PREGNANCY OUTCOME IN HIV POSITIVE WOMEN ON ANTIRETROVIRAL THERAPY DELIVERING IN DURBAN, SOUTH AFRICA

Submitted in partial fulfilment of the academic requirements for the Fellowship of the College of Obstetricians and Gynaecologists of South Africa (FCOG)SA

DR D A KESENE

JUNE 2014

PREGNANCY OUTCOME IN HIV POSITIVE WOMEN ON ANTIRETROVIRAL THERAPY DELIVERING IN DURBAN SOUTH AFRICA

PREGNANCY OUTCOME IN HIV POSITIVE WOMEN ON ANTIRETROVIRAL THERAPY DELIVERING IN DURBAN SOUTH AFRICA

RESEARCHER: DR D A KESENE

Submitted in partial fulfilment of the academic requirements for the Fellowship of the College of Obstetricians and Gynaecologists of South Africa (FCOG) SA

JUNE, 2014

TABLE OF CONTENTS

Chapter 3: Results

CHAPTER 4: DISCUSSION

Appendices

DEDICATION

This dissertation is dedicated to the Almighty God by whose power I was able to complete it.

DECLARATION

I, Dr Dennis Abanum Kesene, do hereby declare that the work on which this dissertation is based is my own original work, under the supervision and mentorship of Professor J.S Bagratee.
This dissertation has not been previously submitted to any other colleges

Candidate

Dr D. A. Kesene

Signature_____

Department of Obstetrics and Gynaecology

Nelson R Mandela School of Medicine

University of KwaZulu-Natal

Durban

Supervisor

Professor J. S. Bagratee

Signature_____

Department of Obstetrics and Gynaecology

Nelson R Mandela School of Medicine

University of KwaZulu-Natal

Durban

ACKNOWLEDGEMENT

I would like to express my gratitude to my wife, Chinyere, and children, Ebenezer, Ruth and Joshua for their understanding, encouragement and support throughout the period of this study

I also want to thank Professor JS Bagratee for his mentorship. He has taught me to always strive for excellence in all my pursuits

To all the staff of medical records King Edward VIII Hospital, especially Mr Derek Lakhan, for allowing me access to the department even after hours, I would like to say thank you.

Thanks to Mrs Fikile Nkwanyana of Department of Public Health Medicine, University of KwaZulu-Natal, for all the assistance.

Glossary

AFI	Amniotic fluid index
APGAR	American Paediatric Gross Assessment Record Score
ART	Antiretroviral therapy
AZT	Azidothymidine
BREC	Biomedical Research Ethics Committee of the University of KwaZulu-Natal
CD4	Cluster of differentiation 4
EFV	Efavirenz
FDC	Fixed dose combination
FTC	Emtricitabine
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
ISSHP	International Society for the Study of Hypertension in Pregnancy
IVH	Intraventricular haemorrhage
KEH	King Edward VIII Hospital
KZN	KwaZulu-Natal Province
LBW	Low birth weight
NEC	Necrotising enterocolitis
NICU	Neonatal intensive care unit
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
PI	Protease inhibitor
PPH	Post-partum haemorrhage
PPROM	Preterm premature rupture of the membranes
RDS	Respiratory distress syndrome
SGA	Small for gestational age babies
3TC	Lamivudine
WHO	World Health Organization

ABSTRACT

Background: Reports in the literature regarding the effect of antiretroviral therapy on pregnancy outcomes are conflicting and are largely from cohorts in the developed world.

Methodology: A retrospective cohort study of all deliveries in King Edward VIII Hospital (KEH) Durban, South Africa, from 1st of March 2013 to 30th of June 2013 was conducted

Aims/Objectives: 1.To describe the demographic profiles of women with HIV on HAART;2.To estimate the risk of preeclampsia in HIV positive women on HAART;3.To determine the prevalence of post-partum hemorrhage in HIV positive women on HAART;4.To determine the prevalence of chorioamnionitis in HIV positive women on HAART;5.To determine the prevalence of preterm delivery either iatrogenic or spontaneous in HIV positive women on HAART;6.To determine neonatal outcome and prevalence of low birth weight at term in neonates of HIV positive women on HAART

Results: There were 970 HIV positive women (39.3%) and 1496 HIV negative (60.7%).HIV Positive women on antiretroviral therapy had lower odds for developing preeclampsia (7.9% vs 12.9%, P< 0.001), abruptio placentae (1.0% vs 2.5%, P =0.003) gestational diabetes mellitus (0.3% vs 1.3%, P = 0.01), than HIV negative women. Women on antiretroviral medications were more likely to have preterm premature rupture of the membranes (PPROM) (5.6% vs 3.4%, P=0.01) and chorioamnionitis (0.95% vs 0.27%, P= 0.02) than HIV negative women. There were no differences in maternal outcomes including chronic hypertension (1.1% vs 1.8%, P =0.87) and gestational hypertension (4.0% vs 3.2% P = 0.33). The odds of having postpartum haemorrhage was not different between the two groups (2.5% vs 3.2%, P = 0.25) for HIV positive women on antiretroviral medications and HIV negative women respectively. There was no difference in the prevalence of preterm delivery at less than 37 weeks of gestation (17.8% vs 19.9%, P = 0.19), and preterm delivery at less than 34weeks of gestation (8.7% vs 7.6%, P = 0.32) between HIV positive women on antiretroviral medication and HIV negative women. Neonatal outcomes including 5-min APGAR score <7(1.9% vs 1%, P = 0.08) intraventricular hemorrhage (0.4% vs 0%, P = 0.05) respiratory distress syndrome (7.7% vs 6.9% P = 0.47), neonatal pneumonia (1.4% vs 2.3% P =0.08), necrotising enterocolitis (0.1% vs 0%, P= 0.52), and culture proven sepsis (1.2% vs 1.3%, P= 0.92) were similar for both groups.

Conclusion

HIV positive women on antiretroviral therapy are at lower risk of adverse maternal outcomes such as preeclampsia, abruptio placentae, and gestational diabetes mellitus. There is no difference in the risk of perinatal complications like 5-min APGAR score < 7, and delivering low birth weight babies between HIV positive and HIV negative women. However, HIV positive women are at increased risk of developing chorioamnionitis compared to HIV negative women.

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Antiretroviral therapy (ART) is effective in improving maternal health as well as in prevention of mother-to-child transmission (PMTCT) in human immunodeficiency virus (HIV) infected women [1, 2]. Reports in the literature regarding the outcome of pregnancies in women seropositive for HIV on antiretroviral therapy are conflicting and are largely from cohorts in the developed world [3-7]. Two million pregnancies occur every year in HIV-infected women, most of whom are in sub-Saharan Africa[8, 9]. This region accounts for two-thirds of the 34million people living with HIV globally[9, 10] and a large number of women infected with HIV are now on highly active antiretroviral therapy(HAART) in pregnancy[9, 10]. This is as a result of concerted efforts by the international community to support attainment of universal access to HAART. The World Health Organization (WHO) recommended, in 2010, that all individuals infected with HIV, with a CD4 count ≤ 350cells/ mm^3 ; and all pregnant women with WHO clinical stage 3 or 4 disease, independent of CD4 cell count, should be commenced on HAART[9]. This recommendation was revised by the WHO in 2013 where the guidelines now recommend that option B+ be implemented by all countries and where this is impossible, option B. Option A should only be implemented as last alternative[11].

In Option B+, all pregnant women infected with HIV are given HAART for the entire duration of pregnancy, labour, delivery and breastfeeding and they continue lifelong, irrespective of CD4 count or clinical stage of the disease. On the other hand, in Option B, HAART is taken throughout pregnancy and continued for life only if CD4 count is ≤350cells/mm^3 beginning as soon as diagnosis of HIV infection is made. Pregnant women with CD4 count >350cells/$mm^3$are given HAART from 14weeks of pregnancy and continue through labour and delivery, if baby is not breastfed, or until 1 week after breastfeeding ends. In Option A, Pregnant women receive HAART throughout pregnancy, labour and delivery and continue for life, again only, if CD4 count≤ 350cells/mm^3 as in option B above. Women with CD4 count > 350cells/mm^3 receive azidothymidine (AZT) from 14weeks gestation and single dose nevirapine(NVP) as well as first dose azidothymidine/lamivudine(AZT/3TC) at the beginning of labour, and daily AZT/3TC for 1 week post-partum[12] Pregnant women who require

antiretroviral therapy either because of low count of CD4 or advanced clinical stage of the disease, have HAART for life[11]. However, eligibility for HAART for life is to be determined by individual country. A CD4 count of ≤ 500 cells/mm^3 (or clinical stage 3 or 4 disease) is recommended by WHO as eligibility criteria for HAART for life[11].

The combination of tenofovir plus lamivudine (or emtricitabine) plus efavirenz is the first-line treatment regimen for HIV-infected pregnant and breastfeeding women. It is made available as a fixed-dose combination(FDC) and it is affordable[11, 13]. This regimen is also well tolerated and safe for both pregnant and breastfeeding women and their infants. Monitoring requirements and drug-resistance profiles are low for this regimen [14-16]. It can be administered together with other drugs used in the clinical care of HIV-infected population including non-pregnant adults[17, 18]. It is simple, affordable and taken as a once daily regimen and also has efficacy against hepatitis B virus (HBV) [11, 13, 19-22].

The goals of treatment with HAART include: minimization of morbidity associated with HIV and improvement in life expectancy and quality of survival [23-26]; prevention of HIV transmission[27-32]; maximum and prolonged viral load suppression; and restoration and preservation of immunological function[33, 34].The changes in the immune system during pregnancy are well documented. The absolute number as well as the percentage CD4 count have been reported to drop in pregnancy and return to their pre-pregnancy range within four months post-delivery[35, 36]. The consequence of this on HIV-infected pregnant women is uncertain. Some studies report a deterioration of immune function during pregnancy[37, 38] and others report no important effect of pregnancy on immune function [39, 40]. Studies before the advent of the use of HAART by large numbers of HIV-infected pregnant women demonstrated that there was either only slight increase or no effect on HIV disease progression attributable to pregnancy [38, 41-45] Pregnancy may be associated, though not strong, with HIV disease progression as demonstrated by a systematic review and meta-analysis[46].

HIV disease progression has been shown to be decreased by HAART[47, 48].There is an association of a marked decrease in morbidity and mortality rates in populations infected with HIV with the use of HAART [49].However, it is also known that use of HAART by pregnant women may increase the risk of preterm birth either iatrogenic or spontaneous[3,

4, 6, 50-53]. There are also reports of increased risk of preeclampsia, fetal death [52, 54, 55], low birth weight[56] and gestational diabetes mellitus[57] with HAART. Maternal complications including hepatic failure and lactic acidosis, though uncommon, have been recognised as complications of HAART, especially with increased duration of use[58]. Pregnancy may also exacerbate the risks of other side effects of HAART such as vomiting and anaemia[59]

Antenatal HIV infection prevalence is particularly high in South Africa at 39.5%[60].Non-pregnancy related infections, mainly due to HIV and acquired immunodeficiency syndrome(AIDS) have been reported as the most common cause of maternal mortality, constituting 43.7% of all maternal deaths in South Africa[61]. Maternal HIV infection is associated with post-partum endometritis and a tendency to a higher stillbirth rate[62].Pregnant women infected with HIV appear to be at significantly higher risk of unfavourable pregnancy and infant outcomes than women seronegative for HIV. These adverse outcomes include increased incidence of miscarriage, fetal abnormality, premature delivery, low birth weight babies, perinatal, neonatal and infant mortalities.[63, 64]

These adverse pregnancy outcomes have not been documented in our local population where up to 40.3% of women delivering in our health facilities are HIV positive[60].Therefore, we sought to estimate the risk of adverse pregnancy outcomes in HIV positive women on HAART compared with non-infected population.

CHAPTER 2

2.1 METHODOLOGY

A retrospective cohort study of all deliveries in King Edward VIII Hospital (KEH) from 1st of March 2013 to 30th of June 2013 was conducted.

King Edward the VIII hospital serves predominantly patients from low socioeconomic circumstances in the Durban area of KwaZulu-Natal. Standard practice at the time of this study was for all women at their first antenatal booking visit to have counselling and testing for HIV. Women who were HIV positive had their bloods tested for CD4 count levels. HIV viral load was not routinely tested.

The department of health policy on antiretroviral therapy at the beginning of the data collection period was the implementation of WHO option B as discussed above. Towards the end of the data collection period the policy was changed to option B+ in line with the WHO recommendations.

2.2 AIMS/OBJECTIVES

1. To describe the demographic profiles of women with HIV on HAART
2. To estimate the risk of developing preeclampsia in women seropositive for HIV on HAART
3. To determine the prevalence of post-partum haemorrhage in women seropositive for HIV on HAART
4. To determine the prevalence of chorioamnionitis in HIV-infected women on HAART
5. To determine the prevalence of preterm delivery either iatrogenic or spontaneous in women seropositive for HIV on HAART
6. To determine the neonatal outcome and prevalence of low birth weight at term in neonates of women seropositive for HIV on HAART

2.3 INCLUSION CRITERIA

All mothers who delivered after 26weeks of gestation from 1st of March 2013 to 30th of June 2013 were included. This included all women seropositive and seronegative for HIV

Women seropositive for HIV on HAART initiated either before or during the index pregnancy were included.

2.4 EXCLUSION CRITERIA

All women delivering before 26 weeks of gestation were excluded as well as those that had multiple gestations.

HAART refers to the use of three or more antiretroviral agents (either as fixed dose combination or individual agents) concomitantly for the purpose of aggressive reduction in viral load and improvement of patient's CD4 cell count.

HIV positive mothers who took antiretroviral drug or drugs in the index pregnancy for the purpose of prevention of vertical transmission were also included. This includes women who used azidothymidine (AZT) from 14weeks of gestation or later, single dose nevirapine and tenofovir/emtricitabine at the onset of labour (Dual therapy).

2.5 DATA COLLECTION

Discharge register in labour ward was used to get inpatient numbers of mothers, and of their babies, that delivered during the study period, 1st March 2013 to 30th June 2013.

Charts of women and, of their babies, delivering in King Edward VIII Hospital during this period were retrieved from medical records department and a detailed chart review was performed.

Data collection using a data sheet designed for the purpose of this study was undertaken

Demographic data were obtained from antenatal records together with inpatient admission history. Gestational age at time of delivery was obtained from patient's chart calculated with the last menstrual period (LMP) reported. In instances where patients were unsure,

ultrasound estimation of gestational age or estimates of gestation based on the earliest palpation as documented in the patient's chart were used. The use of drugs of abuse, smoking, or alcohol use was obtained from patients' charts as self-reported by the patient. HIV status was confirmed by review of serological test result documented in patient's ante natal record.

Adverse obstetric outcomes examined include: preterm delivery iatrogenic or spontaneous, (defined as delivery before 37 weeks of gestation), gestational hypertension, preeclampsia (as defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines), gestational diabetes mellitus either treated by dietary control or requiring hypoglycaemic agents, including either insulin or oral hypoglycaemic agents or both.

Post-partum outcomes investigated included: post-partum haemorrhage (as documented diagnosis by attending health care practitioner) and this was defined as blood loss >500ml at vaginal delivery or >1000ml at caesarean section.

Neonatal outcomes were obtained from delivery and neonatal inpatient records. Outcomes included: low birth weight (<2500g), small for gestational age (birth weight <10th percentile) macrosomia (birth weight >90th percentile), Apgar score <7 at 1 or 5minutes, culture proven sepsis, pneumonia, respiratory distress syndrome, intraventricular haemorrhage, and neonatal jaundice

2.6. Ethical Considerations

Approval was obtained from the Chief Executive Officer of King Edward VIII Hospital (KEH VIII) for permission to retrieve and analyse patients' records.

Ethics approval was obtained from the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal. Ref: BE069/13

2.7. SAMPLING

A total of 2570 deliveries occurred from the period 1st March 2013 to 30th June 2013. Two thousand five hundred and thirty-four charts of mothers were retrieved. Thirty-six charts could not be retrieved (missing). Of the 2534 charts retrieved 68 were excluded because

they were for mothers with twin pregnancies. A total of 2466 charts of mothers and 2420 charts of their babies were reviewed. There were a total of 46 singleton stillbirths during the study period. Twenty-four HIV positive women did not receive any form of antiretroviral therapy and were not included in the study.

2.8. STATISTICAL ANALYSIS

The data was entered in Microsoft Excel and subsequently analysed in Intercooled Stata 13.0 (Stata Corporation, College Station, TX, United States) Descriptive statistics such as frequencies, percentages, means and standard deviations were used to summarize sample results. Pearson chi-squared test or Fisher's exact tests were used to test if there was any association between categorical pregnancy outcomes in women seropositive for HIV on antiretroviral medication and women seronegative for HIV. Two- sample Wilcoxon rank-sum (Mann-Whitney) test was used for continuous variables such as age and birth weight. Logistic regression was performed to calculate the odds ratio of adverse outcomes (maternal and neonatal) for the HIV infected women on ARVs compared with the HIV negative women and reported with 95% confidence intervals. Subgroup analysis of women on antiretroviral medications was further performed by logistic regression for various adverse pregnancy outcomes (maternal and neonatal).

CHAPTER 3

RESULTS

3.1 Maternal Demographics and Antiretroviral Therapy of the Study Cohort

During the study period 1st March to 30th June 2013 a total of 2570 women gave births at or after 26weeks gestation at KEH. Thirty-six charts could not be retrieved (missing). Charts were retrieved for 2534 women and 68 of these had multiple gestations and were excluded from the analysis. Twenty-four HIV positive women did not use antiretroviral medications and were excluded from the study. The ages ranged from 14 - 45yrs for the 2466 women who were included in the study.

There were 1496 HIV negative (60.7%) and 970 HIV positive women (39.3%). One thousand four-hundred and fifty-nine (97.5%) of the women in the study were Africans. There were 18 Indian women (0.7%), 9 coloured women (0.4%), 6 white women (0.2%) and 4 women (0.2%) of other races. All HIV positive women in the study were Africans.

Women seropositive for HIV were significantly older and of higher parity than the HIV seronegative mothers (Table1). Smoking and alcohol use were similar for both groups. A total of 946 women used antiretroviral medications in the study cohort. Two hundred and nine women (22.1%) commenced highly active antiretroviral therapy before they found out that they were pregnant

Four hundred and seventeen HIV positive women (44.1%) used a combination of efavirenz, tenofovir and lamivudine regimen while 335 women (35.4%) used azidothymidine and intrapartum nevirapine (dual therapy). One hundred and twenty five women (13.2%) used a combination of efavirenz, tenofovir and emtricitabine (FDC). Only four women (0.4%) used protease inhibitor (ritonavir/lopinavir) containing regimen (Table 2).

3.2 Maternal Outcomes

HIV positive women had lower odds for developing preeclampsia (7.9% vs 12.9%, P< 0.001), abruptio placentae (1.0% vs 2.5%, P =0.003), gestational diabetes mellitus (0.3% vs 1.3%, P = 0.01), than HIV negative women (Table 3). Women seropositive for HIV were at increased risk of preterm premature rupture of the membranes (PPROM) (5.6% vs 3.4%, P=0.01) and chorioamnionitis (0.95% vs 0.27%, P= 0.02) compared to women seronegative for HIV (Table 3).Maternal outcomes including chronic hypertension (1.1% vs 1.8%, P =0.87), gestational hypertension (4.0% vs 3.2% P = 0.33), were not different between women seropositive for HIV and HIV seronegative women. The odds of having postpartum haemorrhage was not different between the two groups (2.5% vs 3.2%, P = 0.25) for women seropositive for HIV on antiretroviral medications and women seronegative for HIV respectively (Table3).

3.3 Neonatal Outcomes

HIV seropositive women on antiretroviral medication were at higher odds of having SGA (<10th percentile) babies (11.3%vs 9.0% P = 0.002) than women seronegative for HIV (Table 4).There was no difference in the prevalence of preterm birth before 37 weeks of gestation (17.8% vs 19.9%, P = 0.19), and preterm delivery at less than 34weeks of gestation (8.7% vs 7.6%, P = 0.32) between women seropositive for HIV and HIV seronegative women (Table 4). Women seropositive for HIV were less likely to deliver babies with APGAR scores in 1-minute <7(5.6% vs 9.3%, P = 0.001) than women seronegative for HIV (Table4). Babies of women seropositive for HIV were at lower odds of developing neonatal jaundice than babies of women seronegative for HIV (9.2% vs 14.6%, P < 0.001).Neonatal outcomes including 5-min APGAR score <7(1% vs 1.9%, P = 0.08) intraventricular haemorrhage (0% vs 0.4% , P = 0.05) respiratory distress syndrome (6.9% vs 7.7%, P = 0.47), neonatal pneumonia (2.3% vs 1.4%, P =0.08), necrotising enterocolitis (0.0% vs 0.1%, P= 0.52), and culture proven sepsis(1.3% vs 1.2%, P= 0.92) were similar for both groups (Table 4).

3.4 Subgroup Analysis

Logistic regression was performed and it was shown that preeclampsia was more likely to occur in women who were HIV-uninfected when compared with women who were HIV-infected and receiving antiretroviral medications (Table 5)

Subgroup analysis of HIV positive women on antiretroviral therapy was performed comparing various adverse outcomes for these subgroups with HIV negative women and the results are shown (Table 6 and Table7).The subgroups analysed were HIV-infected women on dual therapy and HIV-infected women on pre-pregnancy HAART.

The higher odds of HIV negative women developing preeclampsia compared to HIV positive women on antiretroviral therapy disappears when the comparison is made between the subgroup of HIV positive women on dual therapy and women seronegative for HIV (Table 6). However, there is a stronger association between being seronegative for HIV and increased risk for developing preeclampsia when HIV positive women who commenced HAART before pregnancy are compared with HIV negative women. (Table7).

TABLE 1

DEMOGRAPHIC CHARACTERISTICS OF WOMEN IN THE STUDY

Characteristics	Group		
	HIV seropositive (n= 970)	HIV seronegative (n=1496)	*P* value
Age(yrs)	28 (14-43)[a]	23 (14-45)[a]	<0.001
Parity(range)	0-6	0-5	
Para 0	193(20.4%)	741(49.5%)	<0.001
Para ≥1	753(79.6%)	755(50.5%)	<0.001
Race			
African	970(100%)	1459(97.5%)	
Indian	-	18(1.2%)	
Coloured	-	9(0.6%)	
White	-	6(0.4%)	
Other	-	4(0.3%)	
Marital status			
Single	896(92.4%)	1348(90.1%)	0.06
Married	74(7.6%)	148(9.9%)	
Employment status			
Unemployed	805(82.9%)	1306(87.3%)	0.003
Employed	165(17.1%)	190(12.7%)	
Smoking	6(0.6%)	17(1.1%)	0.19
Alcohol	5(0.5%)	8(0.5%)	0.95
Immunological			
HIV serology	970(39.3%)[b]	1496(60.7%)[e]	
Median CD4(cells/mm^3	358(2-1873)[c]	NA	
Median gestational age at Which CD4 was taken(weeks)	20	NA	
Prepregnancy HAART	209(22.1%)[d]	NA	
Duration of Prepregnancy HAART(days)	1095 (240-3285)[e]	NA	

[a]Median age and range of the groups

[b]Percentage of study cohort

[c]Median and range of CD4 count

[d]Percentage of HIV positive women on Prepregnancy HAART

[e]Median and range of duration of Prepregnancy HAART

TABLE 2

ANTIRETROVIRAL (ARV) MEDICATION-USE BY STUDY COHORT

ARV	Group	
	HIV seropositive (n= 946)	HIV seronegative (n=1496)
Efavirenz/lamivudine/tenofovir	417(44.1%)	NA
Nevirapine/lamivudine/tenofovir	28(3.0%)	NA
Lopinavir/ritonavir-containing regimen	4(0.4%)	NA
Efavirenz/emtracitabine/tenofovir(FDC)	125(13.2%)	NA
Azidothymidine +intrapartum nevirapine + emtricitabine + tenofovir(dual therapy)	335(35.4%)	NA
Nevirapine only	12(1.3%)	NA
Other regimen	25(2.6%)	NA
Prepregnancy HAART[a]	2-09(22.1%)	NA

[a]Highly active antiretroviral therapy initiated before the woman found out she was pregnant

TABLE 3

MATERNAL OUTCOMES

Outcomes	Group		
	HIV seropositive (n=946)	HIV seronegative (N=1496)	*P* value
Preeclampsia	75(7.9%)	193(12.9%)	<0.001
Gestational hypertension	38(4.0%)	48(3.2%)	0.33
Chronic hypertension	27(1.8%)	11(1.1%)	0.87
Gestational diabetes	3(0.3%)	20(1.3%)	0.01
Preterm Premature Rupture of membranes (PPROM)	53(5.6%)	51(3.4%)	0.01
Chorioamnionitis	9(0.95%)	4(0.27%)	0.02
Abruptio placentae	10(1.0%)	38(2.5%)	0.003
Post-partum haemorrhage	24(2.5%)	49(3.2%)	0.25

Pearson Chi square test was used to determine if there was any difference between the groups

TABLE 4

NEONATAL OUTCOMES

Characteristic	Group		
	HIV seropositive (n= 946)	HIV seronegative (n=1496)	*P* value
Preterm deliveries <37weeks			
Total	168(17.8%)	298(19.9%)	0.19
Spontaneous	113(11.9%)	187(12.5%)	0.09
Preterm deliveries <34weeks			
Total	82(8.7%)	113(7.6%)	0.32
Spontaneous	43(4.5%)	52(3.5%)	0.55
Birth weight(g)[a]	3036±653	3044±640	0.76
Term low birth weight(<2500g)	47(5.0%)	56(3.7%)	0.14
Small for gestational age(<10th percentile)	107(11.3%)	136(9.0%)	0.002
1min APGAR score<7	53(5.6%)	136(9.0%)	0.001
5min APGAR score<7	9(1.0%)	27(1.8%)	0.08
Intraventricular haemorrhage(IVH)	0(0.0%)	6(0.4%)	0.05
Respiratory Distress Syndrome(RDS)	66(7.0%)	113(7.6%)	0.47
Neonatal jaundice	88(9.3%)	214(14.3%)	<0001
Neonatal pneumonia	22(2.3%)	20(1.3%)	0.08
Necrotizing enterocolitis(NEC)	0(0.0%)	1(0.1%)	0.52
Culture proven sepsis	12(1.3%)	18(1.2%)	0.92

[a]mean ± standard deviation

Two –sample Wilcoxon rank- sum (Mann-Whitney) and Pearson Chi square tests were used to determine if there was any difference between the groups for continuous and categorical variables respectively

TABLE 5

ADVERSE MATERNAL/NEONATAL OUTCOMES IN HIV POSITIVE WOMEN WHO RECEIVED ANTIRETROVIRAL MEDICATIONS

Outcomes in women seropositive for HIV on ARVs	OR	95% CI
Preeclampsia	0.6	0.4-0.8
Abruptio placentae	0.3	0.2-0.7
Post-partum haemorrhage(PPH)	0.8	0.5-1.3
Chorioamnionitis	3.6	1.1-11.7
Low birth weight(<2500g)	1.1	0.9-4.2
5min APGAR score<7	1.9	0.9-4.2
Culture proven sepsis	1	0.5-2.2

Maternal and neonatal outcomes in women seropositive for HIV on antiretroviral medications were compared with outcomes in HIV seronegative women

Logistic regression was performed, the odds ratio calculated and reported with the 95% confidence intervals

TABLE 6

ADVERSE MATERNAL/NEONATAL OUTCOMES IN HIV POSITIVE WOMEN WHO RECEIVED DUAL THERAPY

Outcomes	OR	95% CI
Preeclampsia	1.1	0.8-1.6
Abruptio placentae	0.9	0.4-2.0
Post-partum haemorrhage	0.5	0.2-1.2
Chorioamnionitis	3.3	0.7-14.9
Low birth weight(<2500g)	1.1	0.9-1.4
5min APGAR score < 7	0.8	0.5-1.3
Culture proven sepsis	1.5	0.6-3.7

Maternal and neonatal outcomes in HIV positive women who received dual therapy(Azidothymidine from 14 weeks gestation and intrapartum azidothymidine + intrapartum single dose nevirapine and a combination of emtricitabine + tenofovir) were compared with outcomes in HIV negative women

Logistic regression was performed, the odds ratio calculated and reported with the 95% confidence intervals

TABLE 7

ADVERSE MATERNAL/NEONATAL OUTCOMES IN WOMEN WHO COMMENCED HAART PRIOR TO PREGNANCY

Outcome	OR	95% CI
Preeclampsia	0.2	0.1-0.5
Post-partum haemorrhage(PPH)	1.6	0.8-3.2
Chorioamnionitis	5.4	1.2-24.4
Low birth weight(<2500g)	1.1	0.7-1.6
5min APGAR score < 7	0.3	0.1-0.7

Logistic regression was performed, the odds ratio calculated and reported with the 95% confidence intervals

CHAPTER 4

4.1 DISCUSSION

The prevalence of HIV in our study cohort of 2466 women was 39.3%, which is similar to the antenatal HIV seroprevalence of 39.5 % reported by the South African national department of Health[60]. We demonstrated that women seropositive for HIV on antiretroviral therapy are at a lower risk of developing maternal complications such as preeclampsia, abruptio placentae and gestational diabetes mellitus compared to women seronegative for HIV. There is no difference in the risk of perinatal complications like 5-minute APGAR score < 7 between women seropositive for HIV on antiretroviral therapy and HIV seronegative women. However, women seropositive for HIV on HAART are at increased risk of developing chorioamnionitis, and showed a trend towards increased risk of delivering babies with low birth weight, compared to women seronegative for HIV.

In our study cohort, women seropositive for HIV on antiretroviral therapy with a median CD4 of 358cells/mm^3 (2-1873) have a significantly lower odds (40% less) of developing preeclampsia (OR 0.6, 95% CI 0.4-0.8) when compared to women seronegative for HIV. The relationship between antiretroviral therapy and reduced risk of preeclampsia is even stronger when the comparison is between women who commenced HAART prior to pregnancy and women seronegative for HIV (OR 0.2, 95% CI 0.1-0.05). This association disappears when only women on dual therapy were compared with HIV negative women (OR 1.1, 95% CI 0.8-1.6). There are conflicting reports in the literature regarding the effect of HIV and HAART on the risk of development of preeclampsia. Suy *et al[54]* in their retrospective study carried out in Barcelona, Spain, found that there was increased rate of preeclampsia and fetal death in women seropositive for HIV treated with HAART. Their study is different from ours in that they had a predominantly white study population (85%) compared to our study population that is 100% black Africans that are seropositive for HIV.

Mattar *et al[65]* on the other hand found lower rates of preeclampsia in women seropositive for HIV on HAART compared with women seronegative for HIV. Their study was a small retrospective study including 123 women seropositive for HIV, having a median CD4

count of 531 cells/mm^3 (200- 1378) receiving monotherapy or HAART and 1708 HIV negative controls. They reported a significantly lower rate of preeclampsia among women seropositive for HIV on antiretroviral therapy compared to healthy controls (0.8% vs 10.6%, *P* = 0.002).

Boyajian *et al* [66] carried out a retrospective matched cohort study including 273 women seronegative for HIV and 91 women seropositive for HIV on HAART and demonstrated that women seropositive for HIV on HAART are not at increased risk of developing preeclampsia(3.3% vs 5.1%, adjusted odds ratio[aOR] 0.59, 95% CI 0.89-5.24).

Haeri *et al [67]*, in their study including 151 women seropositive for HIV on HAART and 302 women seronegative for HIV, also found that women seropositive for HIV on HAART had lower rates of preeclampsia compared with women seronegative for HIV (6% vs 12%, *P*= 0.04). However, after corrections for differences in smoking and cocaine use were made, the difference between the two groups did not reach statistical significance [aOR 0.55, 95% CI 0.26- 1.2]. The study was also a retrospective cohort study similar to ours. The difference between our study and the study by Haeri *et al* is that they had a very small sample size and there were statistically significant differences in cigarette smoking (7% vs 25%, *P*<0.001) and cocaine use(1% vs 7%, *P*< 0.001) between the groups with higher rates in women seropositive for HIV on HAART in their study. The rates of smoking were 0.6% vs 1.1%, *P* = 0.19 in women seropositive for HIV and women seronegative for HIV respectively in our study.

Wimalasundera *et al[55]*, showed in a prospective cohort study including 214 women seropositive for HIV (stratified into untreated, mono, dual and triple therapy) and 214 women seronegative for HIV, that untreated women seropositive for HIV had lower rates of preeclampsia than treated women. They concluded that the immune restorative effect of triple antiretroviral therapy is responsible for the lower rates of preeclampsia in the untreated than the treated HIV seropositive women.

The plausible explanation for the lower rate of preeclampsia in women seropositive for HIV on HAART compared to women seronegative for HIV demonstrated in our study, could be because the immune system plays a role in the aetiology of preeclampsia such that conditions of relative immune deficiency partially prevents the development of preeclampsia[68].

This postulation also explains the higher rates of preeclampsia in treated compared to untreated HIV seropositive women observed by Wimalasundera *et al*. Our observations that women on dual therapy showed a trend towards increased risk of preeclampsia (OR 1.1, 95% CI 0.8-1.6); as opposed to women seropositive for HIV who commenced HAART before pregnancy(OR 0.2, 95% CI 0.1-0.5) can further be explained by this postulation.

Women who received dual therapy had higher CD4 counts (> 350cells/mm^3) than those who received HAART. Women who commenced HAART prior to pregnancy were women who needed HAART for their own health and so had lower CD4 counts than those who commenced HAART in pregnancy. This means the higher the degree of immunosuppression, the lower the rates of preeclampsia.

We demonstrated that there was no significant difference in the incidence of postpartum haemorrhage between women seropositive for HIV on HAART and women seronegative for HIV in our study cohort. Data comparing the prevalence of postpartum haemorrhage between women HIV positive women on HAART and HIV negative women are sparse in the literature. Our finding is similar to that of Azria *et al* [69]. In their retrospective cohort study, including 146 women in each group, comparing the term labour management and outcomes of treated HIV positive to HIV negative women, they demonstrated that the incidence of postpartum haemorrhage (12.3% vs 18.5%, *P* = 0.12) was not significantly different between the two groups.

A recent systematic review and meta-analysis by Calvert *et al* [70]is in concordance with our finding. Their systematic review of 44 studies on HIV and risk of direct obstetric complications including 17dataset on obstetric haemorrhage suggested that there was no increase in odds of postpartum haemorrhage in women for HIV positive women compared to women seronegative for HIV. This finding is important if we consider the fact that postpartum haemorrhage is the leading cause of maternal mortality globally[71]. In South

Africa, non-pregnancy related sepsis mainly due to HIV and AIDS is the leading cause of death[61]. It means therefore that HIV positive on antiretroviral medications compared to HIV uninfected women are not at further increased risk of adverse pregnancy outcome as far as postpartum haemorrhage is concerned. This finding, however, should be interpreted with caution as our study is retrospective and postpartum haemorrhage in this study is taken as documented by the attending health care practitioner at delivery. There are inherent difficulties in estimating blood loss both at caesarean section and at vaginal delivery as most often it is done by visual estimation and there is a real possibility of under reporting.

Women seropositive for HIV on antiretroviral medications were nearly four times more likely to have chorioamnionitis compared to women seronegative for HIV (OR 3.6 95% CI 1.1-11.7). Our finding is similar to the those of Musana *et al [72]*who demonstrated, in a prospective cohort study including 68 HIV positive women with advanced disease(WHO stage 3 and 4) and 68 HIV negative women, that chorioamnionitis was more likely to occur in the HIV infected women(14.8% vs 2% P = 0.004). Our finding is also consistent with the findings of Cavert *et al [70]*. In their systematic review and meta-analysis they suggested that women seropositive for HIV were more likely to develop intrauterine infections than women seronegative for HIV. Our finding is biologically plausible because HIV seropositive women being of lower immunity are more prone to developing infections[73].

We did not demonstrate any association between HIV and either iatrogenic or spontaneous preterm birth. The prevalence of preterm birth, before 37 weeks of gestation, amongst women seronegative for HIV was 19.9% compared to 17.8% for HIV seropositive women on antiretroviral medication, P=0.19. The prevalence of spontaneous preterm birth occurring before 37 weeks of gestation was 11.9 vs 12.5%, P= 0.09 for women seropositive for HIV and seronegative women respectively. Similarly the prevalence of preterm birth occurring before 34 weeks of gestation was not significantly different between women seropositive for HIV and seronegative women. The prevalence of preterm birth before 34 weeks of gestation was 8.7% vs 7.6, P=0.32 for HIV seropositive women and HIV seronegative women respectively. Spontaneous preterm birth occurring before 34 weeks of gestation was 4.5% vs

3.5%, P=0.55 for women seropositive for HIV and seronegative women respectively. Our finding is similar to findings of Ndirangu *et al[74]*. Their study was a non-randomized intervention cohort study in Northern KwaZulu-Natal including 2368 live born singletons. They demonstrated that there was no association between HIV and preterm births.

Our finding is also consistent with the findings of a systematic review and meta-analysis by Kourtis *et al* which showed that combination antiretroviral therapy use compared with no treatment is not associated with increased risk of preterm births [6].

Our finding differs from other reports in the literature regarding the effect of antiretroviral therapy on preterm birth, where antiretroviral therapy has been linked with increased risk of preterm births. Cotter *et al[75]* suggest, in their prospective study that protease inhibitor (PI) based HAART rather than monotherapy or non-PI based HAART was associated with preterm delivery. Watts *et al[76]* also concluded that use of protease inhibitor in early gestation was linked with increased risk of preterm birth. van der Merwe K *et al [77]* suggest that use of non-nucleoside reverse transcriptase inhibitor (NNRTI) based HAART is linked with increased risk of preterm birth. These studies compared preterm births between HIV seropositive women on HAART (or a particular regimen) with HIV seropositive women on no treatment or another regimen. Their hypothesis was that there was an immunological basis for the observation of increased preterm delivery in women on HAART. HIV disease progression is linked with an increase in Th2 cytokines level and a suppression of Th1 cytokines as observed in normal pregnancy[78]. HAART reverses this increased Th2 to Th1 cytokine ratio [78].

Although, the study by Ndirangu *et al* [74]was carried out at a time when HAART was not widely used by pregnant women, their findings are in concordance with ours. A prospective cohort study in a setting such as ours is needed to investigate the effect of antiretroviral therapy on preterm delivery.

Our study found that women seropositive for HIV on antiretroviral therapy are not at increased risk of having low birth weight babies and is consistent with findings of van Der

Merwe *et al* [77].Our findings , however, differ from the findings of Machado *et al* [79] who found that women seropositive for HIV on HAART were at increased risk for delivering low birth weight babies than the general population. Their study was prospective cohort including 696 HIV positive women on antiretroviral medications in Rio de Janeiro. The difference between our finding and that of Machado *et al* could be because of the relatively higher proportion of protease inhibitor use by their study cohort compared to ours (40% vs 0.4%).

4.2 LIMITATIONS OF THE STUDY

This is the first study in our local population comparing pregnancy outcomes in women seropositive for HIV on HAART with uninfected women.

Our study was retrospective and so findings must be interpreted in this context. Many of the outcomes analysed were as documented by attending physicians. There is possibility of some diagnoses being over- or under- diagnosed. We were unable to explore the psychosocial factors that could impact pregnancy outcomes adversely because of the retrospective nature of our study. Smoking, alcohol and illicit drug use were as self-reported by the patient. It is also possible that there was underreporting of use of these substances. Finally, the relatively short duration of the study may be seen as a possible drawback.

CHAPTER 5

CONCLUSION AND RECOMMENDATION

HIV positive women on antiretroviral therapy are at lower risks for developing adverse pregnancy outcomes such as preeclampsia, abruptio placentae and gestational diabetes mellitus compared to HIV negative women. Perinatal complications like 5-minute APGAR score <7 and delivering low birth weight babies are not different between HIV positive women and uninfected women. However, women seropositive for HIV are at increased risk of developing chorioamnionitis compared to women seronegative for HIV. We have demonstrated that the use of HAART in pregnancy is not associated with increased risk of adverse outcome

A large prospective study in our local population is needed to confirm our findings.

REFERENCES

1. De Cock K M, Mercier E, de Vincenzi I, Saba J, Hoff E, Alnwick DJ, et al. *Prevention of Mother-to-Child HIV Transmission in Resource-Poor Countries:Translating Research Into Policy and Practice* JAMA., 2000. **283**(9): p. 1175-82.
2. de Vincenzi I. *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): p. 171-80.
3. Lopez M, Figueras F, Hernandez S *Association of HIV infection with spontaneous and iatrogenic preterm delivery: effect of HAART.* Aids, 2012. **26**(1): p. 37-43.
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**(17): p. 2337-9.
5. Tuomala RE, Watts DH, Li D, Vajaranant M, Pitt J, Hammill H, 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): p. 449-73.
6. 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): p. 607-15.
7. European Collaborative Study; Swiss Mother and Child HIV Cohort Study. *Combination antiretroviral therapy and duration of pregnancy.* Aids, 2000. **14**(18): p. 2913-20.
8. Moodley J, Pattinson RC, Baxter C, Sibeko S, Abdool Karim Q. *Strengthening HIV services for pregnant women: an opportunity to reduce maternal mortality rates in Southern Africa/sub-Saharan Africa.* BJOG 2011. **118**(2): p. 219-25.
9. WHO, *Towards universal access. Scaling up priority HIV/AIDS interventions in the health sector: Progress report*, 2010.
10. WHO, *Global HIV/AIDS Response-Epidemiologic update and Health Sector Progress towards Universal Access.*, 2011: GENEVA.
11. WHO, *HIV/AIDS:Clinical guidance across the continuum of care: antiretroviral therapy. Consolidated ARV guidelines*, 2013: GENEVA.
12. WHO, *HIV/AIDS Programme: Programmatic update, use of antiretroviral drugs for treating pregnant and preventing HIV infection in infants*, 2012.
13. WHO, *Transacction prices for antiretroviral medicines and diagnostics from July 2008 to July 2011: global price reporting mechanism, GPRM, October 2011*, October 2011: Geneva.
14. Shubber Z, Calmy A, Andrieux-Meyer I, Vitoria M, Renaud-Théry F, Shaffer N, et al *Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis.* Aids, 2013. **27**(9): p. 1403-12.
15. Ford N, Calmy A, Mofenson L, *Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis.* Aids, 2011. **25**(18): p. 2301-4.
16. Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE, et al., *Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV.* N Engl J Med, 2006. **354**(3): p. 251-60.
17. Jouquet G, Bygrave H, Kranzer K, Ford N, Gadot L, Lee J, et al *Cost and cost-effectiveness of switching from d4T or AZT to a TDF-based first-line regimen in a resource-limited setting in rural Lesotho.* J Acquir Immune Defic Syndr, 2011. **58**(3).
18. Kenyon C, Colebunders R, *What is the optimal first line antiretroviral therapy in resource-limited settings?* PLoS Med, 2012. **9**(8): p. 14.
19. Scaglione F, Berrino L, *Cytosine deoxyribonucleoside anti-HIV analogues: a small chemical substitution allows relevant activities.* International Journal of antimicrobial agents, 2012 Epub.

20. Gregory J, Dore DAC, Pozniak AL, DeJesus E, Zhong L, Miller MD, Lu B, Cheng AK *Efficacy of Tenofovir Disoproxil Fumarate in Antiretroviral Therapy-Naive and -Experienced Patients Coinfected with HIV-1 and Hepatitis B Virus* Journal of infectious diseases, 2004. **189**(7): p. 1185-92.
21. Ford N, Mofenson L, Shubber Z, Calmy A, Andrieux-Meyer I, Vitoria M, et al., *Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis.* Aids, 2014. **28**(2): p.231.
22. Greenup AJ, Tan PK, Nguyen V, Glass A, Davison S, Chatterjee U, et al *Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of Hepatitis B Virus.* J Hepatol. 2014 Sep;61(3):502-7.
23. Hogg R, Lima V, Sterne JA, Grabar S, Battegay M, Bonarek M, et al *Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies.* Lancet, Jul 26 2008. **372**(9635): p. 293-299.
24. Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al, *Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group.;.* Lancet., Nov 28 1998. **352**((9142)): p. 1725-1730. .
25. Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al *Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators.* N Engl J Med., Mar 26 1998. **338**(13): p. 853-860.
26. Vittinghoff E, Scheer S, O'Malley P, Colfax G, Holmberg SD, Buchbinder SP. *Combination antiretroviral therapy and recent declines in AIDS incidence and mortality. .* J Infect Dis, Mar 1999. **179**(3): p. 717-720.
27. Mofenson LM, Lambert JS, Stiehm ER, Bethel J, Meyer WA , Whitehouse J, et al *Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team.* N Engl J Med., Aug 5 1999. **341**(6): p. 385-393.
28. Wood E, Kerr T, Marshall BD, Li K, Zhang R, Hogg RS, et al *Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. . . .* BMJ, 2009. **338**(b1649).
29. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al *Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group.* N Engl J Med., Mar 30 2000;. **342**(13): p. 921-929.
30. Dieffenbach CW, F.A., *Universal voluntary testing and treatment for prevention of HIV transmission. JAMA.:.* Jun 10 2009. **301**(22): p. 2380-2382.
31. Montaner JS, Hogg R, Wood E, Kerr T, Tyndall M, Levy AR, et al *The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. .* Lancet, Aug 5 2006. **368**(9534): p. 531-536.
32. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al *Prevention of HIV-1 infection with early antiretroviral therapy. ;.* N Engl J Med., Aug 11 2011. **365**(6): p. 493-505.
33. O'Brien WA, Hartigan PM, Martin D, Esinhart J, Hill A, Benoit S, et al *Changes in plasma HIV-1 RNA and CD4+ lymphocyte counts and the risk of progression to AIDS. Veterans Affairs Cooperative Study Group on AIDS.* N Engl J Med., Feb 15 1996. **334**(7): p. 426-431.
34. García F, de Lazzari E, Plana M, Castro P, Mestre G, Nomdedeu M, et al *Long-term CD4+ T-cell response to highly active antiretroviral therapy according to baseline CD4+ T-cell count. J Acquir Immune Defic Syndr. ;.* Jun 1 2004. **36**(2): p. 702-713.
35. Mandelbrot L, *Does pregnancy accelerate disease progression in HIV-infected women?* in *HIV Infection in Women.*, M. Johnson, Johnstone, FD, eds, Editor 1993, Churchill Livingston: Edinburgh

36. Heffron R, Donnell D, Kiarie J, Rees H, Ngure K, Mugo N, et al *A prospective study of the effect of pregnancy on CD4 counts and plasma HIV-1 RNA concentrations of antiretroviral-naive HIV-1-infected women.* J Acquir Immune Defic Syndr, 2014. **65**(2): p. 231-6.
37. Burns DN, Nourjah P, Minkoff H, Korelitz J, Biggar RJ, Landesman S, et al *Changes in CD4+ and CD8+ cell levels during pregnancy and post partum in women seropositive and seronegative for human immunodeficiency virus-1.* Am J Obstet Gynecol, 1996. **174**(5): p. 1461-8.
38. Biggar RJ, Pahwa S, Minkoff H, Mendes H, Willoughby A, Landesman S, et al *Immunosuppression in pregnant women infected with human immunodeficiency virus.* Am J Obstet Gynecol, 1989. **161**(5): p. 1239-44.
39. Temmerman M, Nagelkerke N, Bwayo J, Chomba EN, Ndinya-Achola J, Piot P.*HIV-1 and immunological changes during pregnancy: a comparison between HIV-1-seropositive and HIV-1-seronegative women in Nairobi, Kenya.* Aids, 1995. **9**(9): p. 1057-1060.
40. Brettle RP, Raab GM, Ross A, Fielding KL, Gore SM, Bird AG et al *HIV infection in women: immunological markers and the influence of pregnancy.* Aids, 1995. **9**(10): p. 1177-84.
41. Minkoff H, Nanda D, Menez R, Fikrig S. *Pregnancies resulting in infants with acquired immunodeficiency syndrome or AIDS-related complex: follow-up of mothers, children, and subsequently born siblings.* Obstet Gynecol, 1987. **69**(3 Pt 1): p. 288-91.
42. Berrebi A, Kobuch WE, Puel J, Tricoire J, Herne P, Grandjean H, et al *Influence of pregnancy on human immunodeficiency virus disease.* Eur J Obstet Gynecol Reprod Biol, 1990. **37**(3): p. 211-7.
43. Ryder RW, Temmerman M, *The effect of HIV-1 infection during pregnancy and the perinatal period on maternal and child health in Africa.* Aids, 1991. **5**(1): p. S75-85.
44. Lieve V, Shafer LA, Mayanja BN, Whitworth JA, Grosskurth H, *Effect of pregnancy on HIV disease progression and survival among women in rural Uganda.* Trop Med Int Health, 2007. **12**(8): p. 920-8.
45. Saada M, Le Chenadec J, Berrebi A, Bongain A, Delfraissy JF, Mayaux MJ, et al *Pregnancy and progression to AIDS: results of the French prospective cohorts. SEROGEST and SEROCO Study Groups.* Aids, 2000. **14**(15): p. 2355-60.
46. French R, Brocklehurst P *The effect of pregnancy on survival in women infected with HIV: a systematic review of the literature and meta-analysis.* Br J Obstet Gynaecol, 1998. **105**(8): p. 827-35.
47. Tai JH, Udoji MA, Barkanic G, Byrne DW, Rebeiro PF, Byram BR, et al *Pregnancy and HIV disease progression during the era of highly active antiretroviral therapy.* J Infect Dis, 2007. **196**(7): p. 1044-52.
48. Dioulasso B, Faso B, Meda N, Fao P, Ky-Zerbo O, Gouem C, et al *Maternal HIV-1 disease progression 18-24 months postdelivery according to antiretroviral prophylaxis regimen (triple-antiretroviral prophylaxis during pregnancy and breastfeeding vs zidovudine/single-dose nevirapine prophylaxis): The Kesho Bora randomized controlled trial.* Clin Infect Dis, 2012. **55**(3): p. 449-60.
49. Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al *Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group.* Lancet, 1998. **352**(9142): p. 1725-30.
50. Boer K, Nellen JF, Patel D, Timmermans S, Tempelman C, Wibaut M, 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): p. 148-55.
51. Kowalska A, Niemiec T, El Midaoui A, Burkacka E, Kowalska A. *Effect of antiretroviral therapy on pregnancy outcome in HIV-1 positive women.* Med Wieku Rozwoj, 2003. **7**(4 Pt 1): p. 459-68.

52. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Townsend, CL *Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland.* Aids, 2007. **21**(8): p. 1019-26.
53. Townsend C, Schulte J, Thorne C, Dominguez KI, Tookey PA, Cortina-Borja M, et al *Antiretroviral therapy and preterm delivery-a pooled analysis of data from the United States and Europe.* BJOG, 2010. **117**(11): p. 1399-410.
54. Suy A, Martínez E, Coll O, Lonca M, Palacio M, de Lazzari E, et al *Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy.* Aids, 2006. **20**(1): p. 59-66.
55. Wimalasundera RC, Larbalestier N, Smith JH, de Ruiter A, McG Thom SA, Hughes AD, et al *Pre-eclampsia, antiretroviral therapy, and immune reconstitution.* The Lancet, 2002. **360**(9340): p. 1152-1154.
56. Ekouevi DK, Coffie PA, Becquet R, Tonwe-Gold B, Horo A, Thiebaut R, et al., *Antiretroviral therapy in pregnant women with advanced HIV disease and pregnancy outcomes in Abidjan, Cote d'Ivoire.* Aids, 2008. **22**(14): p. 1815-20.
57. Dube MP, Sattler FR, *Metabolic complications of antiretroviral therapies*: AIDS Clin Care. 1998 Jun;10(6):41-4.
58. Hill JB, Sheffield JS, Zeeman GG, Wendel GD Jr *Hepatotoxicity with antiretroviral treatment of pregnant women.* Obstet Gynecol, 2001. **98**(5 Pt 2): p. 909-11.
59. Watts DH, Balasubramanian R, Maupin RT Jr, Delke I, Dorenbaum A, Fiore S, et al *Maternal toxicity and pregnancy complications in human immunodeficiency virus-infected women receiving antiretroviral therapy: PACTG 316.* Am J Obstet Gynecol, 2004. **190**(2): p. 506-16.
60. Health, D.o., *National antenatal sentinel HIV and Syphilis prevalence survey in South Africa*, 2010: Pretoria.
61. Health, D.o., *Saving Mothers 2005-2007, Fourth Report on Confidential Enquiries into Maternal deaths in South Africa*, 2009: Pretoria.
62. Temmerman M, Chomba EN, Ndinya-Achola J, Plummer FA, Coppens M, Piot P. *Maternal human immunodeficiency virus-1 infection and pregnancy outcome.* Obstet Gynecol, 1994. **83**(4): p. 495-501.
63. Rollins NC, Coovadia HM, Bland RM, Coutsoudis A, Bennish ML, Patel D, et al *Pregnancy outcomes in HIV-infected and uninfected women in rural and urban South Africa.* J Acquir Immune Defic Syndr, 2007. **44**(3): p. 321-8.
64. Penn, ZJ, Ahmed S, *Human immunodeficiency virus in pregnancy.* Current Obstetrics & Gynaecology, 2003. **13**(6): p. 321-328.
65. Mattar, R., et al., *Preeclampsia and HIV infection.* Eur J Obstet Gynecol Reprod Biol, 2004. **117**(2): p. 240-1.
66. Boyajian T, Shah PS, Murphy KE, *Risk of preeclampsia in HIV-positive pregnant women receiving HAART: a matched cohort study.* J Obstet Gynaecol Can, 2012. **34**(2): p. 136-41.
67. Haeri S, Shauer M, Dale M, Leslie J, Baker AM, Saddlemire S, et al, *Obstetric and newborn infant outcomes in human immunodeficiency virus–infected women who receive highly active antiretroviral therapy.* American Journal of Obstetrics and Gynecology, 2009. **201**(3): p. 315.e1-315.e5.
68. Hall D, Gebhardt S, Theron G, Grové D , *Pre-eclampsia and gestational hypertension are less common in HIV infected women.* Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health, 2014. **4**(1): p. 91-96.
69. Azria E, Kane A, Tsatsaris V, Schmitz T, Launay O, Goffinet F *Term labor management and outcomes in treated HIV-infected women without contraindications to vaginal delivery and matched controls.* International Journal of Gynecology & Obstetrics, 2010. **111**(2): p. 161-164.
70. Calvert C, Ronsmans C *HIV and the risk of direct obstetric complications: a systematic review and meta-analysis.* PLoS One, 2013. **8**(10).

71. Gary S *Maternal mortality from hemorrhage.* Semin Perinatol, 2012. **36**: p. 48-55.
72. Musana JW, Ojwang SB, Khisa W, Kiarie JN, Musana JW *Pregnancy outcomes in mothers with advanced human immunodeficiency virus disease.* East Afr Med J, 2009. **86**(10): p. 480-5.
73. van Dillen, J *Maternal sepsis: epidemiology, etiology and outcome.* Curr Opin Infect Dis, 2010. **23**(3): p. 249-54.
74. Ndirangu J, Bland RM, Thorne C, *Maternal HIV infection associated with small-for-gestational age infants but not preterm births:evidence from rural South Africa.* Hum Reprod. , 2012. **27**(6): p. 1846-1856.
75. 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): p. 1195-201.
76. Watts DH *Combination antiretroviral use and preterm birth.* J Infect Dis, 2013. **207**(4): p. 612-21.
77. 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**(42): p. 1758-2652.
78. Fiore S, Newell ML, Trabattoni D, Thorne C, Gray L, Savasi V, et al *Antiretroviral therapy-associated modulation of Th1 and Th2 immune responses in HIV-infected pregnant women.* Journal of Reproductive Immunology, 2006. **70**(1–2): p. 143-150.
79. Machado ES, Hofer CB, Costa TT, Nogueira SA, Oliveira RH, Abreu TF, et al *Pregnancy outcome in women infected with HIV-1 receiving combination antiretroviral therapy before versus after conception.* Sex Transm Infect, 2009. **85**(2): p. 82-7.

APPENDICES

A. APPROVAL: King Edward VIII Hospital

health

Department:
Health
PROVINCE OF KWAZULU-NATAL

OFFICE OF THE HOSPITAL CEO

KING EDWARD VIII CENTRAL HOSPITAL
Private Bag X02, CONGELLA, 4013
Corner of Rick Turner & Sydney Road
Tel 031-3803853/3015; Fax 031-2061457
Email:rejoice.khuzwayo@kznhealth.gov.za
www.kzn.health.gov.za

Ref.: KE 2/7/1/ 19/2013)
Enq.: Mrs. R. Sibiya
Research Programming

25 April 2013

Dr. DA Kesene
Department of Obstetrics & Gynaecology
Nelson R. Mandela –School of Medicine
UNIVERSITY OF KWAZULU-NATAL

Dear Dr. Kesene

Protocol: "Pregnancy Outcome in HIV Positive women on Antiretroviral Therapy Delivering in Durban" REF: BE069/13

Permission to conduct research at King Edward VIII Hospital is provisionally granted, pending approval by the Provincial Health Research Committee, KZN Department of Health.

Kindly note the following: -

- The research will only commence once confirmation from the Provincial Health Research Committee in the KZN Department of Health has been received.
- Signing of an indemnity form at Room 8, CEO Complex before commencement with your study.
- King Edward VIII Hospital received full acknowledgment in the study on all Publications and reports and also kindly present a copy of the publication or report on completion.

The Management of King Edward VIII Hospital reserves the right to terminate the permission for the study should circumstances so dictate.

Yours faithfully

SUPPORTED/~~NOT SUPPORTED~~

DR. H. GOSNELL
CHIEF EXECUTIVE OFFICER

25/4/2013
DATE

B. APPROVAL: Biomedical Research Ethics Committee UKZN

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI
RESEARCH OFFICE
BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

16 August 2013

Dr. DA Kesene
Department of Obstetrics and Gynaecology
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

PROTOCOL: Pregnancy Outcome in HIV Positive women on Antiretroviral Therapy Delivering in Durban. **REF: BE069/13**

EXPEDITED APPLICATION - RATIFICATION

This letter serves to notify you that at a full sitting of the Biomedical Research Ethics Committee meeting held on 09 July 2013, the Committee RATIFIED the sub-committee's decision to approve the above study.

Yours sincerely

Prof. D Wassenaar
Chair: Biomedical Research Ethics Committee

C. <u>ISSHP classification (</u>2001)

In summary, the ISSHP now endorses the following:

1. A correct method of measuring BP in pregnancy.
2. Proper methods for validating the presence of proteinuria, a key component of the diagnosis of preeclampsia.
3. The classification of hypertension in pregnancy as follows:
    - Preeclampsia–eclampsia
    - Gestational hypertension
    - Chronic hypertension (essential or secondary)
    - Preeclampsia superimposed on chronic hypertension
4. A research definition of preeclampsia as follows:
    - *De novo* hypertension after 20 weeks' gestation, returning to normal postpartum
      AND
    - Properly documented proteinuria, as above
5. Further studies are needed to compare maternal and fetal outcomes when preeclampsia is diagnosed according to an "inclusive" versus "restrictive" approach.

D. REVISED WHO CLINICAL STAGING OF HIV/AIDS FOR ADULTS AND ADOLESCENTS

Primary HIV infection
Asymptomatic
Acute retroviral syndrome

Clinical stage 1
Asymptomatic
Persistent generalized lymphadenopathy (PGL)

Clinical stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight)
Recurrent respiratory tract infections (RTIs, sinusitis, bronchitis, otitis media, pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulcerations
Papular pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infections of fingers

Clinical stage 3
Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations
Severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhoea for longer than one month
Unexplained persistent fever (intermittent or constant for longer than one month)
Oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis (TB) diagnosed in last two years
Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Clinical stage 4
Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe or radiological bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's
duration)
Oesophageal candidiasis
Extrapulmonary TB
Kaposi's sarcoma
Central nervous system (CNS) toxoplasmosis
HIV encephalopathy

Conditions where confirmatory diagnostic testing is necessary:
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacteria infection
Progressive multifocal leukoencephalopathy (PML)
Candida of trachea, bronchi or lungs
Cryptosporidiosis
Isosporiasis
Visceral herpes simplex infection
Cytomegalovirus (CMV) infection (retinitis or of an organ other than liver, spleen or lymph nodes)
Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, penicilliosis)
Recurrent non-typhoidal salmonella septicaemia
Lymphoma (cerebral or B cell non-Hodgkin)
Invasive cervical carcinoma
Visceral leishmaniasis

E. WHO Recommendations for second line antiretroviral therpy for adults

- Second line antiretroviral Second-line ART for adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI).
    - The following sequence of second-line NRTI options is recommended:
    - After failure on a TDF + 3TC (or FTC)–based first-line regimen, use AZT + 3TC as the NRTI backbone in second-line regimens.
    - After failure on an AZT or d4T + 3TC–based first-line regimen, use TDF + 3TC (or FTC) as the NRTI backbone in second-line regimens.
    - Use of NRTI backbones as a fixed-dose combination is recommended as the preferred approach *(strong recommendation, moderate-quality evidence).*
- Heat-stable fixed-dose combinations of ATV/r and LPV/r are the preferred boosted PI options for second-line ART. *(strong recommendation, moderate-quality evidence).*