

**OBSTETRIC HAEMORRHAGE-RELATED SEVERE MATERNAL
OUTCOMES IN HIV-INFECTED WOMEN**

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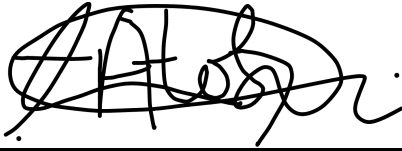
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31 May 2018

DECLARATION

I, Kwadwo Atobra Antwi declare that this thesis is my own unaided work. 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.



31st day of May 2018

IN JOHANNESBURG

Dedicated to the legacy of my parents, the love of my wife and beauty of my daughters.

ORAL AND POSTER PRESENTATIONS

1. Departmental Journal Club, Department of Obstetrics and Gynaecology, Chris Hani Baragwanath Academic Hospital – Oral Presentation. 31 October 2016
2. Soweto Matlosana Collaborating Centre for HIV/AIDS and TB (SoMCHAT) Emerging Researchers Programme, Chris Hani Baragwanath Academic Hospital – Oral Presentation. 18 November 2016
3. 36th Conference on Priorities in Perinatal Care in Southern Africa, Mpekwini Beach Resort, Eastern Cape – Poster presentation. 7-10 March 2017
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ABSTRACT

There is paucity of data on the contribution of HIV infection to obstetric haemorrhage-related severe maternal outcomes (SMO) with some literature suggesting an increased risk in HIV-infected women. Since the leading causes of maternal mortality in South Africa are non-pregnancy related infections, mainly HIV-related, and obstetric haemorrhage, there is a possible relationship between HIV infection and obstetric haemorrhage-related SMO. Hence the aim of this study was to determine whether obstetric haemorrhage-related SMO are increased in HIV-infected women.

A retrospective study of cases of obstetric haemorrhage-related SMO at Chris Hani Baragwanath Academic Hospital, from January to December 2015 was conducted. A total of 73 women had obstetric haemorrhage-related SMO. Of these, 18 (24.7%) women were HIV-infected and 50 (68.5%) uninfected. All the HIV-infected women were on antiretroviral therapy, 50% initiated pre-pregnancy, and the median CD4 count was 409 cells/mm³. There were 65 near-misses, 49 (72.1%) in HIV-infected women, and there were three maternal deaths, two in HIV-infected women.

Previous caesarean section was the commonest identifiable factor associated with obstetric haemorrhage, 6/18 (33.3%) in HIV-infected women and 9/50 (18.0%) in uninfected women. The commonest cause of haemorrhage was postpartum haemorrhage, diagnosed in 65/68 (95.6%) women, and there was no significant difference between HIV-infected and uninfected women. There were no significant differences in the medical and surgical interventions the patients needed.

Obstetric haemorrhage-related SMO were not increased in HIV-infected women in this study likely because it was a relatively healthy population of HIV-infected women. Larger studies are needed to elucidate these findings.

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LIST OF ABBREVIATIONS

APH = Antepartum Haemorrhage

ART = Antiretroviral therapy

BDACS = Bleeding during or after caesarean section

CHBAH = Chris Hani Baragwanath Academic Hospital

ELCS = Elective Caesarean Section

EMCS = Emergency Caesarean Section

FDC = Fixed dose combination

Hb = Haemoglobin

HAART = Highly Active Antiretroviral Therapy

HIV = Human Immunodeficiency Virus

IQR = Interquartile range

NHLS = National Health Laboratory Services

MMR = Maternal Mortality Ratio

OH = Obstetric Haemorrhage

PPH = Postpartum Haemorrhage

REDCap = Research Electronic Data Capture

SAMM = Severe Acute Maternal Morbidity

SD = Standard Deviations

SMO = Severe Maternal Outcome

WHO = World Health Organization

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CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND

Obstetric haemorrhage includes both antepartum haemorrhage (APH) and postpartum haemorrhage (PPH) from any cause, known or unknown.^{1,2} According to a WHO systematic analysis between from 2003 to 2012 it is the leading cause of maternal mortality worldwide accounting for 27.1% of global maternal deaths.³ In Africa it is estimated that up to 25% of maternal deaths were due to obstetric haemorrhage in 2014.³ In the sixth triennial report on the Confidential Enquiries into Maternal Deaths in South Africa (Saving Mothers), obstetric haemorrhage contributed significantly to maternal mortality.⁴ It has been identified as the second most common cause of maternal mortality after non-pregnancy related infections.⁴ According to the report, prolonged labour and anaemia were found to be the commonest underlying factors for obstetric haemorrhage, and bleeding during or after caesarean is increasingly becoming an important cause of obstetric related maternal death.⁴

Although maternal mortality presents a significant public health concern, deaths are rare in absolute numbers. Analysing maternal deaths, especially within the context of an institution, does not allow for comprehensive assessment of the quality of maternal healthcare.⁵ Maternal near-misses, which occur more frequently than maternal deaths, have been identified as better indicators of quality of care.⁶ A maternal near-miss is a woman who nearly died but survived a complication that occurred during pregnancy or childbirth, or within 42 days of termination of pregnancy.⁶ Similar inadequacies in healthcare systems contribute to both maternal deaths and near-misses, together defined as severe maternal outcomes (SMO).⁷ By studying SMO, information can be obtained about the processes that take place in healthcare systems responsible for maternal healthcare, and also identify obstacles that need to be overcome to prevent adverse outcomes. Therefore, assessing SMO provides the most robust indicator for evaluating the quality of maternal health care.^{6,8–10}

Before the widespread availability of antiretroviral therapy (ART), HIV-infected pregnant and postpartum women were said to experience greater morbidity and mortality than HIV-uninfected women.^{11,12} The negative effect of HIV infection on maternal health is well documented in South Africa, with the high HIV seroprevalence among pregnant women and non-pregnancy related infections, largely HIV-related, being the leading cause of maternal deaths.^{11,13,14}

1.2 PROBLEM STATEMENT

Few studies in South Africa have looked into the interrelation of obstetric haemorrhage, HIV-infection and SMO since the widespread availability of ART, and since the adoption of SMO as a tool to assess the quality of maternal care. In a population-based study done in the Pretoria Academic Hospital Complex, South Africa (August 2013 to July 2014), 2.5% of pregnant and postpartum women had severe haemorrhage but contributed to 37.5% of all SMO.¹⁵ The HIV infection rate was 13.7% in women with SMO, lower than the seroprevalence in the study population which was 19.9%.¹⁵ The study found that the risk of obstetric haemorrhage was not higher in HIV-infected women.¹⁵ In another cross-sectional study done in 2012 at four major hospitals in South Africa, it was found that HIV status was not associated with obstetric haemorrhage, but was associated with a greater likelihood of blood transfusion.¹⁶ The study found a significantly higher rate of peripartum transfusion in HIV-infected than HIV-uninfected patients.¹⁶ In those patients who received transfusions, the number of red blood cell units received did not differ significantly by HIV status.¹⁶ These results are a few important steps toward elucidating the impact of HIV on obstetric haemorrhage-related SMO.

1.3 JUSTIFICATION

There is paucity of data on the contribution of HIV infection to obstetric haemorrhage-related SMO. Since the two commonest causes of adverse maternal outcomes in South Africa are non-pregnancy related infections, which are mostly HIV-related, and obstetric haemorrhage, there is the possibility of a relationship between HIV infection and obstetric haemorrhage-related SMO. It is therefore important to determine this relationship, the maternal risk factors involved, and the proportion of maternal deaths

and cases of near-misses from obstetric haemorrhage in HIV-uninfected and -infected women for an accurate comparison. Hence the aim of this study was to determine whether obstetric haemorrhage-related SMO are increased in HIV-infected women, compared to HIV-uninfected women, at Chris Hani Baragwanath Academic Hospital (CHBAH).

CHAPTER TWO

LITERATURE REVIEW

2.1 THE BURDEN OF OBSTETRIC HAEMORRHAGE

Obstetric haemorrhage includes both APH and PPH from any cause known or unknown.¹ APH is defined as bleeding from, or into the genital tract, occurring from 24+0 weeks of pregnancy and prior to the birth of the baby.² It may be due to abruptio placenta, placenta praevia, placenta accreta, uterine rupture, vasa praevia and amniotic fluid embolism, or may be APH of unknown cause.² PPH may be defined in several ways and include blood loss of 500ml or more at vaginal delivery, or 1000ml or more at caesarean section.¹⁷ It is also defined as bleeding associated with a drop in haematocrit of 10% or more, either at vaginal delivery or caesarean section.¹⁷ Defining PPH however as vaginal bleeding or blood loss at caesarean section associated with hypotension and tachycardia, or bleeding at delivery necessitating blood transfusion eliminates the high degree of subjectivity in the measurement of blood loss at delivery and the practical challenges associated with measuring haematocrit routinely.¹⁷

Obstetric haemorrhage is a major public health concern worldwide.¹⁸ As mentioned previously, obstetric haemorrhage is the second leading cause of maternal deaths in South Africa.⁴ According to the sixth Saving Mothers report (2011-2013), the commonest causes of PPH were identified as bleeding during or after caesarean section (BDACS) (32.3%); abruptio placentae (16.1%), uterine rupture (15.1%), uterine atony (7.3%) and retained products of conception (6.6%).⁴ Over the past decade BDACS has become the most important cause of obstetric haemorrhage-related maternal deaths.¹⁹ The case fatality rates have increased from 20.9 per 100 000 caesarean deliveries in the first triennial Savings Mothers report (2002-2004) to 33.6 per 100 000 caesarean deliveries in the sixth report (2011-2013).¹⁹ Though the reasons why these women bleed are mostly difficult to determine, deaths have been attributed to inadequate surgical skill, poor peri-operative monitoring, failure in recognizing on-going bleeding, delay in escalating interventions, insufficient staffing and unavailability of

emergency blood products.¹⁹ A caesarean section duration of between 30 to 50 minutes is deemed to be acceptable.²⁰

2.2 MATERNAL MORTALITY STATISTICS

Maternal death is defined by the World Health Organization (WHO) as “the death of a woman while pregnant or within 42 days of a termination of pregnancy, irrespective of the duration and site of a pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes”.²¹ In 2015, it was estimated that almost 303,000 women die each year from complications of pregnancy and childbirth, and two thirds of them occur in sub-Saharan Africa.⁵ In South Africa, about 1,500 maternal deaths occur every year, representing an estimated maternal mortality ratio (MMR) of 132/100 000 live births in 2015.⁷ This is a reduction from the 2010 ratio of 154/100 000 live births, but fell short of the millennium development goal of a 75% reduction in MMR between 1990 and 2015.⁵ Although maternal mortality presents a significant public health concern, deaths are rare in absolute numbers, and analysing maternal deaths alone does not allow for a comprehensive assessment into the quality of maternal healthcare.⁸ Hence SMO have been suggested as a better indicator of quality of maternal healthcare.

2.3 SEVERE MATERNAL OUTCOME AS A BETTER INDICATOR FOR EVALUATING QUALITY OF MATERNAL CARE

As mentioned in the introduction, severe acute maternal morbidity (SAMM) or maternal near-miss (used interchangeably) is a woman who nearly died, but survived a complication that occurred during pregnancy or childbirth, or within 42 days of termination of pregnancy.⁷ In the late 1990s and early 2000s evaluating SAMM was proposed as a surrogate analysis into maternal deaths and an enormous amount of work has been done to standardize the definition of near-miss.^{6–9,22} The WHO Working Group on Maternal Morbidity and Mortality classification has three approaches for using as a quality of care tool to identify maternal near-miss cases: the clinical criteria related to a specific disease entity, the intervention-based criteria, and the organ system dysfunction-based criteria.⁸ A summary of these approaches is presented in Table 2.1.

Table 2.1 The three approaches used to identify maternal near-miss.⁸

Clinical criteria related to a specific disease entity	Specific diseases are used as the starting points and then for each disease, morbidity is defined. For example, pre-eclampsia is the disease entity, and complications such as renal failure, eclampsia and pulmonary oedema are used to define severe morbidity
Intervention based criteria	Interventions such as admission to an ICU, the need for an emergency hysterectomy, the need for a blood transfusion, caesarean section are used as markers of maternal near-miss
Organ system dysfunction based criteria	In this system, there is a sequence of events: a clinical insult, followed by a systemic inflammatory response syndrome, organ dysfunction and organ failure leading to death. Maternal near-miss cases are those women with organ dysfunction and organ failure who survive. The criteria for defining a maternal near-miss are defined per organ system. Markers for organ system dysfunction or failure are specified

After a systematic review of primary studies that used the various criteria for case finding, the advantages and disadvantages were compared. Application of the organ system dysfunction-based criteria was recommended for case finding because it eliminates the wide variation in outcome that is associated with the clinical criteria and the likely exclusion of many maternal near-miss cases because of variable accessibility when management-based criteria are used⁸. The organ system dysfunction-based criteria for identification of near-miss are summarized below:

Cardiovascular dysfunction

- Shock, cardiac arrest (the absence of pulse/heart beat and loss of consciousness), use of continuous vasoactive drugs, cardiopulmonary

resuscitation, severe hypoperfusion (lactate > 5mmol/l or >45mg/dl) and severe acidosis (pH<7.1).

Respiratory dysfunction

- Acute cyanosis, gasping, severe tachypnoea (respiratory rate >40 breaths/min), intubation and ventilation not related to anaesthesia, and severe hypoxemia (O_2 <90% for >60minutes or more or $PAO_2/Fi O_2$ <200).

Renal Dysfunction

- Oliguria non-responsive to fluids or diuretics, dialysis for acute renal failure, and severe acute azotaemia (creatinine $\geq 300\mu\text{mol/ml}$ or >3.5 mg/dL).

Coagulation/Haematological Dysfunction

- Failure to form clots, massive transfusion of blood or red cells (≥ 5 units), and severe acute thrombocytopenia (50000 platelets/ml).

Hepatic dysfunction

- Jaundice in the presence of pre-eclampsia, and severe acute hyperbilirubinemia (bilirubin $>100\mu\text{mol/ml}$ or 6.0mg/dl).

Neurological Dysfunction

- Prolonged unconsciousness (lasting ≥ 12 hours) or coma and the underlying aetiology include metabolic causes, cerebrovascular accidents, uncontrollable seizures/status epilepticus, and total paralysis.

Uterine dysfunction

- Uterine haemorrhage or infection leading to hysterectomy.⁷

Similarities, and sometimes differences, have been found in the patterns of disease in maternal deaths and SAMM. In 2003, Pattinson et al found that South African women with SAMM have a higher preponderance of conditions like obstetric haemorrhage that were more amenable to interventions.⁶ Maswime et al in 2017 identified previous caesarean section as an important common risk factor for obstetric haemorrhage-related near-miss in Johannesburg, South Africa.²³ Consistently in the Saving Mothers

reports, deaths occur more in women with medical conditions like advanced HIV disease.⁴ Pacagnella et al however described similarities in the delays in care associated with both deaths and near-misses in a multicentre cross-sectional study in Brazil.¹⁰ Despite these differences in findings there appear to be similar inadequacies in the health system leading to both maternal deaths and near-misses. Review of SAMM gives information that complements the findings of maternal death enquiries.⁶

2.4 HIV INFECTION, OBSTETRIC HAEMORRHAGE AND SMO: THE INTERSECTION

At a seroprevalence rate of up to 30% among pregnant women, South Africa has one of the highest HIV prevalence rates in the world.^{12,14} Since 1997, detailed data on maternal deaths in South Africa have been available in the form of triennial Confidential Enquiry reports, the Saving Mothers reports, and consistently, non-pregnancy related infections, largely HIV-related, have been found to be the leading causes of maternal deaths.⁴

Prior to the widespread roll-out of ART in South Africa, HIV-infected women experienced more morbidity and mortality than HIV-uninfected women.¹¹ In 2004, ART was introduced in South African public health facilities for women with CD4 counts of less than 200/ μ L.²⁴ This was expanded to include women with CD4 less than 350/ μ L in 2010 and from 2013, all pregnant and breastfeeding women became eligible to initiate ART irrespective of CD4 count.^{25,26} These periods of changes in government policy regarding ART provision are summarized in Table 2.2. Its impact on direct causes of maternal death is yet to be ascertained.

Table 2.2 Changes in PMTCT and ART guidelines ^{24–29}

Year	Guideline changes
PMTCT guidelines	
2002	Intrapartum single-dose nevirapine
2008	Antenatal zidovudine
2013	ART for all HIV-infected pregnant women, stopped after breastfeeding if not eligible for life-long treatment
2015	Lifelong ART for all HIV-infected pregnant women
ART guidelines	
2004	Life-long ART with CD4 <200 cells/ μ L, or WHO stage 4 disease
2010	For pregnant women, lifelong ART if CD4 $\leq$ 350 cells/ μ L, or WHO stage 3 or 4 disease

Anaemia is the commonest haematological abnormality with HIV infection and the severity of anaemia correlates with the severity of the HIV disease.^{30,31}

Thrombocytopenia is also frequently associated with HIV infection and appears to worsen with progressively lower CD4 counts.³² Pregnant HIV-infected women are observed to have lower pre-delivery haemoglobin (antenatal anaemia) compared with HIV-uninfected women, putting HIV-infected women at an increased risk for obstetric haemorrhage.^{30,31} Antiretroviral therapy has the potential to improve anaemia and thrombocytopenia in HIV-infected pregnant women, and hence to decrease their risks for obstetric haemorrhage.³¹

The evidence on the effect of HIV and its treatment on obstetric haemorrhage is conflicting. While Kourtis et al found no increased odds of APH in HIV-infected women in the United States of America who were not on ART from 1994 to 2003,³³ other studies found that HIV-infected women on ART had increased odds for APH but not PPH, compared to HIV-uninfected women.^{34,35} Also, in a systematic review by Calvert et al to establish whether HIV-infected women are at increased risk of direct obstetric complications, the results were inconsistent.³⁶ Whilst HIV was associated with an increased risk of antepartum haemorrhage in some studies, there was no evidence of an increased risk of placenta praevia, abruptio placenta, postpartum haemorrhage or retained placenta in others.³⁶

Few studies in Southern Africa have looked into the interrelation of obstetric haemorrhage, HIV infection and SMO since the widespread availability of ART, and since the adoption of SMO to assess maternal care. In a retrospective study in Durban to determine an association between increasing rates of obstetric haemorrhage and HIV or its treatment (2009 - 2011), HIV-infected women suffered more maternal near miss (hysterectomy, ICU admission) and deaths than uninfected women.³⁷ In 2012, a cross-sectional study looking at peripartum patients who had an obstetric haemorrhage and, or were transfused, was conducted at four major hospitals in South Africa, including CHBAH.¹⁶ HIV status was not associated with obstetric haemorrhage, but HIV seropositivity was associated with a significantly higher incidence of peripartum transfusion, after controlling for known confounders.¹⁶ Among HIV-infected women,

3.7% received a blood transfusion compared to 2.4% of HIV-uninfected.¹⁶ Risk factors for a peripartum blood transfusion included a prenatal haemoglobin of 9.2 g/dL or less, receiving no prenatal care (unbooked), and high gravidity.¹⁶ There was an association between blood transfusion and combination ART, where women on combination ART received significantly more blood products when compared to no therapy or HIV-uninfected mothers.¹⁶ Interestingly, HIV-infected mothers with a CD4 count less than 200/ μ L were less likely to sustain obstetric haemorrhage compared to those who were HIV-uninfected.¹⁶ An explanation for this finding is difficult, as it is generally expected that the associated poor immune status would predispose such women to greater pregnancy related morbidity.

A descriptive population-based study to determine the spectrum of severe maternal morbidity and mortality in all women who delivered in eight obstetric units in the Pretoria Academic Hospital Complex, South Africa, was conducted between August 2013 and July 2014 and included 26 614 women.¹⁵ The HIV infection rate was 19.9% in the general population and the incidence of obstetric haemorrhage was 2.5%. While obstetric haemorrhage was associated with 37.5% of all SMO, the HIV seropositivity prevalence was 13.7% in the SMO group (less than in the general population).¹⁵

In an analysis of data on 349 women who presented with hypovolemic shock from obstetric haemorrhage as part of a cluster-randomized controlled trial of the non-pneumatic anti-shock garment in Zambia, it was found that HIV-infected women in hypovolemic shock had nearly double the odds of severe haemorrhage compared to HIV-uninfected women in hypovolemic shock.³⁴ The observed increase in haemorrhage-related maternal mortality in HIV-infected women was attributed to exacerbation of iron deficiency anaemia by pregnancy.³⁴

With regards to maternal deaths, an audit to assess the impact of expanded access to ART on maternal mortality at a Johannesburg tertiary hospital for the period 2003-2012, it was found that while deaths from tuberculosis and HIV-associated malignancy declined, mortality from obstetric haemorrhage in HIV-infected women did not change.³⁵

The existing literature contains conflicting data about the interaction between HIV infection, ART and obstetric haemorrhage, with some suggesting a link and others suggesting no link. Given the limited data on the link between HIV infection and obstetric haemorrhage-related SMO, the aim of this study was to determine whether obstetric haemorrhage related severe maternal outcomes were increased in HIV-infected women. The objectives of the study were:

1. To assess the proportion of maternal deaths from obstetric haemorrhage, that occurred in HIV-uninfected and HIV-infected women at CHBAH from January 2015 to December 2015
2. To assess the proportion of cases of near-misses from obstetric haemorrhage, that occurred in HIV-uninfected and HIV-infected women at CHBAH from January 2015 to December 2015
3. To compare factors that are associated with SMO related to obstetric haemorrhage in HIV-uninfected and HIV-infected women

CHAPTER THREE

METHODS

3.1 STUDY SETTING

The study was conducted at CHBAH, a tertiary hospital and the largest hospital in Southern Africa, with the largest obstetrics unit in South Africa. The obstetrics unit at CHBAH serves as a referral centre for seven community health centres from the Greater Soweto area and for more distant areas, including centres outside the Gauteng province. There were 20,324 deliveries in the obstetrics unit at CHBAH in 2015. The HIV prevalence in pregnant women seen at the hospital is around 30%. The staff in the unit are led by a team of obstetricians and gynaecologists, and the unit is also a training centre for registrars, medical officers, interns and midwives.

3.2 STUDY DESIGN

This was a record review of cases of SAMM and maternal deaths, using antenatal and maternal records from the obstetric unit at CHBAH. Data from near-miss and maternal mortality audit reports conducted at CHBAH during the study period were used to supplement information from patients' files. Any outstanding laboratory results not in the patient records were accessed on the National Health Laboratory Services (NHLS) Labtrak website <https://trakcarelabwebview.nhls.ac.za>.

3.3 STUDY POPULATION

The study population included cases of obstetric haemorrhage-related maternal deaths and SAMM at CHBAH's obstetric unit, from 1 January 2015 to 31 December 2015. The management of all mothers with obstetric haemorrhage from the labour ward, antenatal wards, post-natal wards or theatre at CHBAH involves admission to the Obstetrics High Care area for monitoring and transfusion of blood products. Mothers are transferred to the adult intensive care unit (ICU) at CHBAH if they require inotropic support or artificial ventilation. In instances where ICU beds are not immediately available, mothers are managed in the Obstetrics High Care area while waiting to be transferred. When they are discharged from the adult ICU, they transit through the Obstetrics High Care area to

the post-natal wards. Cases were identified from the Obstetrics High Care area admissions register. Patient records were obtained from the records department at in the obstetrics unit at CHBAH. Records of maternal deaths were retrieved from files that are kept in a dedicated area in the office of the Head of Department in the obstetrics unit.

3.4 SUBJECTS

3.4.1 Inclusion criteria

- Pregnant women who died from obstetric haemorrhage, with a gestation age of at least 26 weeks.
- Pregnant women who were managed for obstetric haemorrhage and met the WHO near-miss criteria.

3.4.2 Exclusion criteria

- Maternal deaths that were incidental or not related to the obstetric haemorrhage.
- Near-miss cases that were not obstetric haemorrhage-related.
- Women who were less than 26 weeks of gestation.

3.5 DATA COLLECTION AND DATA ANALYSIS

The broad criteria used to identify SAMM subjects from the Obstetrics High Care area register for potential inclusion in the study included:

- I. Any patients with APH or PPH who had been admitted from the obstetrics theatres or labour ward at CHBAH. Also, patients who were admitted from referring clinics that are part of the maternity complex and needed monitoring for obstetric haemorrhage
- II. Patients who had been admitted intrapartum or postpartum with a low haemoglobin concentration
- III. Patients who had been admitted for blood transfusion
- IV. Patients who had been admitted for ventilation
- V. Patients who were awaiting ICU admission and patients who had been admitted from ICU post-delivery

VI. Patients whose reasons for admission to the Obstetrics High Care area were not clear were also selected for possible inclusion.

Gynaecological patients who had been admitted to the Obstetrics High Care area and monitored for bleeding were excluded. Women who developed SAMM were identified using the WHO organ dysfunction criteria for near-misses.

All data were collected and analysed from February 2016 to October 2016. Antenatal, intrapartum and postpartum information on patients identified with obstetric haemorrhage-related SMO were extracted from the patients' records using a structured questionnaire. (Appendix 1). Data were then captured on Research Electronic Data Capture (REDCap®)³⁸ and exported onto and managed on Microsoft Excel 2010. Analysis was done with Stata®13.0 software. Continuous data were summarized using means and standard deviations (SDs), and medians with interquartile ranges (IQRs) as appropriate. Proportions and percentages were used for analysis of categorical data. Chi-squared test was used for inferential analysis of categorical data, and Student's t-test was used for comparison of means in normally distributed data, and statistical significance was accepted at $p < 0.05$.

3.6 ETHICS

Ethical approval for this study was obtained from the University of the Witwatersrand's Human Research Ethics Committee, Clearance Number: M151133 (Appendix 2). No names or any form of identification were used or entered onto the datasheet. Study numbers were assigned to patients' names and hospital numbers and were collected on a separate document for follow-up and to allow for cross-checking of data.

CHAPTER FOUR

RESULTS

From 1 January to 31 December 2015, there were a total of 20 324 deliveries at CHBAH, and of these, 19 804 were live births. Using the broad criteria described in the data collection section, 222 cases were identified for potential inclusion in the study during the period and records were available for 166/222 (74.7%) of the cases. Of the 166 records available, 73 cases of obstetric haemorrhage-related SMO were identified and 68/73 (93.2%) had a known HIV status and were included in the final analysis.

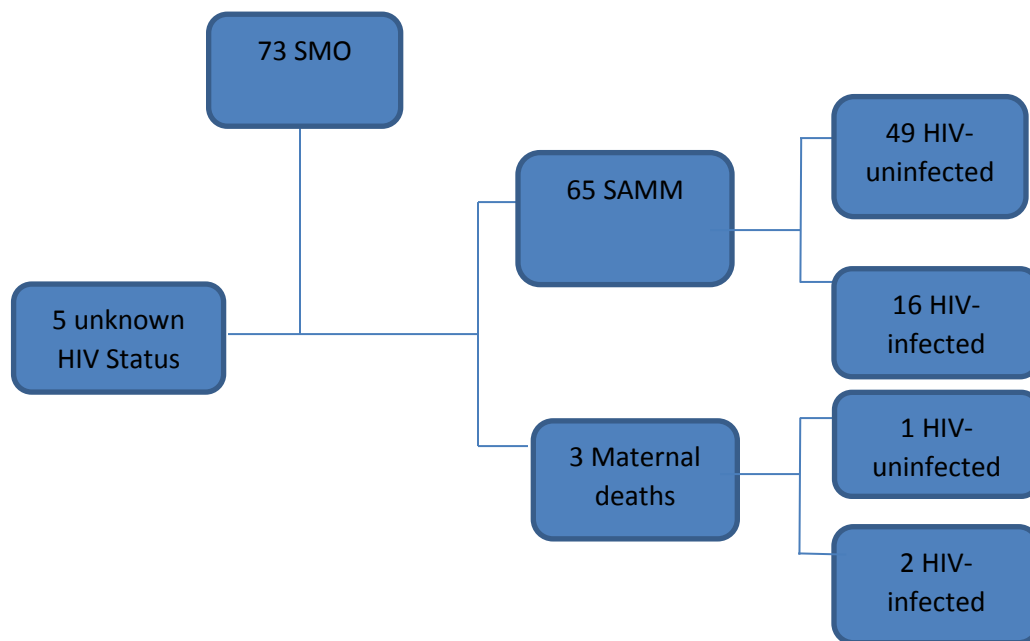


Figure 4.1 A summary of severe maternal outcomes with HIV status.

A total of 18/68 (26.5%) women were HIV-infected and all of them were on the efavirenz-based fixed dose combination (FDC). Of the 18 HIV-infected women, 10/18 (55.5%) were diagnosed prior to the index pregnancy and of these, 90% (9/10) were started on ART pre-pregnancy. The median CD4 count was 409 cells/mm³ (interquartile range (IQR) 222, 636), and viral load results were available for only three women. The viral load results were less than 20 copies/ml for two patients and 48 600 copies/ml for the other patient.

Of the 68 cases of SMO, 65 were SAMM and three were maternal deaths. Among the SAMM cases, 16/65 (24.6%) were HIV-infected, and of the three maternal deaths, two were in HIV-infected women.

4.1 DEMOGRAPHICS AND ANTENATAL DETAILS

The demographics of the 68 cases are presented in table 3.1 below. The mean age of HIV-infected women was 32.8 (SD± 5.8) years while that of HIV-uninfected women was 29 (SD± 6.6) years, $p=0.02$. The median gravidity in HIV-infected women was 3 (IQR 2, 4), and in HIV-uninfected women 2 (IQR 1, 3), $p=0.04$. Most women were booked, 94.4% (17/18) of HIV-infected women and 96% (48/50) of HIV-uninfected women, with a mean gestational age at booking of 15.0 ± 2.1 weeks and 17.6 ± 6.4 weeks, respectively, $p=0.60$.

A total of 24 women were diagnosed with anaemia antenatally, 8 (50.0%) HIV-infected and 18 (36.0%) HIV-uninfected, $p=0.34$. All women who were diagnosed with anaemia had iron deficiency anaemia and were treated with oral iron, with none receiving intravenous iron or blood transfusion. The haemoglobin at delivery was determined from the last known haemoglobin prior to, or at delivery. The definition of anaemia used was a haemoglobin $<11\text{g/dl}$. Overall, 15 women had at least one previous caesarean section, 6/18 (33.3%) of HIV-infected women and 9/50 (18%) of HIV-uninfected women, $p=0.18$.

4.2 DELIVERY DETAILS

The median gestational age at delivery in the HIV-infected women was 39 weeks, (IQR 34, 40) and 38 weeks (IQR 35, 40) for the HIV-uninfected women, $p<0.001$. The onset of labour in majority of the women was spontaneous, 66.7% (12/18) in HIV-infected women and 74.0% (37/50) in HIV-uninfected women, $p=0.60$. Labour was induced with oral misoprostol in one woman; she was HIV-uninfected. Eleven percent (2/18) of HIV-infected women, versus 14% (7/50) of HIV-uninfected received oxytocin for induction of labour, $p=0.71$. The median duration of labour was identical in both groups of women; 720 minutes (IQR 545,1165) in HIV-infected women and 720 minutes (IQR 350,1365) in HIV-uninfected women, $p=0.83$.

Table 4.1: Demographics and antenatal details

	HIV-infected	HIV-uninfected	p-value
	n=18	n=50	
Age in years, mean (SD)	32.5 (5.8)	29 (6.6)	0.02
Age category, n (%)			
<18	0 (0.0)	3 (6.0)	0.28
18-35	13 (72.2)	39 (78.0)	0.62
≥35	5 (27.8)	8 (78.0)	0.27
Parity, median (IQR)	2 (1, 2)	1 (0, 2)	0.16
	3 (2, 4)	1 (2, 3)	0.04
Booked, n (%)	17 (94.4)	48 (96.0)	0.78
Gestational age at booking, mean (SD)	15 (2.1)	17 (6.4)	0.60
<20 weeks, n (%)	8 (53.3)	28 (62.2)	0.54
≥20weeks, n (%)	7 (46.7)	17 (37.8)	0.55
Previous caesarean section, n (%)	6 (33.3)	9 (18.0)	0.18
Diagnosis of anaemia, n (%)	8 (50)	16 (36)	0.47
Gestational age of anaemia diagnosis, mean (SD)	23.5 (10.1)	20 (8.7)	0.63
Haemoglobin at delivery, mean (SD)	9.6 (1.8)	11.7 (2.1)	0.97

Table 4.2: Labour and delivery details

	HIV-infected n=18	HIV-uninfected n=50	p-value
Gestation age at delivery, median (IQR)	39 (34, 40)	38 (35, 40)	<0.001
Onset of labour			
Spontaneous (%)	12 (66.7)	37 (74.0)	0.60
Induced (%)	0	1(2.0)	
Antepartum haemorrhage	6 (33.3)	7 (46)	0.35
Mode of delivery, n (%)			
NVD	6 (33.3)	14 (28.0)	0.55
Assisted	0 (0.0)	1 (2.0)	0.54
EMCS	12 (66.7)	33(66.0)	0.90
ELCS	0 (0.0)	2(4.0)	0.39
Duration of labour in minutes, median (IQR)	720 (545,1165)	720 (350,1365)	0.83
Indications for caesarean section, n (%)			
Antepartum haemorrhage of unknown origin	2 (11.1)	7 (14.0)	0.80
Abruptio placenta	2 (11.1)	10 (20.0)	0.41
Placenta praevia	0 (0.0)	3 (6.0)	0.08
Prolonged labour	3 (16.7)	3 (6.0)	0.14
Cephalopelvic disproportion	1 (5.6)	3 (6.0)	0.97
Caesarean section duration, minutes, median (IQR)	87.5 (55,185)	100.0 (50,189)	<0.001

NVD= normal vaginal delivery; EMCS=emergency caesarean section; ELCS = elective caesarean section

The labour and delivery details are summarized in the table 4.2. The duration of labour was calculated from the documented onset of labour (rupture of membranes, detectable contractions, or cervical dilatation), whether spontaneous or induced, to the delivery of the fetus, regardless of mode of delivery.

4.3 ANTEPARTUM HAEMORRHAGE

Twenty nine of the 68 women (42.7%) in the study had SMO from APH. This number was made up of 33.3% (6/18) of HIV-infected women and 38.3% (23/60) of HIV-uninfected women. The causes of APH are summarized in table 4.3. Thirteen of the women with abruptio placenta were initially managed as an APH of unknown origin with no known risk factors for abruptio placenta but were later confirmed to have had abruptio placenta after delivery.

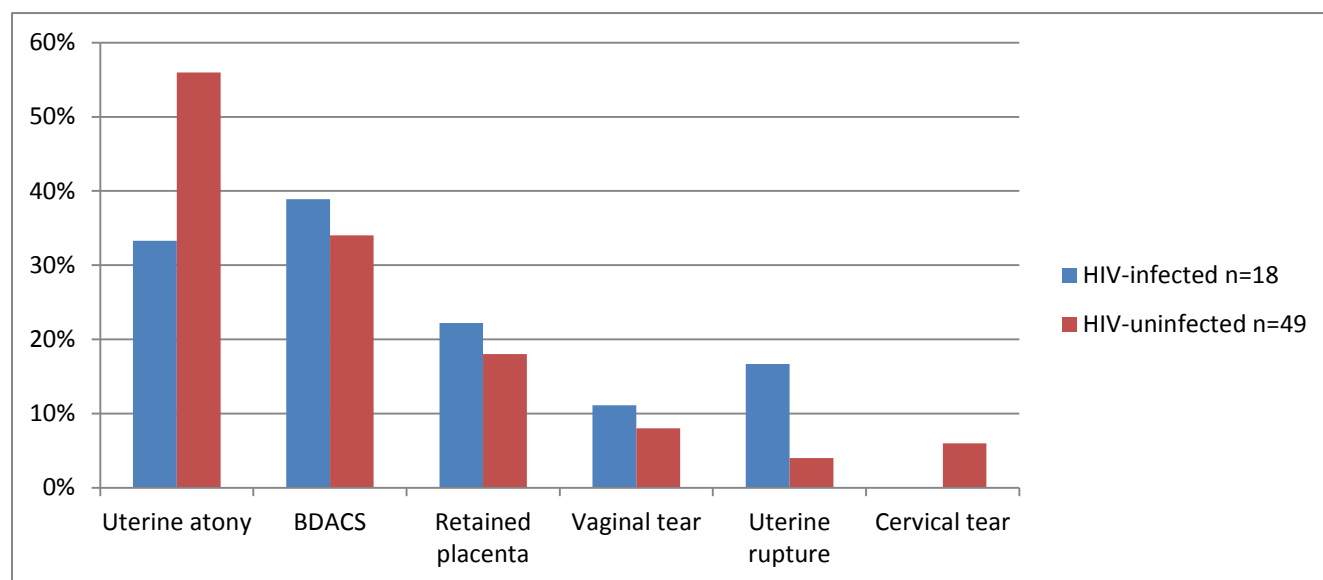
Table 4.3 Causes of Antepartum haemorrhage, n=29

	HIV-infected	HIV-uninfected
	n=6	n=23
	n (%)	n (%)
Placenta praevia	0 (0.0)	3 (13.0)
Abruptio placenta	4 (66.6)	19 (82.6)
Uterine rupture	2 (33.3)	1 (4.4)

4.4 POSTPARTUM HAEMORRHAGE

Postpartum haemorrhage was diagnosed in most women (65/68; 95.6%) who had an obstetric haemorrhage-related SMO – 88.9% (16/18) in HIV-infected women and 98.9% (49/50) in HIV-uninfected women, (p=0.07). The causes of PPH in the women in this study are presented in figure 4.2. Most of the women had more than one cause of PPH. Other causes of PPH in the population included disseminated intravascular coagulopathy (HIV-infected) and placenta percreta (HIV-uninfected). The majority (64/67; 95.5%) of cases of PPH were diagnosed in the first 24 hours after delivery, i.e. primary PPH. Half (8/16) of HIV-infected women with PPH were diagnosed in the first

hour after delivery, compared to 73.5% (36/49) of HIV-uninfected women ($p= 0.08$). One HIV-infected woman had secondary PPH (diagnosed 7 days post-delivery).



BDACS=Bleeding during or after caesarean section

Figure 4.2: Causes of postpartum haemorrhage

4.5 INTERVENTIONS USED IN THE MANAGEMENT OF POSTPARTUM HAEMORRHAGE

Medical and surgical interventions were employed in the management of obstetric haemorrhage in the study population. Figure 4.3 gives a breakdown of the agents used in the medical management of obstetric haemorrhage; most women received more than one agent.

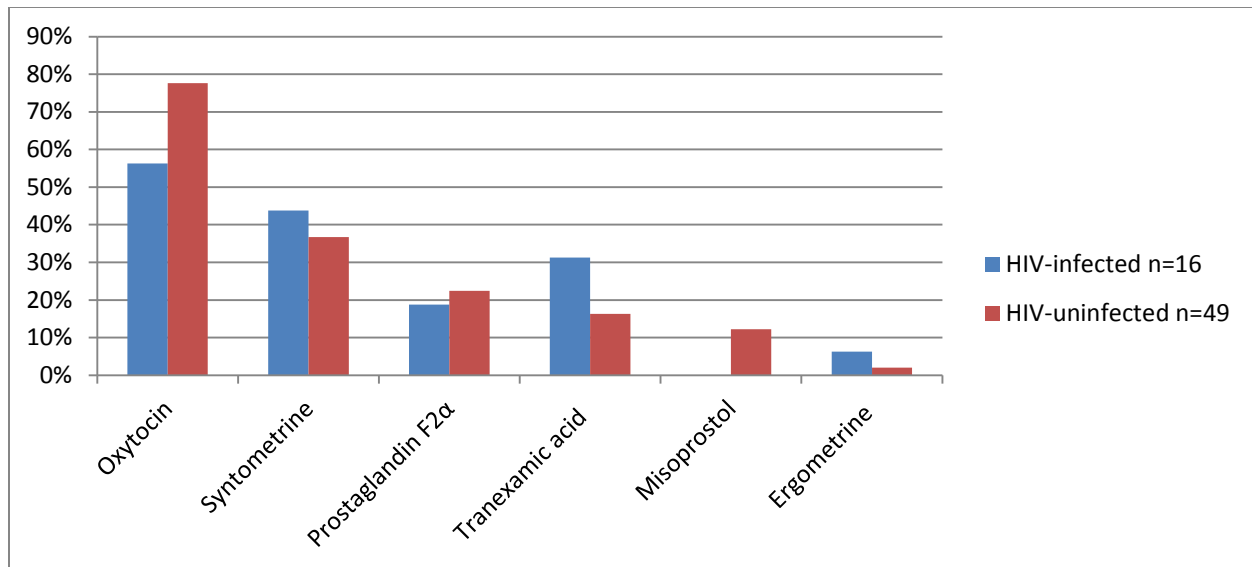


Figure 4.3: The frequency of medical agents used in the management of postpartum haemorrhage

The surgical interventions used in the management of postpartum haemorrhage are presented below.

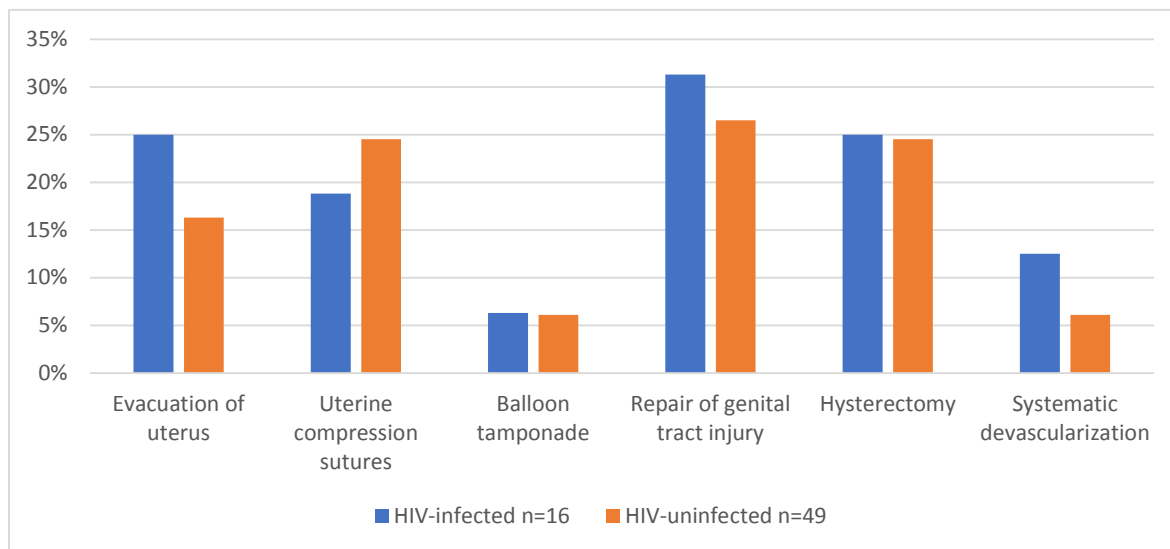


Figure 4.4: The frequency of surgical interventions used in the management of postpartum haemorrhage

4.6 BLOOD TRANSFUSIONS IN WOMEN WITH OBSTETRIC HAEMORRHAGE

All 68 women in the study received blood products (red blood cells, fresh frozen plasma, platelets, and cryoprecipitate) ranging from at least one unit of blood to a total of 27 units. A summary of the blood products received are presented below.

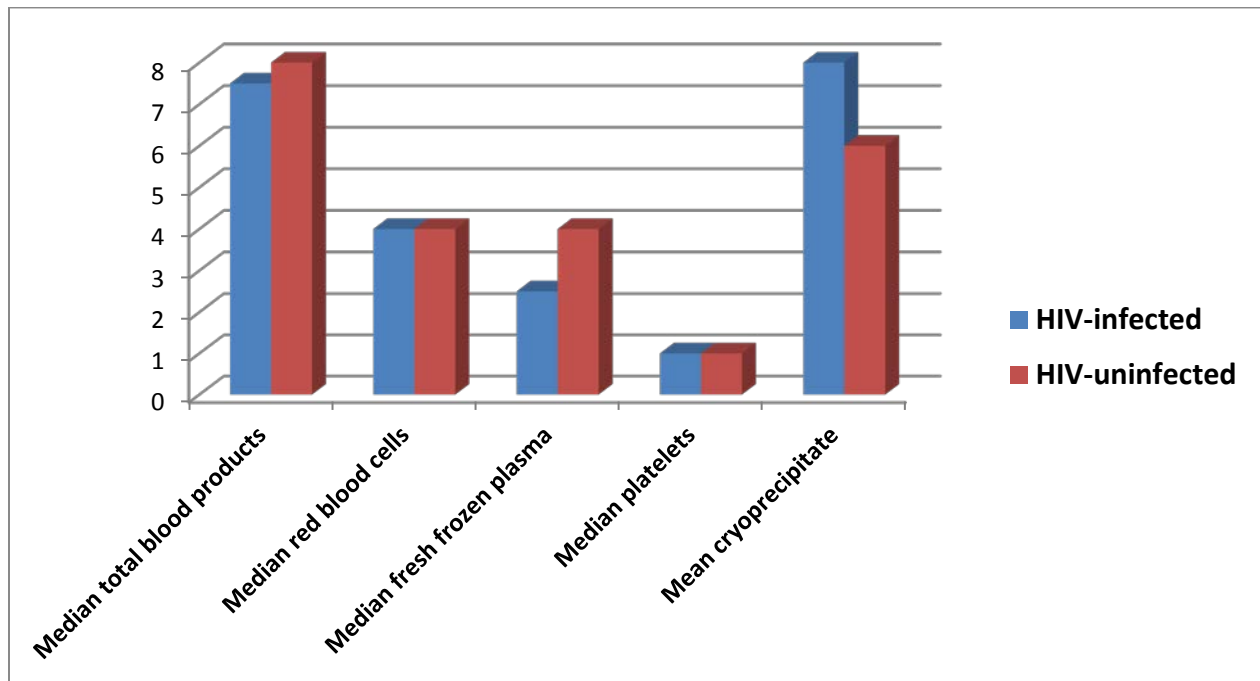


Figure 4.5: Amount of blood products transfused

4.7 BLOOD RESULTS

Table 4.4 presents the worst biochemistry and haematology results for both HIV-infected and HIV-uninfected women during their hospital stay. There was a significant difference in the pH, lactate, base deficit and creatinine levels between the HIV-infected and HIV-uninfected women.

Table 4.4: Worst blood results during hospital admission

	HIV-infected n=18	HIV-uninfected n=50	p-value
Haemoglobin, mean (SD) g/dL	6.0 (1.89)	5.9 (1.36)	0.19
Platelets, mean (SD) ×10 ⁹ /L	68 (23.2)	65 (23.5)	0.75
pH, median (IQR)	7.2 (7.1, 7.26)	7.25 (7.2, 7.3)	0.004
Bicarbonate, median (IQR) mmol/L	15.5 (14.0, 16.1)	14 (11.4, 17.5)	0.97
Lactate, median (IQR) mmol/L	5.5 (4.3, 8.8)	4.3 (3.2, 9.8)	<0.001
Creatinine, median (IQR) umol/L	147 (137, 160)	137 (113, 208)	<0.001
Base deficit, median (IQR) mEq/L	12.6 (10.2, 15.8)	9.8 (7.2, 114)	0.01

4.8 SEVERE MATERNAL OUTCOMES

All 68 women in the study (maternal deaths and SAMM) were diagnosed with at least one organ system dysfunction. Many of them fell into more than one category. Relook laparotomy and ICU admission, both in the management criteria were included as markers of near-miss in the study. The occurrence of markers of near-miss is summarized in Table 3.5. Twenty-two women, (27.8%) HIV-infected and (34.0%), HIV-uninfected in the study needed ventilator support, and were managed in either theatre or Obstetric High Care area while awaiting transfer to the main adult ICU. Duration of

ventilation ranged from one hour to 48 hours. The average duration of ventilation in HIV-infected women was 12.3 (SD±0.6) hours and 14.6 (SD±0.5) hours in HIV-uninfected women, p=0.78. Massive blood transfusion was defined as receiving 5 or more units or blood products.

Table 4.5: Markers for near-miss to obstetric haemorrhage

	HIV-infected n=18 n (%)	HIV-uninfected n=50 n (%)	p-value
Massive transfusion	13 (72.2)	43 (86.0)	0.18
Relook laparotomy	7 (38.9)	16 (32.0)	0.89
Artificial ventilation	5(27.8)	17 (34.0)	0.62
Hysterectomy	4 (22.2)	12 (24.0)	0.87
ICU admission	1 (5.6)	9 (18.0)	0.20
Hypoxemia	1 (5.6)	6 (12.0)	0.44
Shock	1 (5.6)	6 (12.0)	0.44
Oliguria	2 (11.1)	4 (8.0)	0.68
Vaso-active drug use	1 (5.6)	3 (6.0)	0.94
Cardiac arrest/CPR	0 (0.0)	2 (4.0)	0.39
Need for dialysis	0 (0.0)	1 (2.0)	0.50
Seizures	1 (5.6)	0 (0.0)	0.09

4.9 DETAILS OF THE MATERNAL DEATHS

There were three maternal deaths related to obstetric haemorrhage in the study period. Two of them were HIV-infected and one was HIV-uninfected.

4.9.1 Case 1

The first maternal death case was a 28-year old gravida 2 para 0 old HIV-infected woman who was initiated on ART in the index pregnancy. Her CD4 count and viral load were unknown. She had mild anaemia (booking haemoglobin of 10.0 g/dL) and did not receive treatment for anaemia. She delivered vaginally at 39 weeks gestation, at a primary healthcare facility, and had primary PPH, diagnosed within one hour of delivery. The causes of the PPH were uterine atony and vaginal lacerations, and she had no identifiable intrapartum risk factors for PPH. There was a three-hour transportation delay in referring the patient from the primary healthcare facility to CHBAH, after the PPH was diagnosed.

On arrival at CHBAH, the patient received oxytocin, syntometrine, tranexamic acid, and prostaglandin F2 α as part of her medical management. When the medical management failed, surgical management was instituted, initially with a balloon tamponade, followed by a subtotal hysterectomy 60 hours later when she continued to bleed. She received a massive transfusion consisting of 15 units of red packed cells, 8 units of fresh plasma and 4 mega units of platelets in total. She spent 27 days in hospital and died of severe respiratory sepsis with multiple organ failure.

4.9.2 Case 2

The second maternal death case was a 35-year old gravida 3 para 1 HIV-infected woman who was on ART, initiated pre-pregnancy. Her antenatal CD4 count was 616 cells/mm³. She booked at 9 weeks gestation, with a haemoglobin of 13.2 g/dL, and had a history of one previous lower uterine segment caesarean section. She was brought to hospital by ambulance and presented with a history of acute collapse at 29 weeks gestation. On arrival at CHBAH, cardiopulmonary resuscitation (CPR) was initiated. She had a perimortem caesarean section as part of ongoing CPR and was diagnosed with a

uterine rupture intraoperatively. She received 4 units of red packed cells, 4 units of fresh frozen plasma and 1 mega unit of platelets. She died within 7 hours of arrival in hospital.

4.9.3 Case 3

The third maternal death case was of a 32-year-old gravida 3 para 1 HIV-uninfected woman, who booked at 11 weeks with a normal haemoglobin. She had one previous caesarean section and was diagnosed with a placenta praevia major on ultrasound at 31 weeks gestation. She was hospitalised until a planned elective caesarean section at 36 weeks. Notably, her surgery was done by a registrar and placenta percreta was diagnosed intraoperatively, upon which a consultant was called to assist. She had a caesarean hysterectomy and a re-look laparotomy within an hour after the initial operation for on-going PPH. She developed a DIC and the abdomen was packed to aid haemostasis. The patient had a relook laparotomy 48 hours later for removal of the abdominal packs. She received a massive transfusion with 7 units of red packed cells, 4 units of fresh frozen plasma and 8 units of cryoprecipitate in total. She had a hypoxic event after the second re-look laparotomy followed by multiple seizures. She later had a cardiac arrest and died 12 days post-delivery after an unsuccessful CPR. She was in hospital for 65 days, including her antenatal stay.

CHAPTER FIVE

DISCUSSION

In this retrospective record review of cases of obstetric haemorrhage at CHBAH, from 01 January to 31 December 2015, there was no difference in the incidence of obstetric haemorrhage-related near-misses and maternal deaths between HIV-infected and uninfected women. The HIV-infected women in the study were a relatively healthy group, with a median CD4 count of 409 cells/mm³ and all of them were on ART. Diagnosis and causes of obstetric haemorrhage did not differ between the HIV-infected and uninfected women.

Previous caesarean section was the commonest identifiable risk factor for obstetric haemorrhage that was identified, and nearly a quarter of the women in the study had a previous caesarean section. The finding of such a significant proportion of previous caesarean section related SMO agrees with Maswime et al in their description of risk factors for maternal death due to BDACS in Johannesburg (July to December 2014).²³ They identified previous caesarean section as one of the most important common risk factors for near-miss.²³ With the increasing rate of caesarean section deliveries in South Africa, this finding reflects the increasing importance of previous caesarean section as a risk factor for obstetric haemorrhage-related severe maternal outcomes.

5.1 ANTENATAL AND INTRAPARTUM FACTORS ASSOCIATED WITH OBSTETRIC HAEMORRHAGE

More than a third of women in the study had anaemia at the first antenatal visit. Adhering to the recommendations from the sixth Saving Mothers report to prevent anaemia as a measure to prevent obstetric haemorrhage related deaths,⁴ the mean haemoglobin concentrations of the women in the study had improved with oral haematinics by the time of delivery. In all the HIV-uninfected women, the haemoglobin levels were normal at the time of delivery, while HIV-infected women were still mildly anaemic. Anaemia was however not associated with severe obstetric haemorrhage-related maternal outcomes in this study. Correction of antenatal anaemia appears to

have decreased the risk for obstetric haemorrhage in both HIV-infected and uninfected women.

The duration of the caesarean sections was significantly longer in HIV-uninfected women. This is difficult to explain, especially as it is rather expected that HIV-infected women who were significantly older and had a higher parity, would be more likely to have had a previous caesarean section, and therefore a longer caesarean section duration than uninfected women. The long duration of caesarean sections in both HIV-infected women (median 100 minutes) and uninfected women (median 87.5 minutes) in the study is worth noting. While comparing caesarean section surgical techniques in over 15 000 women in the CORONIS trial, secondary outcomes were measured. The incidence of ICU admission and postpartum haemorrhage were not increased in their study and a median duration of the operation of 40 minutes was deemed acceptable.²⁰ The finding in my study represents a more than twofold increase in the acceptable average caesarean section duration as demonstrated in the CORONIS study.²⁰ Typically, junior members of the team are assigned to perform caesarean sections. Though their competencies are verified before they work unsupervised, the prolonged duration of surgery in this study may reflect both the relative inexperience of the surgeons and the inherent difficulty encountered during caesarean sections for women who end up with severe outcomes. The extended operating time also reflects the time needed to correct the underlying pathology associated with a severe outcome. The contribution of BDACS to maternal deaths at district and secondary level facilities is well recognized,¹⁹ but this study brings to the fore the importance of BDACS as a significant factor associated with adverse pregnancy outcomes at all levels of care when near-misses are also studied.

Prolonged labour was associated with 8.8% of SMO in this study and there was no significant difference in the duration of labour between HIV-infected women and uninfected women. This association of prolonged labour with maternal near-miss is consistent with findings by Pacagnella et al in their descriptions of delays associated with severe maternal outcomes.¹⁰ In contrast with the sixth Saving Mothers report however, prolonged labour was not associated any deaths in this study.⁴

5.2 CAUSES OF OBSTETRIC HAEMORRHAGE

There was no significant difference in the causes of obstetric haemorrhage between HIV-infected and HIV-uninfected women. The incidence of uterine atony retained placenta, uterine rupture, abruptio placenta and genital tract tears, as causes of obstetric haemorrhage, did not differ between HIV-infected and HIV-uninfected women. PPH was the leading cause of obstetric haemorrhage-related SMO in this study. The incidence of PPH was not increased in HIV-infected women. This agrees with the findings from the systematic review and meta-analysis by Calvert et al who also found that there was no evidence that HIV increases the odds of postpartum haemorrhage.³⁶ Three women had placenta praevia and all of them were HIV-2uninfected. It appears to be coincidental with no explanation to suggest that seropositivity may be protective against placenta praevia. There was no difference in the incidence of abruptio placenta and uterine rupture between HIV-infected and uninfected women, and this is consistent with findings from the systematic review by Calvert et al.³⁶ The incidences of other causes of PPH (uterine atony, retained placenta and genital tract tears) followed a similar trend of no demonstrable difference between HIV-infected and HIV-uninfected women. This was however contrary to the findings by Shabalala et al who found that HIV increased the risk of PPH in a study done in Durban, South Africa (2009-2011).³⁷ It must be noted that my study and that of Shabalala et al were done during different ART guideline eras.²⁴⁻²⁹ The improvement in anaemia and general health of HIV-infected women in this study, from improved ART regimens, is likely to explain why they were not at an increased risk of obstetric haemorrhage.

5.3 INTERVENTIONS USED IN THE MANAGEMENT OF POSTPARTUM HAEMORRHAGE

In the management of PPH, pharmacological agents and surgical techniques were employed. There was no significant difference in the requirements for oxytocin, ergometrine, syntometrine, prostaglandin F2 α , tranexamic acid and misoprostol between HIV-infected and HIV-uninfected women. Neither did evacuation of uterus, uterine compression sutures, balloon tamponade, repair of genital tract injury,

hysterectomy nor systematic devascularization occur more frequently in one group than the other.

All the women in this study were transfused with blood products. The HIV-infected women received similar amounts of total blood products as the HIV-uninfected women. The amount of red blood cells, platelets and cryoprecipitates received did not differ significantly between HIV-infected women and uninfected women. This finding differs from what Bloch et al found in their cross-sectional study of peripartum patients in South Africa.¹⁶ In their study to determine the incidence and predictors of transfusion in relation to HIV infection, they found significantly higher risk of peripartum transfusion in HIV-infected patients than uninfected women.¹⁶ They attributed their findings to a high prevalence of unaddressed antenatal anaemia among HIV-infected women. In my study however, all iron deficiency anaemia had been corrected prior to delivery and that may explain why the total blood products received did not differ between HIV-infected and uninfected women. The HIV-infected women received slightly less units of fresh frozen plasma (4 vs 2.5 units, $p=0.28$) than infected women. HIV-infected women are rather expected to be more likely to have clotting disorders than uninfected women and would therefore require more units of fresh frozen plasma to help manage bleeding. This was another unexpected finding in my study as seropositivity is not expected to confer protection from transfusion with fresh frozen plasma.

5.4 NEAR-MISSES AND MATERNAL DEATHS

Massive transfusion, artificial ventilation, hysterectomy, hypoxemia, shock, and oliguria, in order of decreasing frequency, occurred at similar rates among HIV-infected and uninfected women. Other markers for near-misses which occurred to lesser degrees like continuous use of vaso-active drugs, cardiac arrest (with cardiopulmonary resuscitation), requirement for dialysis and seizures followed a similar pattern. Relook laparotomy and ICU admission which are management-based criteria for near-miss, included as markers of near-miss in this study because of their frequency, also showed no differences in incidence when HIV-infected women were compared to HIV-uninfected women. The finding of no difference in near-miss between HIV-infected and HIV-uninfected is similar to that reported by Soma-Pillay et al in 2014, who found no

correlation between HIV status and obstetric haemorrhage-related maternal near-misses.¹⁵

There were three obstetric haemorrhage-related maternal deaths in the study period; two in HIV-infected women and one in an uninfected woman. They all required massive transfusion of blood products. The number of deaths in this study was too small for any attributions to be made to the HIV status of the women who died. The deaths highlight some of the important events that lead to maternal deaths nationally at all levels of care. Previous caesarean section was the underlying risk factor leading to the deaths of two of the women; one HIV-infected, the other uninfected. One woman had a uterine rupture remote from term, with severe antepartum haemorrhage and required a peri-mortem caesarean section as part of a resuscitation which was unsuccessful. The use of illegal uterotonics is known to be common among women in the Greater Soweto area, for inducing labour and termination of pregnancy. It was not clear from the limited information available that any such substance was used. A catastrophic uterine rupture through the previous caesarean section scar is the only possible explanation. This death was probably unavoidable. Another had a planned caesarean section for placenta praevia, done by a junior surgeon without the requisite skill to manage complications associated with placenta praevia. This was an avoidable death. The other death was due to delays on two levels: a transportation delay (administrative delay) in referring the patient to the tertiary facility, and a delay in instituting definitive management (health worker related). These delays are mirrored in the Brazilian multi-centre study in 2014 by Pacagnella et al in which they noted that transportation delays, untimely and improper management were significantly associated with maternal deaths.¹⁰

Buchmann et al in a retrospective cross-sectional study to determine causes and trends of maternal deaths in Johannesburg (1997 to 2012) suggested that it was likely that sustainable strengthening of HIV diagnosis and ART programmes would reduce deaths from direct obstetric causes.¹² All the HIV-infected women in my study were on treatment and generally healthy. The result of the current ART guideline where all pregnant women became eligible to initiate ART may have achieved the desired results in reducing deaths from obstetric haemorrhage.

5.5 LIMITATIONS

A limitation of this study is that it was a retrospective study and the sample was small. Also, poor recording of entries in the obstetric high care admissions register made patient identification difficult. This limitation was overcome by making the inclusion criteria wide so that no patients would be missed. Another limitation was the poor filing of patients' records in the records department, due to lack of space. This made retrieval of patient records difficult, but eventually 75% of patient records were found. Another important limitation was that the HIV status of five women with severe maternal outcomes were unknown and were therefore excluded from the study. Furthermore, an association between HIV viral load and severe maternal outcomes could not be established because viral load levels were measured in only three women.

5.6 STRENGTHS

The strength of this study is that although the sample size was small, very detailed information could be collected for each patient. The detailed analysis of data allowed for good examination of factors associated with severe maternal outcomes. It is unlikely that women with severe maternal outcomes related to obstetric haemorrhage were missed as the obstetric high care area is a central point where all mothers with life-threatening conditions transit through from theatre, labour or antenatal ward to the post-natal wards or ICU. Wide inclusion criteria were also used to identify patients for potential inclusion into the study.

5.7 CONCLUSION

In this study, there was no significant difference in obstetric haemorrhage-related severe maternal outcomes in HIV-infected women compared to HIV-uninfected women. This may be because it was a relatively healthy population of HIV-infected women, with a high median CD4 count and all of them were on ART. The antenatal and intrapartum risk factors for maternal near-miss and maternal deaths were similar between the two groups. Previous caesarean section was the commonest underlying risk factor for obstetric haemorrhage. Larger studies are needed to describe these findings in better detail.

5.8 RECOMMENDATIONS

A great deal of attention needs to be given to the training of junior staff on the clinical and surgical management of women with postpartum haemorrhage. Doctors in referral centres should be better trained to safely perform caesarean sections and to appropriately manage associated complications. The recommendation from the sixth Saving Mothers report to provide onsite emergency transport from district hospitals to higher centres should be upscaled. Lastly, there needs to be improvement in the routine viral load monitoring of HIV-infected women, especially during pregnancy and for long term management.

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APPENDICES

Appendix 1: Data Collection Tool

STUDY ID [][]

Date of data collection: _____

A. ANTENATAL INFORMATION

Age: ____ years Gravidity: ____ Parity: ____

Summary of previous pregnancies:

Year	Outcome	Mode of delivery	Birth weight	Gestation at delivery	Complications

☐Booked ☐Unbooked ☐Date of booking _____

Gestational age at booking: ____ weeks

Place of booking; specify

☐Clinic _____ ☐Hospital Level 1 ☐Hospital Level 2 ☐Tertiary Hospital

☐Private

1. Booking bloods:

Booking Haemoglobin: ____ g\dl 1st repeat ____g\dl 2nd repeat ____g\dl

3rd repeat ____g\dl

Rhesus: ☐Positive ☐Negative ☐Unknown

RPR: ☐Positive ☐Negative ☐Unknown

2. Information on HIV disease

HIV status: ☐Positive ☐Negative ☐Unknown

If negative 1st repeat date _____ 2nd repeat date _____

Period of diagnosis of HIV: ☐Pregnancy ☐Antenatal ☐Intrapartum

☐Post-partum

If positive CD4 count: _____ cells/mm³

Date of latest CD4 count testing _____ Gestational age at which CD4 was done _____ weeks

On Antiretrovirals: ☐Yes ☐No ☐Unknown

When where ARVs started? ☐Pregnancy ☐Antenatal ☐Intrapartum

☐Post-partum

Duration of treatment at time of incident (SAMM/Mortality) _____ years

Which treatment?

☐FDC ☐TDF ☐FTC ☐3TC ☐AZT ☐D4T ☐EFV
☐NVP ☐Alluvia ☐Other; specify _____ ☐Information not available

Any treatment switches/failure? ☐Yes ☐No

Viral load at booking _____ copies/ml ☐Not available

Latest Viral load _____ copies/ml

Date _____ Gestational age at which viral load was done _____ weeks

3. Comorbidities in the index pregnancy

- ☐ Diabetes Mellitus (IDDM/NIDDM) ☐ Chronic hypertension ☐ Asthma
☐ Epilepsy ☐ Tuberculosis ☐ Hypothyroidism ☐ Hyperthyroidism
☐ Cardiac disease ☐ Other(s); specify _____

Chronic medication(s),

Haematinics: ☐ Ferrous sulphate ☐ Folic acid

Vitamins: ☐ Vitamin C

Antihypertensives: ☐ Lisinopril ☐ Enalapril ☐ Hydrochlorothiazide

☐ Methyldopa ☐ Nifedipine ☐ Other(s) please specify _____

Anticoagulants: ☐ Warfarin ☐ Aspirin ☐ Fractionated heparin

Hypoglycaemics: ☐ Metformin ☐ Gliclazide ☐ Pioglitazone ☐ Insulin

Antiepileptics _____

Anti-TB treatment _____

4. Information on diagnosis and management of anaemia

Was the patient diagnosed with anaemia during the pregnancy? ☐ Yes ☐ No

Severity of anaemia:

☐ Mild 9.0-10.9g/dL ☐ Moderate 7.0-8.9g/dL ☐ Severe Less than 7g/dL

Gestational age at diagnosis of anaemia _____ weeks Date _____

Was she treated for anaemia during the pregnancy? ☐ Yes ☐ No

If treated for anaemia, where was she treated?

☐ Local clinic ☐ CHBH Antenatal clinic ☐ CHBH ANC Anaemia Clinic

☐ Other; specify _____

Gestational age at treatment of anaemia _____ weeks Date _____

Cause of anaemia identified? ☐Yes; specify _____ ☐No

Treatment available at facility? ☐Yes ☐No

Gestational age at referral to CHBAH _____ weeks Date _____

When seen at CHBH? Gestational age _____ weeks Date _____

Did the patient receive any of the following during the pregnancy?

☐Oral haematinics ☐Parenteral (IV) iron ☐Blood transfusion

Reason for receiving parenteral iron

☐Not absorbed ☐Not tolerated ☐Close to delivery

Reason for receiving blood transfusion

☐Severe anaemia ☐Symptomatic anaemia ☐Obstetric indication

Last haemoglobin level at delivery _____g/dL Haemoglobin corrected? ☐Yes ☐No

Was the patient diagnosed with thrombocytopenia during the pregnancy? ☐Yes ☐No

Cause; specify _____

Was the patient admitted at any time during the index pregnancy? ☐Yes ☐No

If admitted, reason for admission:

☐Threatened miscarriage ☐Excessive vomiting in pregnancy

☐Prelabour rupture of membranes ☐Preterm labour ☐Chorioamnioinitis

☐Lower respiratory tract infection ☐Other non-pregnancy related infections

☐Hypertension in pregnancy ☐Antepartum haemorrhage

☐Postdates ☐Other(s) _____

Comments _____

B. INTRAPARTUM DETAILS

Onset of labour Date _____ Time _____

☐ Spontaneous ☐ Induced. If induced what was the indication? _____

Duration of induction _____ hours

Induction agent

☐ Oral Misoprostol ☐ Vaginal Misoprostol ☐ Prostaglandin gel

☐ Oxytocin ☐ Catheter induction

Was there prolonged rupture of membranes ☐ Yes ☐ No

If yes, what was the duration? _____ hours

Were antibiotics given? ☐ Yes ☐ No

If yes, which antibiotic(s)

☐ Ampicillin ☐ Metronidazole ☐ Erythromycin

☐ Co Amoxicillin-Clavulanic acid ☐ Other(s)

Was labour augmented? ☐ Yes ☐ No

If yes, duration of augmentation _____ hours

Intrapartum Diagnosis

☐ Singleton ☐ Multiple gestation ☐ Cephalic presentation

☐ Breech presentation ☐ Transverse lie ☐ Preeclampsia

☐ Other; specify _____

Was antepartum haemorrhage diagnosed? ☐ Yes ☐ No

If yes, was it...

☐ Placenta praevia ☐ Suspected abruptio placenta ☐ Confirmed abruptio placenta

☐ APH of unknown origin ☐ Other; specify _____

Date of delivery_____ Time of delivery_____

Gestational age at delivery _____weeks.

Intra partum diagnosis of chorioamnionitis? ☐Yes ☐No

Place of delivery:

☐Home ☐En route to hospital ☐Clinic ☐Hospital Level 1

☐Hospital Level 2 ☐Tertiary Hospital

Mode of delivery:

☐Normal vaginal delivery ☐Assisted vaginal delivery

☐Emergency caesarean section ☐Elective caesarean section

Indication(s) for caesarean section:

Date and time of Caesarean section _____

Duration of Caesarean section _____minutes

Total duration of labour _____minutes

If referred from local clinic, was there a delay in referral to hospital ☐Yes ☐No

Reason for delay:

☐Patient related ☐Healthcare worker related ☐Administrative related

Other (specify) _____

C: POSTPARTUM DETAILS

Was postpartum haemorrhage diagnosed? ☐Yes ☐No

If yes, was it ☐Primary or ☐Secondary

How soon after delivery was PPH diagnosed?

☐Immediately after delivery ☐Within 1st hour of delivery

☐ More than 1 hour after delivery ☐ Other; _____ specify hours/days

Cause of postpartum haemorrhage

☐ Retained placenta ☐ Cervical trauma ☐ Vaginal trauma ☐ Perineal tears

☐ Uterine atony ☐ Uterine rupture ☐ Bleeding after Caesarean

☐ Other(s) specify _____

Management of postpartum haemorrhage:

Medical management:

☐ Oxytocin ☐ Syntometrine ☐ Ergometrine ☐ Prostaglandin F2 α

☐ Tranexamic acid ☐ Other (s) _____ specify

Surgical management:

☐ Evacuation of uterus ☐ Uterine compression sutures ☐ Balloon tamponade

☐ Repair of genital tract injury ☐ Systematic devascularization ☐ Hysterectomy

☐ Uterine artery ligation

Time between vaginal delivery and repair of genital tract injury _____ hours

Time between vaginal delivery and evacuation of uterus and, or removal of placenta
_____ hours

Time between caesarean section and hysterectomy/ surgical management _____ hours

Time between initial operation and relook laparotomy _____ hours

Category of SMO

☐ Severe Acute Maternal Morbidity ☐ Maternal Mortality

SAMM Criteria

☐ ICU Admission ☐ Hysterectomy ☐ Relook Laparotomy

☐ Artificial ventilation/intubation not related to anaesthesia ☐ Acute cyanosis

- ☐ Gasping ☐ Severe tachypnoea (respiratory rate >40 breaths/min)
☐ Severe hypoxemia ($O_2 < 90\%$) ☐ Massive transfusion of blood products (≥ 5 units)
☐ Shock ☐ Cardiac arrest ☐ Continuous vaso active drugs
☐ Cardiopulmonary resuscitation ☐ Oliguria ☐ Need for dialysis
☐ Cardiopulmonary resuscitation ☐ Prolonged unconsciousness
☐ Stroke ☐ Fits ☐ Paralysis

D. BLOOD RESULTS AND TIMING

	1 hour	6 hours	12 hours	24 hours	48 hours	120 hours	168 hours
pH							
Base excess							
Haemoglobin							
Haematocrit							
Platelets							
Glucose							
Lactate							
Urea							
Creatinine							
Bicarbonate							
Bilirubin							

Duration of ICU stay _____ days

Duration of artificial ventilation/Intubation _____ hour(s)

Blood products given

☐ Red cell _____ units ☐ Fresh frozen plasma _____ units

☐ Platelets _____ mega units ☐ Cryoprecipitate _____ units

Duration of hospital stay _____ day(s)

If maternal death, cause of death _____

Date _____

Time _____

Place of death _____

Time (minutes/hours) between delivery and death _____

Appendix 2: Ethics clearance certificate



R14/49 Dr Kwadwo Atobra Antwi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M151133

NAME: Dr Kwadwo Atobra Antwi
(Principal Investigator)

DEPARTMENT: Obstetrics and Gynaecology
Chris Hani Baragwanath Academic Hospital

PROJECT TITLE: Obstetric Haemorrhage-Related Severe Maternal Outcomes in HIV Infected Women

DATE CONSIDERED: 27/11/2015

DECISION: Approved unconditionally

CONDITIONS: Title Change (04/12/2015)

SUPERVISOR: Dr Coceka Nandipha Mnyani

APPROVED BY: 
Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 04/12/2015

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 Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized 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 the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature _____

Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 3: Turnitin Originality Report

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