)	1 508	
Lower than detectable limit		826(54.7%)
Detectable	682	658[81; 15 200]
Infant		
Birth HIV PCR result	2 907	
Negative		2 859(98.4%)
Positive		24(0.8%)
Indeterminate		24(0.8%)

Abbreviations: SD – standard deviation, IQR – interquartile range, ETE – standard issue fixed dose combination: emtricitabine, tenofovir and efavirenz, HAART – highly active antiretroviral therapy, VL – viral load, PCR – polymerase chain reaction.
*Study participants for whom this information was available.

Table 2.3 – Maternal and infant characteristics plus logistic regression analysis for low birth weight as compared to normal birth weight.

Variable	N$	NBW Expressed as n(%) or mean(±SD)	LBW Expressed as n(%) or mean(±SD)	Crude OR [95% CI]	P	Adjusted OR [95% CI]	P
Maternal							
Age (per year increase)	36 807	27.5(±6.2)	28.2(±6.5)	1.016 [1.01-1.02]	<0.001	1.015 [1.01-1.02]	<0.001
Race	36 755						
Black		30 593(97.2%)	5 060(95.7%)	1.00		*	
Caucasian		14(0.04%)	10(0.19%)	4.32 [1.92-9.73]	<0.001		
Coloured		765(2.4%)	196(3.7%)	1.55 [1.32-1.82]	<0.001		
Asian		58(0.2%)	11(0.2%)	1.15 [0.60-2.18]	0.678		
Other		40(0.1%)	8(0.2%)	1.21 [0.57-2.58]	0.624		
MUAC (per 1cm increase)	34 614	29.3(±4.4)	28.4(±4.4)	0.95 [0.94-0.96]	<0.001	0.93 [0.92-0.94]	<0.001
Booking anaemia(<10g/dL)	35 318	4 580(15.1%)	785(16.0%)	1.07 [0.99-1.17]	0.086	*	
Syphilis positive	33 917	266(0.9%)	58(1.3%)	1.38 [1.04-1.84]	0.026	1.38 [0.90-2.13]	0.144
Smoked in pregnancy	29 827	981(3.8%)	231(5.5%)	1.47 [1.27-1.71]	<0.001	1.58 [1.26-1.98]	<0.001
Alcohol in pregnancy	29 667	1 650(6.5%)	303(7.3%)	1.14 [1.00-1.29]	0.046	1.05 [0.86-1.27]	0.647
Prior pregnancies	36 725						
primigravida		9 246(29.4%)	1 465(27.8%)	1.00			
1		9 996(31.7%)	1 556(29.5%)	0.98 [0.91-1.06]	0.651	*	
2		7 143(22.7%)	1 232(23.4%)	1.09 [1.00-1.18]	0.042		
3		3 330(10.6%)	633(12.0%)	1.20 [1.08-1.33]	<0.001		
≥4		1 741(5.5%)	383(7.3%)	1.39 [1.23-1.57]	<0.001		
Prior stillbirth	25 929						
0		21 014(94.9%)	3 473(91.7%)				
1		1 026(4.6%)	251(6.6%)	1.48 [1.28-1.71]	<0.001	1.44 [1.18-1.75]	<0.001
2		87(0.4%)	47(1.2%)	3.27 [2.29-4.67]	<0.001	3.36 [2.06-5.49]	<0.001
≥3		15(0.1%)	16(0.4%)	6.45 [3.19-13.07]	<0.001	3.70 [1.45-9.43]	0.006
Prior miscarriage	25 927						
0		18 234(82.4%)	2 939(77.6%)				
1		3 272(14.8%)	649(17.1%)	1.23 [1.12-1.35]	<0.001	1.44 [1.27-1.63]	<0.001
2		470(2.1%)	113(3.0%)	1.49 [1.21-1.84]	<0.001	1.41 [1.05-1.89]	0.021
≥3		163(0.7%)	87(2.3%)	3.31 [2.55-4.31]	<0.001	4.23 [3.03-5.91]	<0.001
Maternal death	35 411	4(0.01%)	6(0.12%)	2.99 [1.59-5.64]	0.001	0.99 [0.25-3.97]	0.988
Maternal hypertension	32 383	2 829(10.2%)	1 145(24.3%)	2.82 [2.61-3.05]	<0.001	3.36 [2.98-3.79]	<0.001
Maternal diabetes	31 777	219(0.8%)	48(1.1%)	1.32 [0.96-1.81]	0.084	*	
Maternal HIV infection	36 808	9 054(28.7%)	1 936(36.6%)	1.43 [1.35-1.52]	<0.001	1.49 [1.35-1.64]	<0.001
Foetal							
Caesarean section delivery	36 806	12 307(39.1%)	2 880(54.4%)	1.86 [1.76-1.97]	<0.001	2.13 [1.93-2.35]	<0.001
Female gender	36 804	15 282(48.5%)	2 815(53.2%)	1.21 [1.14-1.28]	<0.001	1.21 [1.10-1.33]	<0.001

Abbreviations: MUAC – mid upper arm circumference, SD – standard deviation, NBW – normal birth weight, LBW – low birth weight, OR – odds ratio, CI – confidence interval.

$ Study participants for whom this information was available.

* not included in multivariate model – either not statistically significant or deemed not to be clinically relevant.

Table 2.4 – ARV exposure as related to LBW for HIV exposed infants.

ARV exposure	N*	Total	NBW	LBW	OR [95% CI]	P-value
Any ARV treatment vs no treatment	10 106	9 564(94.6%)	7 926(94.8%)	1 638(93.7%)	0.80 [0.647-0.995]	0.045
ARV regimens						
HAART vs all other ARV regimens	9 056	9 002(99.4%)	7 472(99.4%)	1 530(99.4%)	0.90 [0.45-1.79]	0.767
ETE vs other HAART regimens	9 002	8 881(98.7%)	7 377(98.7%)	1 504(98.3%)	0.74 [0.48-1.15]	0.185

Abbreviations: NBW – normal birth weight, LBW – low birth weight, OR – odds ratio, CI – confidence interval, ARV – antiretroviral, HAART – highly active antiretroviral therapy, ETE – standard issue fixed dose combination: emtricitabine, tenofovir and efavirenz.
*Study participants for whom this information was available.

DISCUSSION

Main Study Findings

We found that maternal HIV infection is associated with infant LBW in the setting of HAART usage, although the association is not strong. We also found that infants born to HIV positive mothers have lower birth weights than infants born to HIV negative mothers although the small difference may not be clinically significant. Additionally, any maternal ART use is protective against LBW compared to no ART, but residual confounding is possible. There was no significant association between in utero HIV infection of infants and birthweight, however this result was limited by low MTCT rates and the trend suggested HIV infected infants to have lower birth weights. We did not find any association between LBW and the different ART regimens.

Secondary findings revealed that LBW is strongly associated with 2 or more prior stillbirths and 3 or more prior miscarriages as well as maternal hypertension and poor maternal nutrition (low MUAC). LBW was also associated with increasing maternal age, smoking in pregnancy, caesarean section delivery and female gender, but these associations were not strong.

Results in Context

The association we found between maternal HIV infection and infant LBW is weaker than the association that was shown in the meta-analyses done by Brocklehurst et al and Xiao et al, done prior to wide spread HAART usage in pregnancy (10,11). This suggests that ART has improved birth weight outcomes for infants exposed to HIV in utero and is in agreement with other South African research (8,21). Although weaker, the association remains, and has been similarly shown in a large study from Botswana (24). This is contradictory to other studies which have not shown an association (22,25). Dadabhai et al looked at 1299 women and found an adjusted OR for LBW as related to HIV infection of 1.62 (95% CI 0.97-2.71) (22). Malaba et al looked at 1554 women and similarly found an adjusted OR for LBW as related to HIV infection of 1.47 (95% CI 0.90-2.40) (25). Neither of these studies found a significant association. This contradiction may be as a result of the weak association which exists that was better evaluated in our much larger study population.

Our results showed a non-significant trend towards lower birthweight in HIV infected infants compared to HIV exposed uninfected infants. This finding has been shown to be significant in other research (17,26–29), which was done prior to HAART being recommended for prevention of MTCT and had higher numbers of HIV infected infants. The small percentage of birth PCR results that we were able to match to study participants and the low rate of MTCT, resulting in only 24 infants testing HIV positive at birth, under powering this analysis in our study.

An efavirenz based HAART regimen has been shown in several studies to be the safest HAART regimen for pregnant women (30–34). We did not find a significant difference in the risk of LBW between the emtricitabine/tenofovir/efavirenz regimen and other HAART regimens but the power of this analysis was limited by the low number of participants on other regimens (only 1.3%).

Other factors found to be associated with LBW included maternal hypertension which was strongly associated with LBW. This is consistent with other research (8,28,35) and not surprising as hypertensive disease is known to affect the placenta and cause intrauterine growth restriction (IUGR). We also found increasing MUAC to

be protective of LBW. This is consistent with other studies showing that poor maternal nutritional status (measured as either MUAC, body mass index or maternal weight) is associated with LBW (16,22,27,34). A history of previous pregnancy loss is associated with LBW in our population. This is in line with other evidence (36) but it is interesting to note that the adjusted OR increases as the number of prior pregnancy losses increases.

Strengths and Limitations

The strengths of our study include the large study population with a large percentage of HIV infected mothers and an HIV negative control group, which made it possible to accurately review weak associations. We also included a large number of other variables that could have resulted in confounding and were accounted for in the multivariate logistic model. The limitations of our study include the low number of CD4+ cell count and viral load results that we were able to correctly match to study participants. This has limited the accuracy with which we were able to describe the health of our HIV infected population. As already mentioned we were also limited by the low number of birth HIV PCR results that we were able to match. Not all variables were clearly defined in the data set (such as maternal hypertension). This limits the conclusions that can be drawn from the effect of these variable on our outcome. Another limitation of the study was that not all information on confounding variables was available for each study participant. This meant that not all participants were able to be included in the final multivariate logistic model and may therefore bring bias into the study results. Several models were run excluding some of the more limiting confounding variables but all gave similar adjusted ORs for maternal HIV infection, the final model was the one including the largest number of confounding variables. LBW is an outcome variable that includes infants who are growth restricted and infants who are born premature, the use of this composite variable limits the inferences that can be deduced regarding underlying cause.

Implications and Recommendations

This review highlights the importance of HAART for improved maternal health and prevention of MTCT, but also for improved birth outcomes. Future research should focus on the effect of new ART drugs and regimens on birth outcomes, but to keep in

mind that certain adverse birth outcomes may still be acceptable in the context of preventing MTCT. Where possible, populations with accurate gestational age calculations should be used to give further insight into the cause of adverse birth outcomes. Importantly we should not allow our "partial success in saving lives and stopping new HIV infections to give way to complacency (37)."

CONCLUSION

Infant low birth weight is associated with maternal HIV infection in the context of wide spread HAART usage in pregnant women, although the association is not strong and is lower than estimates prior to HAART usage, suggesting that HAART has reduced LBW for HIV exposed infants.

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APPENDIX 1 – Data sheet

Booking Information

Mother's age _____years

Number of previous pregnancies _____

Number born alive _____

Number stillborn _____

Number of miscarriages _____

Number of TOPs _____

Booking Hb _____g/dL

Syphilis result ☐ non-reactive ☐ reactive

Most recent HIV test result ☐ positive ☐ negative ☐ unknown

If positive: on treatment? ☐ yes ☐ no

If yes: ARVs _____

_____

_____

Start date: D D / M M / Y Y Y Y

Most recent: CD4 _____/mm^3 Viral load _____copies

Mid upper arm circumference _____cm

Smoking during pregnancy ☐ yes ☐ no

Alcohol use during pregnancy ☐ yes ☐ no

Delivery Information

Date of delivery D D / M M / Y Y Y Y

Gestation at delivery _____weeks _____days

Determined by ☐ fundal height ☐ last menstrual period

☐ ultrasound ☐ Ballard score

Placental weight _____grams

Maternal complications: ☐ none
☐ antepartum haemorrhage
☐ postpartum haemorrhage
☐ hypertension(gestational/pre-eclampsia/eclampsia)
☐ gestational diabetes
☐ died
other specify: _____

Infant Information

Mode of delivery ☐ vaginal cephalic
☐ vaginal breech
☐ vaginal assisted (vacuum/forceps)
☐ emergency caesarean section
☐ elective caesarean section

Infant gender ☐ male ☐ female ☐ unknown

Birth Weight _____grams

Infant outcome ☐stillbirth (≥ 28 wks gestation) ☐miscarriage (< 28 wks)
☐died after birth (if yes specify date of death D D / M M / Y Y Y Y)
☐alive ☐congenital abnormalities

If HIV exposed, birth PCR result: ☐positive ☐negative ☐unknown

APPENDIX 2 – RMPRU permission letter

11th Floor, Central-West wing, Nurses residence
Chris Hani Baragwanath Hospital
P.O. Box 90753, Bertsham, 2013
Tel +27-11-985-2515
Fax: +27-11-989-9886



DST/ NRF VPD
RMPRU
respiratory & meningeal pathogens research unit

2nd November 2017

Professor Cleaton-Jones
Human Research Ethics Committee (Medical), University of the Witwatersrand

Dear Prof Cleaton-Jones

Permission for use of data from V98_28OBTP study for M.Med

This letter grants Dr. Juliette Phelp (Wits student number 1596003) permission to utilize the data collected in the 'V98_28OBTP' study for her MMed project entitled 'The association between maternal HIV infection and low birth weight at Chris Hani Baragwanath Academic Hospital'.

Conditions relevant to Dr Phelp's use of these data include (i) assurance that personal details of participants will be kept confidential, (ii) the funder, the Novartis vaccine division, is acknowledged in M.Med report and publications and (iii) inclusion of V98_28OBTP lead investigators as co-authors on publications.

The full details of the V98_28OBTP study are:

Title: Establishing a sero-correlate of protection against invasive Group B Streptococcus disease in newborns and young infants aged ≤90 days.
Principal Investigator: Shabir A. Madhi
HREC reference: 140203
Study abbreviation: V98_28OBTP
Please do not hesitate to contact me (cutlandc@rmpru.co.za) if any further clarifications are required.

Yours truly



Clare L. Cutland
Clinical lead investigator, V98_28OBTP
Deputy director
Medical Research Council: Respiratory and Meningeal Pathogens Research Unit

APPENDIX 3 – Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr J Phelp

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M171107

NAME: (Principal Investigator)	Dr J Phelp
DEPARTMENT:	School of Clinical Medicine Department of Obstetrics and Gynaecology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	The association between maternal HIV infection and low birth weight at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	24/11/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Drs C Cutland and S Maswime
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	14/03/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

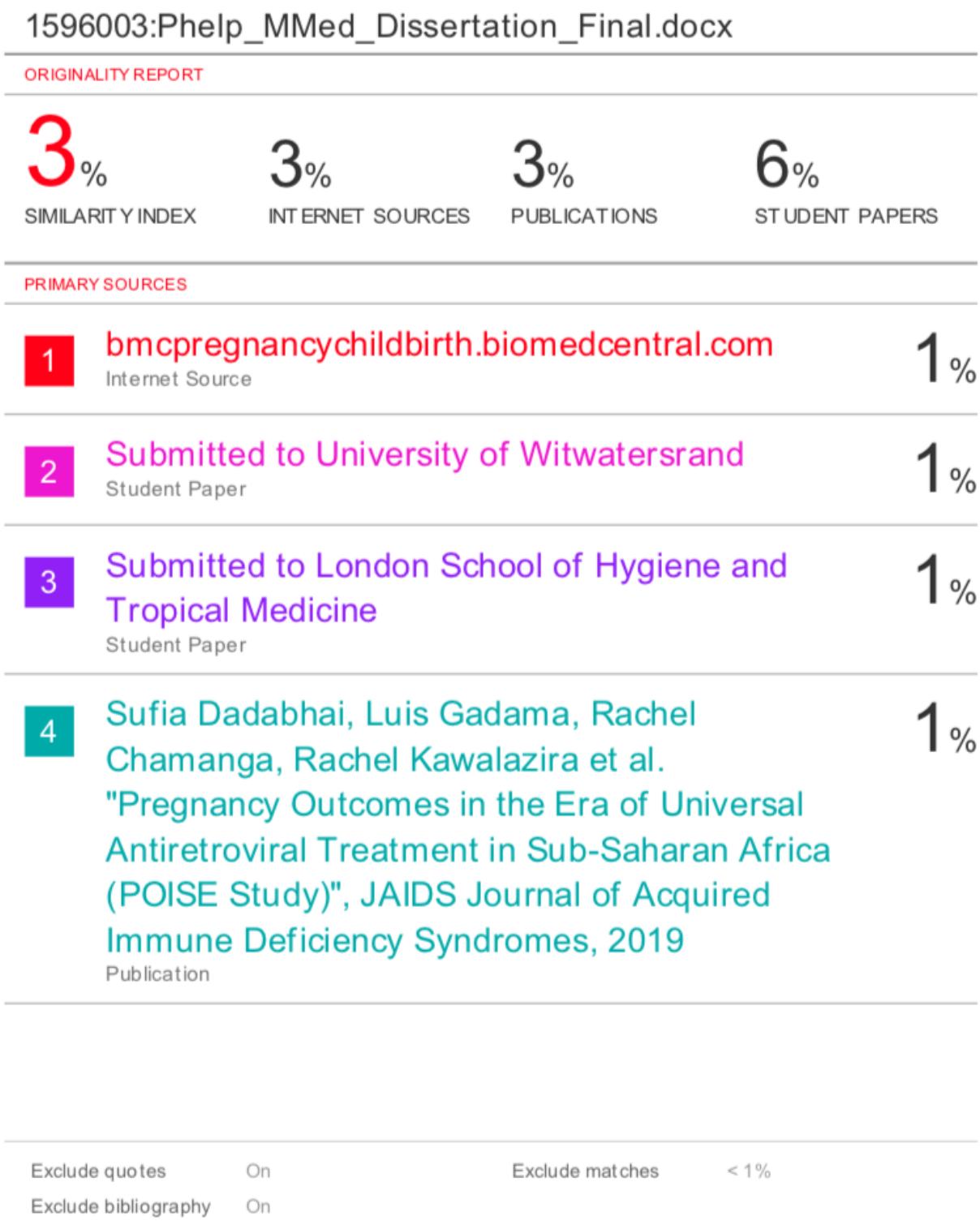
DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially reviewed in **November** and will therefore be due in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 4 – Turn it in report



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