THE EFFECT OF HIV INFECTION ON THE INCIDENCE AND SEVERITY OF POST-PARTUM HAEMORRHAGE.

BY

GARVEY CHIPILIRO CHILOPORA
CHLGAR003

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN
In fulfilment of the requirements for the degree

MPhil (Maternal and Fetal Medicine)

Faculty of Health Sciences
UNIVERSITY OF CAPE TOWN

06 March 2012

Supervisor:

Professor S.R. Fawcus
Department of Obstetrics and Gynaecology
University of Cape Town

DECLARATION

I…….. hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: ……...

Date: …….....

Table of contents:

List of Tables

Acknowledgements

I would like to thank my wife, Gloria, and our children, Mphatso, Samuel and Stacy, for their continued support and understanding. I thank them for enduring my prolonged periods of absence from home during the data collection period and thereafter.

I would also particularly like to acknowledge the invaluable contribution and support of Dr Greg Petro in the statistical analysis of this work without whose help this data would be without meaning.

Most of all, I would like to acknowledge the help of my supervisor, Professor Susan Fawcus in transforming all the data into this complete dissertation.

Executive summary

Background: Postpartum haemorrhage (PPH) accounts for more than 75% of maternal deaths from obstetric haemorrhage. In South Africa, maternal mortality resulting from postpartum haemorrhage has persistently been shown to be higher in HIV positive compared to HIV negative women. It is unknown whether the incidence of PPH is higher in HIV positive women; and/or whether HIV positive women have more severe bleeding and suffer greater morbidity as a result of PPH.

Aim. The aim of the study was to investigate the effect of HIV infection on the incidence and severity of PPH.

Methods: All women delivering at Mowbray Maternity and Groote Schuur Hospital in 2009 who had PPH were identified through a manual search of labour ward and operating theatre records. The women were categorized according to their HIV status as HIV positive, negative and untested. Data was also obtained on HIV status of the whole delivery population at these two hospitals. For women with PPH, data regarding background characteristics:- blood loss; cause of PPH and management provided; severity of and morbidity from PPH was analysed by comparing the HIV positive with the HIV negative group. Severity was assessed in terms of blood loss alone. Morbidity on the other hand was a composite assessment of blood loss, need for blood products, interventions required and complications of the PPH. Data was also collected on CD4 counts and treatment provided although the study was not powered to investigate these factors as associations.

Results: During the period under study, Mowbray Maternity Hospital and Groote Schuur Hospital registered a total of 15384 deliveries in 2009. 2738 (17.8%) of these deliveries were HIV positive, 12151 (79.0%) HIV negative and 495 (3.2%) HIV untested.

A total of 1230 (8.0%) women had recorded blood loss of 500ml or more at the time of delivery and fulfilled the criteria for PPH. 270 of these women (22%) were HIV positive, 915 (74.4%) were HIV negative and 45 (3.6%) were HIV untested. The rate of PPH in the HIV positive group was 9.9% compared to 7.5% in the HIV negative group and this difference was significant ($p<0.001$). Uterine trauma at caesarean section was the most common cause of PPH in the two groups of patients. It was the cause for 92% of PPH cases in HIV positive and 88% in HIV negative women. Uterine atony accounted for up to 30% of PPH in the HIV positive group and 29% in the HIV negative. Other important causes of PPH included retained placenta and products of conception, abruptio placentae and uterine rupture. HIV infection, regardless of severity as determined by the level of CD4 count, did not affect the severity of PPH. However, more HIV positive women suffered morbidity ($p=0.008$) from PPH despite the similar mean blood loss between the two groups of women ($p=0.697$). Maternal age and obesity did not appear to influence the incidence of PPH in HIV positive women. The mode of treatment of HIV also did not influence the severity of and the morbidity from PPH.

Conclusion: The results of the study show that postpartum haemorrhage was more common and was associated with increased morbidity in HIV positive compared to HIV negative women. However, due to the limitations in the study design and the impact of other biases, the study cannot conclude that HIV infection is an independent

risk factor for postpartum haemorrhage. Future research needs to explore the impact of CD4 count and antiretroviral treatment regimens on the incidence and severity of PPH.

Chapter 1

Introduction

Postpartum haemorrhage (PPH) remains a major direct cause of maternal mortality worldwide. It accounts for 25% of maternal deaths world wide. This is the prevailing trend especially in poorly resourced settings such as in sub-Saharan Africa[1]. In South Africa, obstetric haemorrhage is the third most common cause of maternal death. It accounts for 12.4% of the total number of maternal deaths with PPH making up more than 75% of these deaths[2].

Despite measures to prevent death from postpartum haemorrhage, the Saving Mothers reports between the trienniums 2002 – 2004 and 2005 – 2007 have shown no decrease in the trend of deaths due to PPH. The maternal mortality ratio (MMR) due to PPH has remained constant at14.7 per 100,000 livebirths during this time. Of particular interest and equally troubling is the finding of an increased number of maternal deaths due to PPH in HIV positive compared to HIV negative women. The MMR from PPH was 13.8 deaths per 100,000 livebirths in HIV positive women compared to 5.7 per 100,000 livebirths in HIV negative women. MMR from PPH was highest in HIV untested women at 38.3 per 100,000 livebirths[2,3].

According to the confidential enquiry into maternal deaths in the United Kingdom for the triennium 2003 – 2005, PPH was also the third commonest cause of maternal mortality responsible for 6.6 deaths per million maternities. This rate as in South Africa remained unchanged from the previous triennium[4,5,6]

The World Health Report of 2005 notes that the progress in Maternal and Child Health has stumbled particularly in sub-Saharan Africa due to the direct and indirect effects of HIV/AIDS [7].

About half of the 38 million people living with HIV in 2005 were women. Sixty three percent of these women lived in sub-Saharan Africa [8]. The prevalence of HIV infection in antenatal clinics varied from 1% to 40%, the highest rates being in the same region [9]. In 2003, the Western Cape region of South Africa registered an antenatal HIV seroprevalence of 12.4%. This rate was projected to increase in subsequent years [10]. Additionally, HIV positive women are known to have a 9.5 times greater risk of maternal mortality than HIV negative women. The Saving Mothers report for the triennium 2005 – 2007 shows MMR was 327.7 per 100,000 livebirths in HIV positive compared to 34.4 per 100,000 livebirths in HIV negative women[2]. In the United Kingdom, this risk is 1.5 to 2 times higher [5].

As such, HIV/AIDS has become the leading cause of maternal mortality in the sub-Saharan region, with the adult lifetime risk of dying in pregnancy and childbirth for a 15 year old woman at a staggering high of 1 in 22 as opposed to 1 in 7,300 in the developed world [11].

Although it is generally understood that most of the maternal deaths occur in the hospital setting, an uncertain proportion of such deaths occur outside the hospital and may also go unreported. In 1998, about 4% of the reported maternal deaths in South Africa occurred either at home or an unknown location[12]. This is an underestimate of the number of maternal deaths occurring at home since the Saving Mothers reports

focus on institutional deaths and do not seek to collect home deaths. In the most recent report looking at home maternal deaths in the Demographic Surveillance Area (DSA) in Hlabisa sub-district in northern Kwa-Zulu Natal Province, 23.1% - 63.5% of maternal deaths occurred at home[13]. Considering that death due to PPH takes place very rapidly once bleeding starts it is very likely that PPH contributes a sizeable proportion of the deaths taking place outside the health institutions. In addition, although as many as 91% of livebirths in South Africa are attended by a skilled birth attendant, there are strong urban/non-urban differences in the type of birth attendant. According to the South African Demographic and Health Survey (SADHS) of 2003, the proportion of births assisted by a doctor was higher (34%) in urban areas compared to non-urban areas (13%)[14,15].

Women living with HIV/AIDS may be more susceptible to direct obstetric causes of maternal mortality such as PPH [9]. This could be due to an increased incidence of PPH in HIV positive women due to the effect of the disease itself or its treatment.

On the other hand, AIDS related anaemia may be an important factor, with these women presenting in labour with lower levels of haemoglobin and therefore not tolerating what would have otherwise been acceptable blood loss at delivery.

HIV infection is also associated with impairment of other haematological indices such as platelets thereby predisposing the women to bleeding post partum. Thrombocytopenia may be a result of decreased platelet production or increased destruction [16].

With increasing access to Prevention of Mother to Child Transmission of HIV (PMTCT) programmes as well as Highly Active Anti-Retroviral Therapy (HAART), the impact of the drug side effects of Zidovudine (AZT) and other anti-retroviral drugs on PPH has not been documented. AZT is known to cause pancytopenia with anaemia, thrombocytopenia and leukopenia the most observed [17]. To date, no studies have been reported to evaluate the effect of HIV and its treatment in pregnancy on the incidence and severity of post partum haemorrhage.

Chapter 2

Literature review

2.1 Definition and Classification of PPH

According to the 1990 World Health Organisation (WHO) definition, PPH is any blood loss from the genital tract more than 500ml during delivery. Caesarean deliveries are associated with an average estimated blood loss of 1000ml[18,19,20]

There is great difficulty to measure PPH with accuracy. To date, there is no gold standard method to measure PPH. Though unreliable, clinical visual estimation of blood loss during delivery is a widely accepted method.

In addition, defining PPH simply as blood loss greater than 500ml fails to take into account predisposing health factors that are reflected in such a definition. The quantity of blood loss is often less important than the actual effect that it has on the labouring woman. As such it has been suggested that the definition of PPH takes into account any blood loss that causes a major physiological change such as low blood pressure which threatens the woman's life[18]

PPH is also classified by different methods. The objective of classifying PPH is three fold. Firstly, it helps to determine the urgency of intervention based on the rate of the patient's deterioration due to the rapidity of progression of the bleeding.

Secondly, classification helps in the assessment of the prognosis which may help to determine the intermediate, medium and long term clinical outcome. This also helps in the decision as to whether the patient requires referral to a higher level of care

Thirdly, classification allows for standardisation of the estimated degree of haemorrhage which makes communication easier and more effective between health care personnel.

A classification system that assesses volume loss in conjunction with clinical signs and symptoms should be the ideal in fully functional and well equipped hospitals and obstetric units. A perceived blood loss of 500ml to 1000ml in the absence of clinical signs of cardiovascular instability should be regarded as an alert line prompting basic measures of monitoring and readiness for resuscitation.

A perceived blood loss of more than 1000ml or a smaller loss with clinical signs of shock should prompt a full protocol of measures to resuscitate, monitor and arrest bleeding[18,21].

Table (i) below summarises such a classification system as proposed by Benedetti et al[21].

Table i

Proposed Classification of PPH. Adapted from Benedetti[21]

Haemorrhage class	**Estimated blood loss (ml)**	**Blood volume loss (%)**	**Clinical signs and symptoms**
0 (normal loss)	< 500	< 10	None
A L	E	R	T
1	500 – 1000	15	Minimal (palpitations, dizziness, tachycardia)
A C	T I	O	N
2	1200 – 1500	20 – 25	Decreased urine output, raised pulse rate, raised respiratory rate, postural hypotension, narrow pulse pressure
3	1800 – 2100	30 – 35	Hypotension, tachycardia, cold and clammy, tachypnea
4	> 2400	> 40	Profound shock

2.2 Pathophysiology

The control of bleeding post partum depends on primary mechanical events which are hormonally mediated to produce strong uterine muscular contraction. The powerful and prolonged contractions of the third stage of labour compress the spiral arteries while also helping to separate the placenta and membranes.

Uterine atony accounts for 75% to 90% of primary PPH. This may be a result of a retained placenta or placental fragments which act as a physical impediment to uterine contraction[22,23]. In the third world setting, prolonged obstructed labour remains an important cause of uterine atony. It also contributes significantly to the number of cases of PPH following rupture of the uterus. In the triennium 2005 – 2007 in South Africa, uterine atony following prolonged labour accounted for 17.5% of all PPH deaths. On the other hand, ruptured uterus accounted for 20% of all deaths. Many of these deaths (54%) occurred in women with unscarred uteri[2].

Overdistention of the uterus prior to delivery as the case may be with multiple pregnancy and polyhydramnios also affects the ability of the uterine muscle to contract effectively to arrest bleeding post partum.

Furthermore, conditions such as leiomyomata increase the surface area for potential bleeding with tissue that is non contractile thus increasing blood loss. Antepartum haemorrhage secondary to abruptio placentae on the other hand may also predispose to postpartum haemorrhage due to poor uterine contraction as a result of impairment of the physiological uterine contraction/retraction haemostatic process[22].

About 20% of primary PPH results from traumatic causes including obstetric lacerations, uterine inversion and rupture. Congenital and acquired clotting abnormalities are rare but significant causes of PPH accounting for about 3% of cases[22].

2.3 Prediction of PPH

Severe primary PPH requiring blood transfusion can be predicted in the majority of patients by assessment of antenatal risk factors. In a study by Balki et al, assessment of antenatal risk factors predicted up to 61% of cases of PPH requiring blood transfusion. The remaining 39% of patients developed intra-partum risk factors[23].

Antenatal risk factors for PPH include maternal anaemia, multiple gestation, abnormal placentation, previous caesarean delivery, previous history of PPH due to uterine atony, fetal macrosomia, pregnancy induced hypertension, chorioamnionitis as well as bleeding or coagulation disorders[24,25].

Intrapartum risk factors include prolonged first stage of labour (latent labour longer than 20 hours in nullipara or longer than 14 hours in multipara), cervical dilatation of less than 1.2cm per hour in nullipara or less than 1.5cm in multipara, prolonged second stage of labour (more than 2 hours in nullipara without epidural or more than 3 hours in nullipara with epidural or more than 1 hour in multipara without epidural or more than 2 hours in multipara with epidural) and a prolonged third stage of labour more than 30 minutes.

Labours that are induced or augmented with oxytocin are also associated with increased risk for PPH[24,26,27]

2.4 Role of anaemia in pregnancy

Anaemia is defined as the reduction in circulating haemoglobin mass below the critical level. WHO defines anaemia in pregnancy as a haemoglobin level less than 11.0g/dL. In most developing countries, a lower cut off of 10.0g/dL is used to define anaemia.

Anaemia in pregnancy can be classified as mild, moderate, severe and very severe depending on the level of haemoglobin as shown below[28].

Class of anaemia	**Haemoglobin level (g/dL)**
Mild	9 – 11
Moderate	7 – 9
Severe	4 – 7
Very severe	< 4

Anaemia in pregnancy can be physiological or acquired. Physiological anaemia in pregnancy occurs as a result of a disproportionate increase in plasma volume compares to red blood cell mass resulting in a drop in haemoglobin level.

Iron deficiency anaemia accounts for almost 60% of all cases of acquired anaemia in pregnancy. This is largely due to dietary iron deficiency. Other causes include folic

acid and/or Vitamin B12 deficiency, dimorphic and protein deficiency anaemia which is both due to deficiency of iron and folic acid and/or vitamin B12 and protein deficiency in extreme malnutrition. Anaemia can also be a consequence of haemolysis or haemorrhage[28].

Severe anaemia in pregnancy may predispose to high output cardiac failure, infection and inability to withstand what would otherwise be normal blood loss during delivery. Anaemia delays general physical recovery especially after caesarean section and other operative procedures[29].

In a study by Hoque M et al, the prevalence of anaemia in a rural population of Kwazulu Natal was found to be 30% according to the national definition of 10.0g/dL. This was as high as 57% by WHO criteria[30].

Worldwide rates of anaemia in pregnancy range from 30% to 70%[31]. In 2000, between 9 and 12% of pregnant women in South Africa were found to have iron deficiency anaemia[32].

Anaemia in pregnancy is a well known risk factor for many maternal and fetal/neonatal complications. Maternal complications include poor weight gain, preterm labour, pregnancy induced hypertension, placenta previa, eclampsia and preterm pre-labour rupture of membranes.

Intrapartum, anaemia can result in dysfunctional labour, antepartum haemorrhage, shock, cardiac failure as well as anaesthethic risks[31]. Post partum, anaemia may predispose to PPH, sepsis, uterine sub-involution and embolism.

Fetal/neonatal complications include prematurity, poor Apgar scores, fetal distress requiring neonatal resuscitation, neonatal anaemia due to poor reserve and low birth weight. Anaemia in pregnancy is also associated with adverse behavioural and cognitive development of children. Low birth weight is one of the main risk factors for infant mortality[33,34].

The effects of anaemia in pregnancy may be extended into adult life of the affected fetus. Children exposed to anaemia in the first trimester of pregnancy have higher rates of cardiovascular morbidities and mortality than those of non anaemia in pregnancy children.

Death from anaemia is a result of heart failure, shock or infection since the patient develops an impaired immune status. Less severe anaemia contributes to morbidity and mortality from PPH due to the fact that anaemic women do not tolerate blood loss as well as healthy women and are therefore more likely to die from haemorrhage.

About 20% of the maternal deaths in sub-Saharan Africa are associated with anaemia in pregnancy[35,36]. Infection with the Human Immunodeficiency Virus (HIV) is also a known risk factor for anaemia. This may be a result of enhancement of nutritional deficiencies, opportunistic infections as well as the use of antiretroviral drugs for

patients with AIDS. HIV infection increases the chance of developing anaemia in pregnancy twofold[37,38,39].

2.5 Complications of PPH

Massive obstetric haemorrhage especially PPH is responsible for up to 25% of maternal deaths worldwide[1]. In developing countries, PPH may be responsible for as many as 28% of maternal deaths.

The risk of maternal death increases with advancing maternal age particularly for those women aged 35 years and above. Massive haemorrhage with coagulopathy also significantly increases the risk of dying.

Other direct maternal consequences of major blood loss include hypovolaemic shock characterised by persistent severe hypotension defined as a systolic blood pressure <90mmHg with a pulse rate of at least 120 beats per minute[40], disseminated intravascular coagulation and hepatic failure presenting with coagulopathy with elevated international normalized ratio (INR) and prolonged activated partial thromboplastin time (aPTT) and deranged liver function, acute renal failure manifest as oliguria/anuria and elevated blood urea and creatinine[41], Sheehan's syndrome and adult respiratory distress syndrome[42].

Severe PPH with haemorrhagic shock has been found to be associated with myocardial ischemia. In a study by Karpati et al, 51% of 55 women admitted for severe PPH had elevated serum levels of cardiac troponin I which were also associated with electrocardiographic changes consistent with ischaemia and reduced

myocardial contractility. The magnitude of these changes also correlated with severity of haemorrhagic shock[43].

2.6 Complications arising from the management of PPH

The administration of large amounts of intravenous fluids and blood products to correct hypovolaemia predisposes patients with PPH to fluid overload and left ventricular failure. Such complications may be severe enough to warrant admission to intensive care unit with intubation and ventilation as well as invasive haemodynamic monitoring.

Surgical procedures to stop bleeding are also associated with certain complications. Evacuation of the uterus to remove retained products of conception may be complicated by perforation of the uterus. Over curettage may also give rise to Asherman's syndrome.

Brace procedures such as the B-Lynch and modified B-Lynch sutures placed to compress an atonic uterus may result in direct trauma to the bladder, ureters, and bowel.

Despite overall good reports of success following stepwise uterine devascularization and arterial embolization, isolated cases of maternal death have been reported following such procedures. In a series of 49 cases of bilateral hypogastric artery ligation, Ledee et al reported success rates of up to 90%. Failure of the procedure was higher in women transfused more than 8 units of blood and those who developed

coagulopathy. Three cases of maternal death were also reported following the procedure[44,45].

On the other hand, complications of selective arterial embolization include post procedure fever, feet ischaemia, bladder and rectal wall necrosis and sciatic nerve injury. Late re-bleeding is also a rare but serious complication[44].

Pelage et al, in an evaluation of 35 patients who underwent selective arterial embolization reported one case of re-bleeding occurring 5 days after the procedure that was severe enough to necessitate a hysterectomy[44,46].

Hysterectomy is a life saving procedure when all other measures to control bleeding have failed. A subtotal hysterectomy is often sufficient if bleeding originates from the upper segment of the uterus. It is associated with less need for blood transfusion and reduced intra-operative and post-operative complications[44,47]. However, a total abdominal hysterectomy is indicated if bleeding is from the lower uterine segment or the uterine cervix. Complications that may arise from a hysterectomy include urological injuries to the bladder and ureters and injury to bowel[48,49,50].

Surgery for PPH may be complicated by sepsis. The risk of sepsis is compounded by the patient's HIV status as well as the stage of disease. Common sites of infection are the wound site, respiratory tract and the urinary tract. These patients may also be predisposed to nosocomial infections due to their often prolonged stay in hospital.

According to the Saving Mothers report of 2005 – 2007, the biggest cause of maternal mortality was non pregnancy related infections of which AIDS was the predominant infection responsible for 22.4% of all deaths during the triennium[2].

2.7 HIV and haematology

Advanced HIV disease with profoundly low CD4 count is associated with the development of thrombotic microangiopathy. These patients may present with haemolytic anaemia and thrombocytopenia.

Patients with HIV associated thrombotic microangiopathy are also thought to have a smouldering disseminated intravascular coagulation and may benefit from plasma infusion to replace missing or decreased antithrombin III[51].

Thrombocytopenia is thought to be secondary to HIV infection of megakaryocytes and/or deposition of antigen-antibody complexes on platelets leading to their rapid clearance[52].

CD4, which is the receptor for HIV on T cells has also been demonstrated on megakaryocytes thus indicating that those cells can also be infected with HIV[52,53]. Endothelial cells are also infected with HIV leading to endothelial injury. As such, these patients may be predisposed to haemorrhage[52,54,55,56].

The normal range of platelet count is 150,000/mm^3 to 300,000/mm^3. A count of less

than 100,000/mm^3 is considered to constitute thrombocytopenia. Spontaneous bleeding usually does not occur until the count falls below 20,000/mm^3. Counts between 20,000/mm^3 and 50,000/mm^3 are associated with post traumatic bleeding. Platelet counts of less than 50,000/mm^3 are associated with an increased risk of bleeding following operative procedures such as caesarean section[53,57].

Typically, bleeding associated with thrombocytopenia is associated with prolonged bleeding time with normal prothrombin and partial thromboplastin time[53].

2.8 The coagulation cascade

Platelets have a central role in normal haemostasis. On contact with extracellular matrix following vascular injury, platelets undergo three general reactions of adhesion and shape change, secretion and aggregation.

The adhesion of platelets to the extracellular matrix is largely mediated via interaction with von Willebrand's factor (vWF). vWF acts as a bridge between platelet surface receptors and exposed collagen[58].

Such interaction stabilizes the initial platelet adhesion against the high shear forces of flowing blood. The process by which platelets facilitate clot formation are summarised in the steps below[59].

1. Platelets adhere to extracellular matrix at sites of endothelial injury and become activated.
2. On activation, platelets secrete granule products such as adenosine diphosphate (ADP) and synthesize thromboxane (TXA2).

3. Platelets also expose phospholipids complexes important in the intrinsic coagulation pathway.
4. Injured or activated endothelial cells expose tissue factor which triggers the extrinsic coagulation cascade.
5. Released ADP stimulates formation of a primary haemostatic plug which is eventually converted (via ADP, thrombin and TXA2), into a large definitive secondary plug.
6. Fibrin deposition stabilizes and anchors the aggregated platelets.

2.9 Association between HAART and bleeding

It is well known that the mainstay for treatment of patients infected with HIV is the use of HAART. However, treatment with these drugs is not without side effects.

HIV protease inhibitors have been found to cause spontaneous bleeding in patients with haemophilia. In a study comparing the protease inhibitors ritonavir, indinavir and saquinavir with zidovudine among HIV positive haemiphiliacs, more episodes of bleeding were reported in patients on protease inhibitors (58%) compared to zidovudine (3.2%).

This effect was also found in non haemophiliacs. Of the 6035 reports for indinavir, saquinavir and ritonavir to the FDA's spontaneous adverse event reporting system by 28 February 1997, 161(2.7%) were for bleeding. Similarly, 2.6% (71 of 2718) of reports for zidovudine were for bleeding. These reports were for both haemophiliacs and non haemophiliacs.

It is important to note that in all the cases described, there was no report on uterine bleeding. Common sites of bleeding for haemophiliacs included skin/soft tissue and joints. On the other hand, for persons without haemophilia, bleeding predominantly occurred in the gastrointestinal tract and mucus membranes. There was also a substantial frequency of intracranial bleeding in both groups of patients[60].

2.10 Prevention of mother to child transmission of HIV (PMTCT)

The consecutive Saving Mothers reports for triennia 1999 – 2001, 2002 – 2004 and 2005 – 2007 all show non pregnancy related infections to be the leading cause of institutional maternal death in South Africa. The biggest majority of these infections (23.1% in 2005 – 2007) are from AIDS[2,3,61]. The importance of the PMTCT program in South Africa can therefore not be overemphasized. Initially this program was primarily aimed at reducing the rates of HIV transmission from the mother to her unborn child. However with time the program has evolved to incorporate comprehensive care for those women with CD4 counts of less than 350cells/mm^3 who benefit from expedited initiation of lifelong treatment with highly active antiretroviral drugs. Such an approach is expected in the long term to help reduce the burden of disease as well as maternal and child mortality while also improving life expectancy[62].

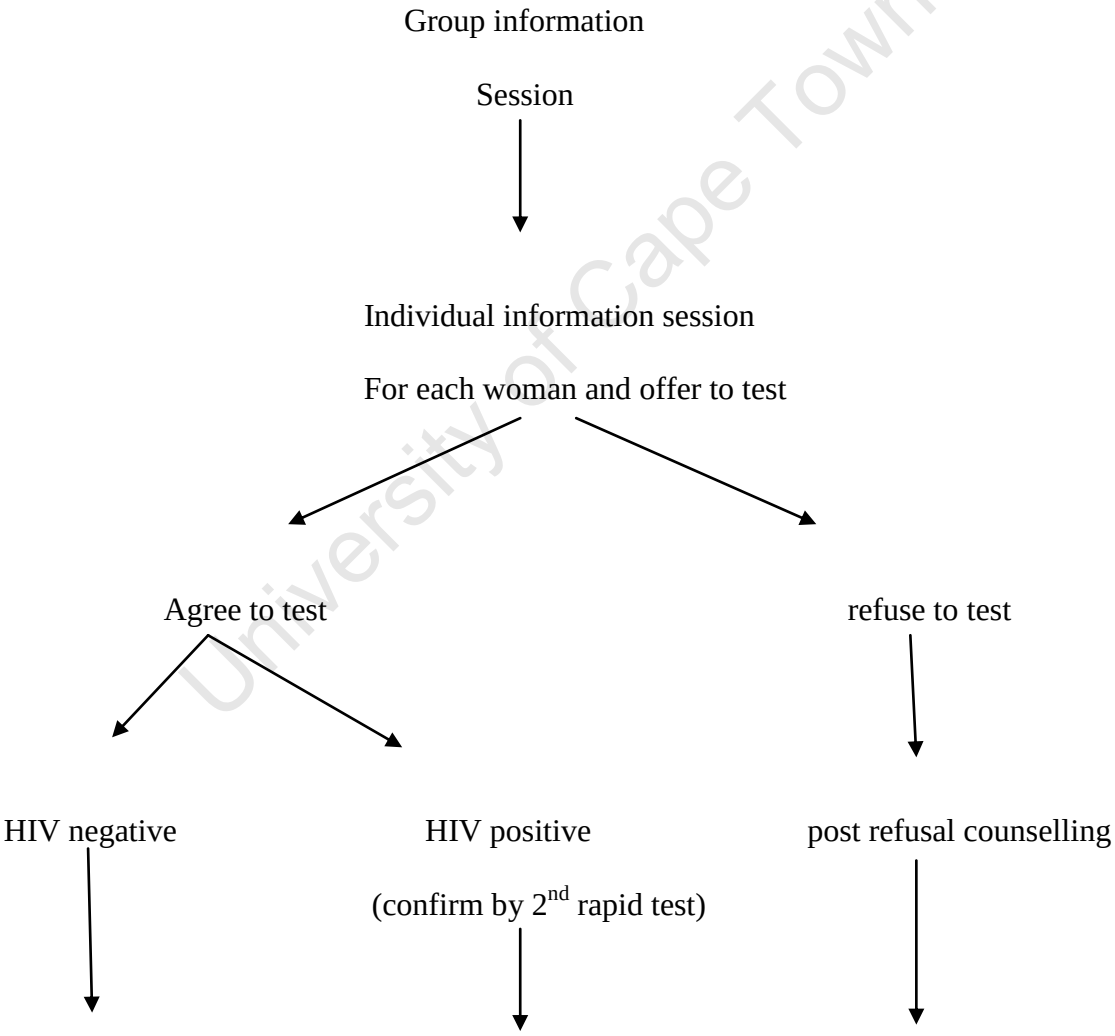
The PMTCT program is a comprehensive program that works on four important elements namely:

- Primary prevention of HIV especially among women of childbearing age
- Preventing unintended pregnancies among women living with HIV
- Preventing HIV transmission from a woman living with HIV to her infant and

- Providing appropriate treatment, care and support to women living with HIV and their children and families.

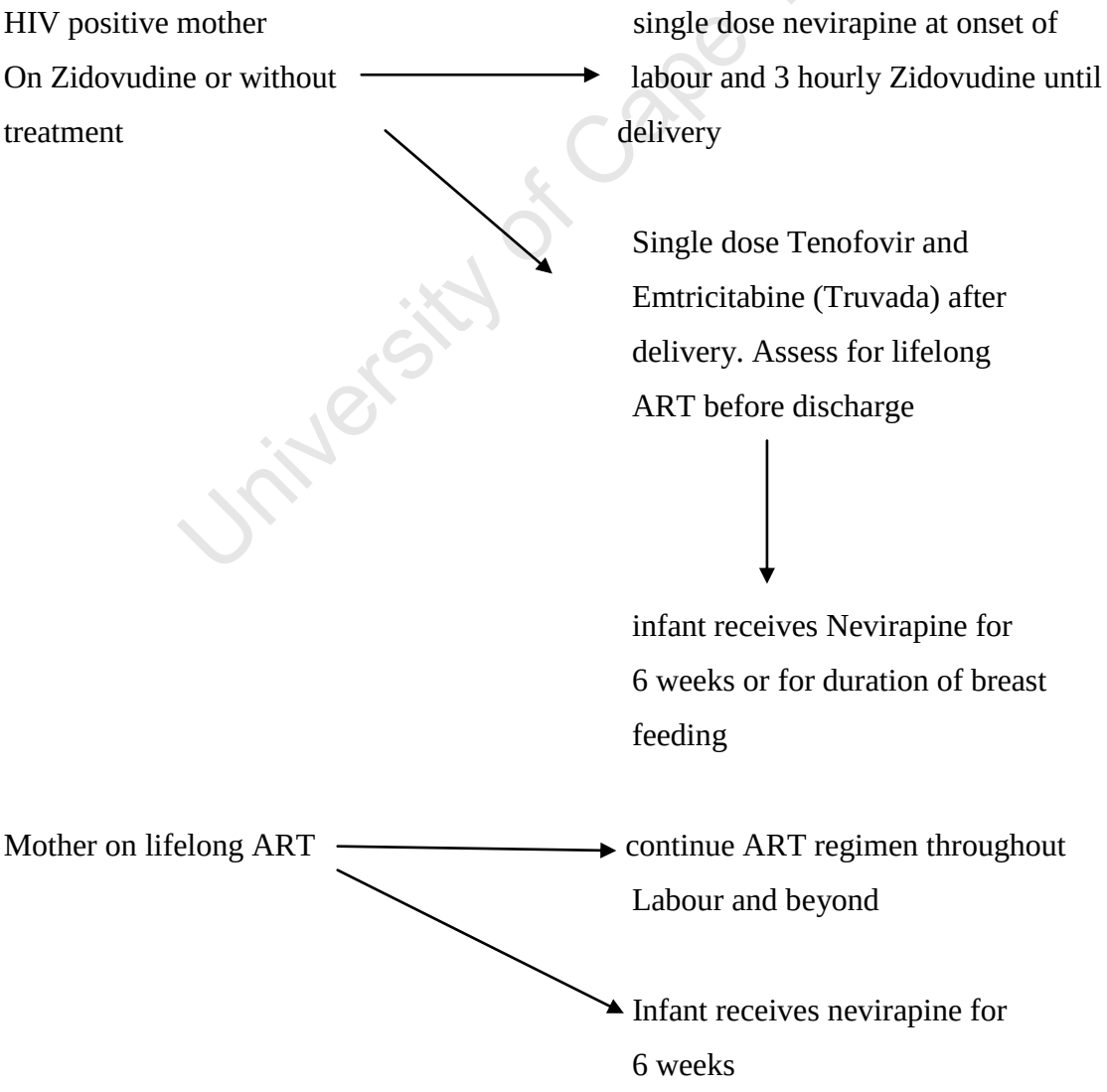
To attain these goals, the National Department of Health of South Africa produced revised (2010) guidelines for the prevention of mother to child transmission of HIV. In these guidelines, all women presenting for antenatal clinic are offered HIV counselling and testing[62]. This protocol was fully implemented in the Western Cape in October 2010.

Below is an algorithm showing this provider initiated counselling and testing (PICT).



HIV positive women with CD4 count > 350 are started on Zidovudine at 14 weeks gestation. Those with a count of 350 and below or those with clinical HIV disease stage 3 or 4 are started on lifelong antiretroviral therapy (ART) within 2 weeks of diagnosis. Patients with an initial negative test result are offered a repeat test at 32 weeks to identify those that develop seroconversion during their pregnancy and offer them appropriate treatment.

During labour and delivery, women on Zidovudine receive 3 hourly Zidovudine until delivery and single dose Nevirapine at the onset of labour as depicted in the algorithm below.



Identification of HIV positive women through the PMTCT program therefore facilitates identification of women at risk of morbidity and mortality from PPH and other HIV associated causes of maternal morbidity and mortality.

Prior to the 2010 revision of the PMTCT guidelines, HIV positive antenatal women were started on Zidovudine 300mg 12 hourly at 28 weeks gestation. They received single dose Nevirapine at the onset of labour and 300mg Zidovudine 3 hourly while in labour. Women with CD4 count less than 200/mm^3 or Stage IV disease were recommended for immediate commencement of highly active antiretroviral therapy. This was in accordance with the February 2008 national PMTCT policy[63].

2.11 Haematological antiretroviral side effects

According to the 2010 PMTCT guidelines formulated by the National Department of Health of South Africa, the most commonly used antiretroviral drugs for those women with CD4 count more than 350 cells/mm^3 are Zidovudine and Nevirapine .

For women requiring lifelong ART, the first line regime comprises a combination of Tenofovir, Lamivudine/Emtracitabine and Nevirapine. Zidovudine is used in place of Tenofovir if the latter is contraindicated as the case may be in patient with renal disease. Patients on lifelong ART comprising Efavirenz prior to pregnancy are switched to Nevirapine in the first trimester. If however such patients present after the first trimester, treatment with Efavirenz is continued[62].

Below are some of the reported haematological side effects of these commonly used antiretroviral drugs[16].

a. Nevirapine: anaemia, granulocytopenia, neutropenia, thrombocytopenia and

eosinophilia

b. Tenofovir: decreased neutrophils in up to 3% of cases
c. Efavirenz: neutropenia (less than 750/mm^3) in up to 10% of cases. It also rarely causes haemolytic anaemia.
d. Truvada: neutropenia in up to 3% of cases
e. Lamivudine: bone marrow toxicity in doses up to 20mg/kg/day. Neutropenia (7.2%), anaemia (2.9%) and thrombocytopenia (0.4%) has been reported when it is used with zidovudine.
f. Zidovudine: Anaemia (Hb<8g/dL) in 1% of patients and granulocytopenia (<750cells/mm^3) in 2% of patients.

2.12 PPH and blood transfusion

Transfusion of blood components plays a central role in the management of life threatening haemorrhage. It is a life saving procedure and an important criteria of quality of care for pregnant women[64].

In a study by Balki et al, the rate of blood transfusion for PPH was 0.31%. 0.49% of women undergoing a caesarean section during labour had PPH requiring blood transfusion while those women undergoing a normal vaginal delivery had a transfusion rate of 0.28%. The rate of blood transfusion for PPH following elective caesarean section was 0.23%[24].

A larger study of 57,000 deliveries by Rouse et al showed a 3.2% transfusion rate for women undergoing primary caesarean section and 2.2% for those undergoing repeat caesarean section. This study identified maternal anaemia with a haematocrit of less

than 25%, placenta previa and general anaesthesia as significant risk factors for PPH requiring blood transfusion[65].

Transfusion of blood products is not without risk. Such risks include transmission of infectious diseases such as HIV and hepatitis B and C, transfusion reactions and alloimmunisation. It is also associated with significant cost to both the patient and the health care system.

In the USA, the risk of HIV transmission per unit of blood transfused is 1 in 450,000 to 1 in 660,000. This risk may be higher in the South African setting due to the high prevalence of HIV I the population as well as the higher demand for blood transfusion[66].

Over the years, rates of blood transfusion have decreased due to improved prevention, surveillance and treatment of PPH. This is shown in the studies by Klapholz and Sherman where transfusion rates decreased from 4.6% in 1976 to 1.9% in 1986 and 0.9% in 1990[67,68].

Recognizing the magnitude of the problem of PPH in South Africa, the national committee for the confidential enquiries into maternal deaths (NCCEMD) developed a handbook of PPH management to help health care workers at all levels of care to recognize and rapidly institute measures to deal with life threatening haemorrhage[69]. The overview of the 4th Saving Mothers report (Chapter 1) indicates that MMR from PPH is not decreasing. This is associated with high level of clinical avoidability of

such deaths (>80%)[2]. However if HIV infection is associated with PPH or PPH mortality then this may also be a factor in why MMR from PPH has not diminished.

2.13 Problem statement and hypothesis

PPH as a cause of maternal death is increasing in South Africa and, according to the Saving Mothers 2005-2007 report on maternal deaths, the maternal mortality ratio due to PPH is higher in HIV positive than HIV negative women. This raises questions as to whether this is a real increase or an artefact due to misclassification of causes of death. If it is a real effect, is this due to an increase in the incidence of PPH in HIV positive women, or an increase in morbidity from PPH due to co-morbidities such as anaemia associated with HIV, or could it be an effect of ARV medications?

The aetiology of PPH in HIV positive women may be multi-factorial and may differ between patients who are on highly active antiretroviral therapy and those who are treatment naïve. In poorly resourced settings where HIV seroprevalence is high among reproductive age women and maternal mortality from PPH is also common, iron deficiency anaemia and HIV associated anaemia and/or thrombocytopenia may be the most important factors affecting both the incidence and severity of PPH.

On the other hand, although the literature does not indicate any cases of haemorrhage associated with treatment with HAART, evidence from the field of haematology suggests that certain medications such as protease inhibitors predispose to bleeding. This may also apply in pregnancy and childbirth.

It is also important to note that the apparent increased mortality from PPH in HIV

positive women compared to HIV negative women may be as a result of misclassification of the causes of maternal death from less experienced maternal death assessors especially in the rural areas. As such, HIV infection may in fact not be associated with increased mortality from PPH.

It is against this background of the reported increased mortality from PPH among HIV positive women compared to HIV negative women that this study set out to investigate whether HIV seropositivity is associated with an increase in the incidence and severity of PPH to justify the apparent increased mortality.

The hypothesis being tested was that PPH is more common and more severe among HIV positive women compared to HIV negative women.

Chapter 3

Aim of the study

The main aim of the study was to investigate the relationship between HIV infection and the incidence and severity of postpartum haemorrhage in women delivering at Mowbray Maternity and Groote Schuur Hospitals in 2009.

Specific objectives

1. To establish the incidence of PPH in HIV positive women compared to HIV negative women.
2. To describe the causes of PPH in HIV positive women compared to HIV negative women.
3. To determine the severity of and morbidity associated with PPH in HIV positive women compared to HIV negative women.
4. To compare the severity of PPH and morbidity from PPH with respect to age, parity, BMI, mode of delivery, HIV seropositive status and mean haemoglobin level on admission for delivery.
5. To describe the characteristics of HIV positive women with PPH with respect to CD4 count at booking, the nature of Antiretroviral Therapy and the duration of treatment.

Chapter 4

Methods

4.1 Study Design

The study design was a retrospective cross-sectional analytic study of all cases of postpartum haemorrhage occurring at Mowbray Maternity and Groote Schuur Hospitals from 1 January 2009 to 31 December 2009.

4.2 Inclusion Criteria

Women who experienced blood loss more than 500ml following delivery of a fetus weighing more than 500 grams or gestational of 24 weeks or more were identified for the study. The recorded blood loss was based on clinical estimation by the attending health care provider at the time of delivery. Only patients who delivered at Mowbray Maternity and Groote Schuur Hospitals during the study period were included in the study.

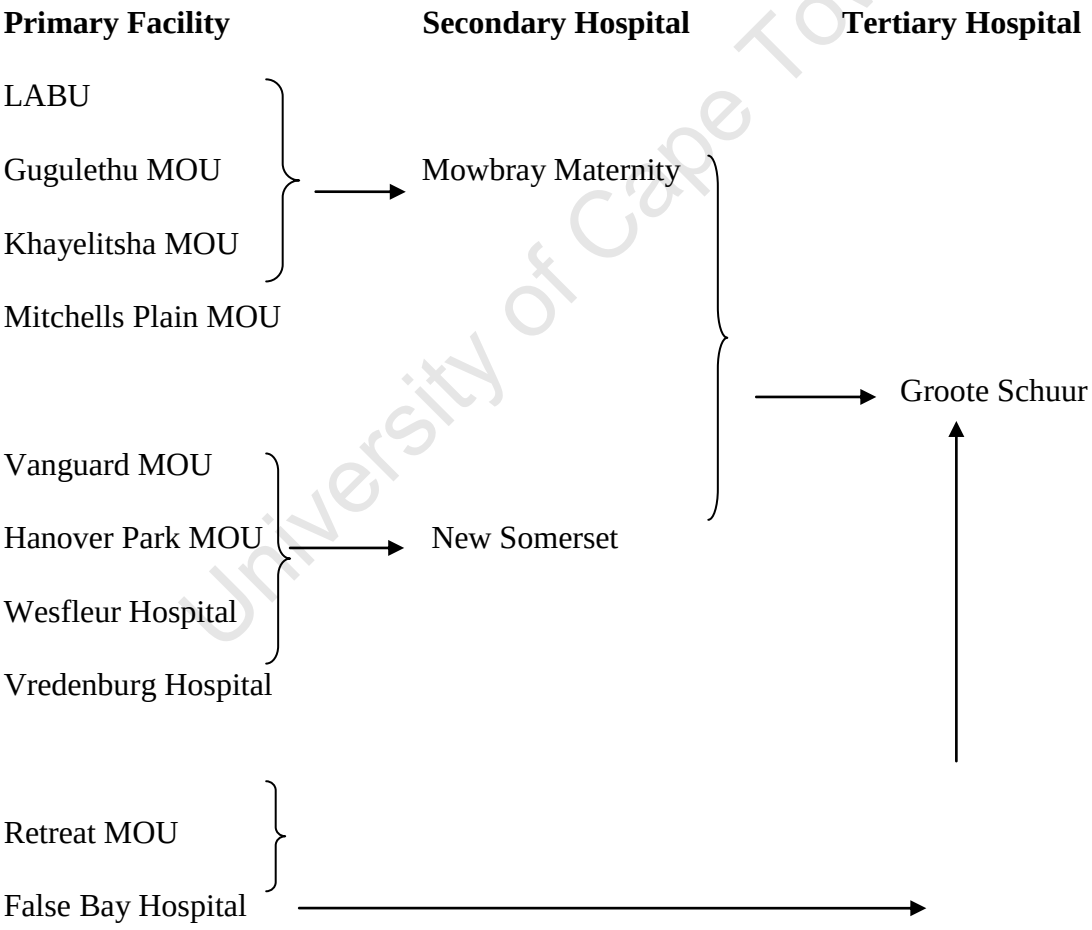
The choice of 500ml of blood loss as the cut-off for the definition of PPH was based on three factors. Firstly, the use of visual estimation to quantify blood loss may result in significant underestimation of blood loss. As such an estimated blood loss of 500ml may be accompanied by significant physiological effects with hypotension and tachycardia.

Secondly, in a population where the prevalence of anaemia is high such as is the case in South Africa, blood loss of 500ml or more may result in significant adverse outcomes in the patient.

Thirdly, although critical of the low threshold of 500ml for PPH, the cited literature used the same cut-off as proposed by the World Health Organization in 1990 to define PPH[1,17,22]. In order to maintain uniformity with available literature, blood loss of 500ml or more at the time of delivery was therefore used to define PPH in this study.

4.3 Study Population

The Metro West maternity service comprises one tertiary hospital, two secondary hospitals and ten primary care obstetric units. The flow chart below outlines the obstetric care units and their route of referral.



Referral criteria for the different levels of care are clearly outlined and are accessible to all health care workers in the different facilities. Emergency referrals are triaged by registrars who are in training to become obstetricians and gynaecologists, to the

appropriate level of care as well as type of ambulance transfer depending on severity and urgency of the reason for referral. Three categories of ambulance transfer are in place namely ordinary ambulance, urgent ambulance and flying squad. Primary level midwife obstetric units refer all women with post-partum haemorrhage to their referral hospital by flying squad.

The study was conducted on deliveries at Mowbray Maternity and Groote Schuur Hospitals, thus including women who had been referred antepartum or intrapartum to the two hospitals from satellite MOUs. It was originally intended by the investigators to conduct the study on all deliveries in all the health facilities of the Metro West area for the year 2009. However due to time constraints to meet deadlines for submission of the completed work, this was not achievable. The selection of the two hospitals as study sites was based on convenience and in recognition that the majority (89%) of cases of PPH in the Metro West occur at the hospitals rather than the MOUs due to the prompt system of referrals from the MOUs of women at risk for PPH (eg with prolonged labour, suspected abruption placentae etc)[70].

4.4 Patient Identification

The names and folder numbers of patients who delivered at the two hospitals and had PPH were retrospectively identified by a physical review of the labour ward and theatre registers at Mowbray Maternity Hospital and at Groote Schuur Hospital.

Once a case of PPH was identified, the patient's hospital folder was retrieved from the records department in the health facility for a review of the patient's booking information including age, parity, HIV status, CD4 count, and past obstetric history.

Information about labour and delivery including duration, mode of delivery, amount of bleeding and interventions instituted among other things were also recorded on a Microsoft Excel formulated data collection sheet (Appendix 1).

Severity of bleeding was classified according to a modification of the proposed classification described in Table (i) as follows:

Severity	**Amount of blood loss (ml)**
Mild	500 – < 1200
Moderate	1200 – < 1800
Severe	1800 – < 2400
Very severe	2400 or more

Such modification was necessary in order to set clear cut offs for each of the severity classes. In addition, the need for blood transfusion, hysterectomy and mechanical ventilation were used as markers of severe morbidity. A morbidity score was assigned following internationally accepted guidelines depending on the presence of certain clinical findings and interventions instituted [40,71].

Severe lowest recorded haemoglobin of 6g/dL or less, transfusion of 5 or more units of packed cells or whole blood, transfusion of any other blood products such as fresh frozen plasma, platelets and cryoprecipitate, hypovolaemic shock, admission to ICU, need for mechanical ventilation, any organ failure or need for an emergency hysterectomy.

Mild to moderate lowest recorded haemoglobin of >6 g/dL to 10g/dL,

transfusion of up to 4units packed cells or whole blood, placement of B- Lynch suture and placement of an intrauterine catheter for balloon tamponade

No morbidity when none of the above occurred.

4.5 Data Collection

Data was entered on a standard data collection sheet specifically designed for the study (Appendix 1). Delivery records from the cradle software were accessed for purposes of quantifying the total number of deliveries that took place during the study period in the two hospitals.

HIV registers were also reviewed in the two health facilities involved to quantify the proportion of delivered women who were HIV positive, negative, untested and those who declined testing.

4.6 Data analysis

Descriptive data were analysed by using Microsoft Excel Statistical package. This package was used to calculate frequencies and proportions, means and median parity.

Stata software package version 10.1 was used for significance testing of the observed differences in the different variables between HIV positive and HIV negative women. Odds ratios were calculated using this statistical package with a 95% confidence interval (CI) and a p value of 0.05 for statistical significance using the 2 sided Fisher's exact test.

The t-test mean comparison test was used to test for statistical significance of the difference between means.

The power for this cross-sectional study was calculated using the OpenEpi, version 2 open source calculator based on normal approximation. A two-sided confidence interval of 95% was used. The exposed group comprised HIV positive women while the non-exposed group comprised HIV negative women and the occurrence of PPH as the outcome of interest.

4.7 Sample size

The study planned to include all deliveries complicated by PPH occurring at Mowbray Maternity and Groote Schuur Hospitals during one calendar year from 1st January 2009 to 31st December 2009. A sample size calculation was performed to ascertain whether data for this duration would be sufficient to determine a statistically significant difference in the incidence of PPH between HIV positive and HIV negative women delivering at the two hospitals.

The sample size calculation was based on the observation that the maternal mortality ratio from PPH in South Africa during the triennium 2005 – 2007 in HIV positive women was almost three times as high as that of HIV negative women (13.7 vs 5.7 per 100,000 live births)[2]. In addition the PPH rate at MMH and GSH in previous years was 10% for all deliveries (HIV positive and HIV negative women combined). An assumption was made for the current study that the proportion of HIV positive women with PPH delivering at the two hospitals would be 15% of all the deliveries and that of HIV negative women with PPH would be 5% .

In order for the study to have a power of at least 80% to determine a statistically significant difference (95% confidence) in the incidence of PPH between HIV positive and HIV negative women, a minimum sample size of 432 women with PPH was required. 72 of these needed to be HIV positive and 360 women needed to be HIV negative.

4.8 Ethics

Before proceeding with the study, ethics approval was obtained from the University of Cape Town ethics committee. Permission was also obtained from the Medical Superintendents at the institutions involved.

Chapter 5

Results

Mowbray Maternity Hospital and Groote Schuur Hospital registered a total of 15384 deliveries in 2009. 2738 (17.8%) of these deliveries were HIV positive, 12151 (79.0%) HIV negative and 495 (3.2%) HIV untested. The untested group included women who declined testing and those who were unbooked at the time of delivery and therefore untested.

A total of 1230 (8.0%) women had recorded blood loss of 500ml or more at the time of delivery. 270 of these women (22%) were HIV positive, 915 (74.4%) were HIV negative and 45 (3.6%) were HIV untested.

5.1 The rate of PPH in HIV positive compared to HIV negative women

Out of the 2738 HIV positive deliveries at the two hospitals in 2009, 270 (9.9%) had PPH. On the other hand, 915 of the 12151 HIV negative deliveries (7.5%) had PPH. The difference in the mean blood loss between HIV positive and HIV negative women was not statistically significant (Table 1).

Table 1

PPH rate and mean blood loss in HIV positive and HIV negative women.

PPH rate in HIV positive compared to HIV negative women	**HIV positive (n=2738)**	**HIV negative (n=12151)**	**Untested (n=495)**	***OR (95% CI)**	***P value**
PPH rate	270 (9.9%)	915 (7.5%)	45 (9.1%)	1.34 (1.16 – 1.55)	0.001
Mean blood loss (ml)	736	725	858		0.697

*Odds Ratios and P values comparing HIV positive with HIV negative group

These findings give this cross-sectional analytic study the power of 98.74% based on normal approximation using the OpenEpi, version 2, open source calculator.

5.2 Demographic, pregnancy and labour details of HIV positive women with PPH compared to HIV negative women with PPH (Table 2)

The mean age in the three groups of women was 28 years and the median parity was 1. Of the 906 women whose body mass index (BMI) was measured at the time of antenatal care booking, 51% had BMI of more than 30kg/m². Amongst the HIV positive women with PPH, there was a significantly lower proportion of women aged 35 years or more; and BMI greater than 36kg/m^2 when compared to HIV negative women with PPH.

Table 2

Background characteristics of women with PPH

	HIV positive (n=270)	**HIV negative (n=915)**	**Untested (n=45)**	**Total (n=1230)**	***OR (95% CI)**	***P-value**
Age (mean)	27.79	27.64	27.84	27.68	-	0.738
Up to 18	11 (4.1%)	65 (7.1%)	2(4.4%)	1004	0.555 (0.26 – 1.08)	0.089
19 to 35	245(90.7%)	719 (78.6%)	40(88.9%)	148	2.670 (1.71 – 4.33)	<0.0001
More than 35	14 (5.2%)	131(14.3%)	3(6.7%)		0.327 (0.17 – 0.58)	<0.0001
Parity (median)	1.12	1.19	1.00		-	0.398
BMI						
up to 30	111(41.0%)	324(35.4%)	12(26.7%)	447	1.273 (0.95 – 1.69)	0.098
31 to 35	62(23.0%)	160(17.5%)	4(8.9%)	226	1.406 (0.99 – 1.98)	0.051
36+	35 (13.0%)	189 (20.7%)	9 (20.0%)	233	0.572 (0.38 – 0.85)	0.005
unknown	62(23.0%)	242 (26.4%)	20(44.4%)	324	0.828 (0.59 – 1.15)	0.267
Previous caesarean delivery						
X1	75(27.8%)	206 (22.5%)	9 (20.0%)	290	1.323 (0.86 – 1.81)	0.087
X2+	9 (3.3%)	36 (3.9%)	2 (4.4%)	47	0.841 (0.35 – 1.81)	0.721
None	186 (68.9%)	673 (73.6%)	34 (75.6%)	893	0.796 (0.59 – 1.09)	0.141
GA at delivery						
a. < 34 weeks	32 (11.9%)	119 (13.0%)	13 (28.9%)	164	0.899 (0.57 – 1.38)	0.678
b. 34 or more	238 (88.1%)	796 (87.0%)	32(71.1%)	1066		
Mean Hb on admission to labour/prior to caesarean section	10.7	10.8	10.3			0.627

*Odds Ratios and P values comparing HIV positive with HIV negative Group

There was no difference in the level of haemoglobin at the time of admission for delivery between the HIV positive and HIV negative women who had PPH (Table 2).

Table 3 compares pregnancy and labour complications in HIV positive and negative women with PPH. Hypertension was significantly less common as a pregnancy complication in HIV positive women with PPH compared to HIV negative. Hypertension was defined as any rise in blood pressure of 140/90 mmHg or more on at least two occasions at least six hours apart at any gestation with or without the presence of proteinuria. There was no difference in the incidence of complications such as cephalopelvic disproportion, fetal distress, twin gestation, abruptio placentae and placenta previa in HIV positive women with PPH compared to HIV negative women with PPH.

Table 3

The incidence of other pregnancy/labour complications in HIV positive women with PPH compared to HIV negative women with PPH

	HIV positive (n=270)	**HIV negative (n=915)**	**Untested (n=45)**	***OR (95% CI)**	***P value**
Hypertension	24 (8.9%)	149 (16.3%)	8 (17.8%)	0.50 (0.30 – 0.80)	0.002
Cephalopelvic disproportion	25 (9.3%)	90 (9.8%)	4 (8.9%)	0.56 (0.56 – 1.51)	0.91
Twins	18 (6.7%)	57 (6.2%)	1 (2.2%)	1.08 (.58 – 1.89)	0.77
Fetal distress	43 (17.9%)	169 (18.5%)	4 (8.9%)	0.84 (0.57 – 1.22)	0.37
Abruptio placentae	19 (7.0%)	73(8.0%)	8 (17.7%)	0.87 (0.49 – 1.50)	0.69
Placenta praevia	2 (0.74%)	3 (0.33%)	2 (4.4%)	2.27 (0.19 – 19.89)	0.32

*Odds Ratios and P values comparing HIV positive with HIV negative group

Table 4 shows the mode of delivery by HIV status of all the women who had a PPH. Seven hundred and thirty-three (60%) of the women with postpartum haemorrhage were delivered by emergency caesarean section. 276 (22.4%) had elective caesarean section while 198 (16.1%) had normal vaginal delivery. 12 women had assisted

vaginal delivery with vacuum extraction, 4 women had forceps delivery and 6 had vaginal breech delivery. One patient had a laparotomy for an advanced extrauterine pregnancy.

Table 4

Comparison of mode of delivery between HIV positive and HIV negative women with PPH

	HIV positive with PPH (n=270)	**HIV negative with PPH (n=915)**	**Untested with PPH (n=45)**	***OR (95% CI)**	***P value**
Elective c/s	61 (22.6%)	206 (22.5%)	9 (20.0%)	1.004 (0.71 – 1.40)	1.00
Emergency c/s	158 (58.5%)	551(60.2%)	24 (53.3%)	0.93 (0.70 – 1.24)	0.62
NVD	49 (18.1%)	139 (15.2%)	10 (22.2%)	1.24 (0.85 – 1.79)	0.255
Breech	0 (0.0%)	5 (0.55%)	1 (2.2%)	-	-
Forceps	1 (0.37%)	3 (0.33%)	0 (0.0%)	1.13 (0.21 – 14.14)	**
Vacuum	1 (0.37%)	10 (1.1%)	1 (2.2%)	0.34 (0.01 – 2.39)	**
Laparotomy	0 (0.0%)	1 (0.11%)	0 (0.0%)	-	-

*Odds Ratios and P values comparing HIV positive with HIV negative group

**Numbers were too small for comparison between the HIV positive and HIV negative group

Among the women with PPH who had emergency caesarean sections, the mean blood loss was higher in HIV positive compared to HIV negative women. HIV negative women delivering vaginally, however, had a significantly higher mean blood loss than HIV positive women (Table 5).

Table 5

Mean blood loss by mode of delivery for HIV positive and negative women with PPH

	HIV positive with PPH (millilitres) N=270	**HIV negative With PPH (millilitres) N=915**	**Untested (millilitres) N=45**	***P value**
Elective c/s	670	697	711	0.651
Emergency c/s	762	695	800	0.067
NVD	744	878	1135	0.049
Vacuum	500	810	500	**
Forceps	500	900	-	**
Breech	-	690	1200	-

*P value comparing HIV positive with HIV negative group

** numbers were too small for comparison between the HIV positive and HIV negative group

5.3 Causes of PPH in HIV positive women compared to HIV negative women

Uterine trauma at caesarean section was the most common cause of postpartum haemorrhage in all the three groups of women. This was bleeding from the uterine incision or its extension whether intended or accidental which required extra suturing other than the standard two layer closure. Such trauma included tears extending from the incision area and bleeding points along the incision after a two layer closure

among others. Other causes of post-partum haemorrhage included uterine atony, abruptio placentae, retained placenta, retained products of conception and ruptured uterus (Table 6). Not uncommonly, more than one cause of PPH was ascribed to a case of PPH. As such, the numbers add up to more than the total for the column (n).

Table 6

Causes of PPH in HIV positive compared to HIV negative women

	HIV positive (n=270)	**HIV negative (n=915)**	**Untested (n=45)**	***OR (95% CI)**	***P value**
Atony	81 (30.0%)	268 (29.3%)	13 (28.9%)	1.03 (0.76 – 1.40)	0.820
**Uterine trauma	201 (91.8%)	667 (88.1%)	29 (87.9%)	1.50 (0.87 – 2.72)	0.143
***Retained placenta	4 (7.8%)	26 (16.6%)	0 (0.0%)	0.429 (0.104 – 1.34)	0.169
Retained POC	4 (1.5%)	11 (1.2%)	1 (2.2%)	1.23 (0.28 – 4.22)	0.756
Abruptio placentae	19 (3.3%)	73 (8.0%)	8 (17.8%)	0.87 (0.49 – 1.50)	0.698
Ruptured uterus	1 (0.37%)	9 (0.98%)	1 (2.2%)	0.37 (0.01 – 2.72)	0.471

*Odds Ratios and P values comparing HIV positive with HIV negative group

**Total number of caesarean sections used as denominator

*** Total number of vaginal deliveries used as denominator

5.4 Treatment provided for PPH in HIV positive compared to HIV negative women

Following the diagnosis of PPH, interventions instituted depended on the cause as well as the severity of the bleeding. Such interventions ranged from medical management with uterotonics to surgical procedures for specific causes. Some women also required the administration of blood products. Tables 7 to 9 outline the different interventions that were instituted.

Table 7

Medical interventions for the management of PPH

	HIV positive (n=270)	**HIV negative (n=915)**	**Untested (n=45)**	***OR (95% CI)**	***P value**
No medical intervention	58 (21.5%)	258 (28.2%)	7 (15.6%)	0.69 (0.49 – 0.97)	0.028
Oxytocin only	129 (47.8%)	388 (42.4%)	23 (51.1%)	1.24 (0.94 – 1.65)	0.124
Oxytocin + ergometrin only	5 (1.9%)	9 (0.98%)	1 (2.2%)	1.89 (0.50 – 6.37)	0.331
Oxytocin + misoprosol only	62 (23.0%)	203 (22.2%)	11 (24.4%)	1.04 (0.74 – 1.46)	0.803
Oxytocin+misoprostol+ ergometrin	9 (3.3%)	33 (3.6%)	2 (2.4%)	0.92 (0.38 – 2.00)	1.00
Other + Prostaglandin F2alpha	7 (2.6%)	24 (2.6%)	1 (2.2%)	0.98 (0.36 – 2.40)	1.00

*Odds Ratios and P values comparing HIV positive with HIV negative group

Table 8

Surgical interventions for the management of PPH

	HIV positive (n=270)	**HIV negative (n=915)**	**Untested (n=45)**	***OR (95% CI)**	***P value**
Manual removal of placenta	3 (1.1%)	17 (1.9%)	1 (2.2%)	0.59 (0.11 – 2.08)	0.591
Evacuation of uterus	4 (1.5%)	21 (2.3%)	2 (4.4%)	0.64 (0.16 – 1.92)	0.629
**Suturing	207 (94.5%)	677 (89.4%)	25 (75.8%)	2.04 (1.08 – 4.19)	0.025
***Repair of perineal tear	5 (9.8%)	28 (17.8%)	3 (25%)	0.50 (0.14 – 1.43)	0.194
***Repair of cervical tear	3 (5.9%)	8 (5.1%)	0 (0.0%)	1.16 (0.19 – 5.10)	0.733
**B Lynch suture	12 (5.5%)	36 (4.8%)	0 (0.0%)	1.16 (0.54 – 2.33)	0.722
Balloon tamponade	3 (1.1%)	6 (0.66%)	0 (0.0%)	1.70 (0.27 – 8.03)	0.433
Hysterectomy	1 (0.37%)	3 (0.33%)	0 (0.0%)	1.13 (0.21 – 14.14)	1.00

*OR and P value comparing HIV positive and HIV negative group

**Suturing includes repair of extensions of the uterine incision, uterine tears extending from the incision, suturing of bleeding points from the dissection of adhesions on the anterior uterine wall and figure of 8 sutures for bleeding points along the incision following a 2 layer closure among others. Total number of caesarean sections in each HIV group was used as the denominator for this intervention since the interventions only took place during caesarean delivery.

*** Total number of vaginal deliveries was used as the denominator for these interventions since these only took place during vaginal delivery

Table 9

Blood products for the management of PPH

	HIV positive (n=270)	**HIV negative (n=915)**	**Untested (n=45)**	***OR (95%CI)**	***P value**
Packed cells					
0	217 (80.4%)	736 (80.4%)	27 (60.0%)	0.99 (0.70 – 1.43)	1.00
1 – 4 units	45 (16.7%)	152 (16.6%)	13 (28.9%)	1.00 (0.68 – 1.46)	1.00
5 or more	8 (2.9%)	27 (3.0%)	5 (11.1%)	1.00 (0.39 – 2.30)	1.00
Fresh frozen plasma	15 (5.6%)	51 (5.6%)	10 (22.2%)	0.99 (0.51 – 1.84)	1.00
Cryoprecipitate	0 (0.0%)	4 (0.44%)	2 (4.4%)	-	-
Platelets	3 (1.1%)	6 (0.66%)	3 (6.7%)	1.70 (0.27 – 8.03)	0.43

*Odds Ratios and P values comparing HIV positive with HIV negative group

5.5 The severity of and morbidity associated with PPH in HIV positive women compared to HIV negative women

Table 10 shows the complications associated with PPH in HIV positive and HIV negative women. More HIV positive women had a lowest haemoglobin level of more than 10g/dL following PPH compared to HIV negative women, and a significantly higher proportion of HIV positive women had mild anaemia (Hb >6g/dL to 10g/dL) compared to HIV negative.

A higher proportion of HIV negative women (2.6%) had documented hypovolaemic shock while only 0.4% of HIV positive women had documentation of hypovolaemic shock.

Table 10

Complications associated with PPH

	HIV positive (n=270)	**HIV negative (n=915)**	**Untested (n=45)**	***OR (95% CI)**	***P value**
Anaemia (lowest Hb)					
a. No anaemia	73 (27.0%)	313 (34.2%)	14 (31.1%)	0.699 (0.52 – 0.97)	0.0032
b. Hb > 6 – 10	187 (69.3%)	542 (59.2%)	22 (48.9%)	1.55 (1.15 – 2.10)	0.0028
c. Hb 6 or less	10 (3.7%)	60 (6.6%)	9 (20.0%)	0.638 (0.25 – 1.10)	0.218
Hypovolaemic Shock					
Yes	1 (0.37%)	24 (2.6%)	2 (4.4%)	0.138 (0.003 – 0.84)	0.026
No	269 (99.6%)	891 (97.4%)	43 (95.6%)		
Acute renal failure					
Yes	5 (1.9%)	12 (1.3%)	2 (4.4%)	1.449 (0.39 – 4.38)	0.559
No	265 (98.1%)	903 (98.7%)	43 (95.6%)		

*Odds Ratios and P values comparing HIV positive with HIV negative group

Table 11 shows a comparison of the severity of PPH between HIV positive and HIV negative women. The severity of postpartum haemorrhage, defined by the estimated amount of blood lost at the time of delivery was not affected by the HIV status.

Table 11

Severity of PPH in HIV positive women with PPH compared to HIV negative women with PPH

	HIV positive (n=270)	**HIV negative (n=915)**	**Untested (n=45)**	***OR (95%CI)**	***P value**
Mild	240 (90.7%)	820 (89.6%)	35 (77.8%)	0.926 (0.59 – 1.48)	0.735
Moderate	25 (9.3%)	72 (7.9%)	7 (15.6%)	1.19 (0.71 – 1.95)	0.45
Severe	2 (0.7%)	12 (1.3%)	3 (6.6%)	0.56 (0.61 – 2.55)	0.748
Very severe	3 (1.1%)	11 (1.2%)	0 (0.0%)	0.803 (0.16 – 3.53)	0.441

*Odds Ratios and P values comparing HIV positive with HIV negative group

Table 12 below shows a comparison of the severity of PPH in relation to maternal age, parity, BMI, mode of delivery, HIV status and mean haemoglobin level at the time of admission to labour ward or prior to caesarean section. To simplify the table, the severity of PPH was divided into two categories of 'mild' and 'moderate to severe' depending on whether blood loss was less than 1200ml or 1200ml or more respectively. This table shows that there was no difference in mean age, parity, BMI

and HIV status when all women with mild PPH were compared with all women with moderate/severe PPH.

There was a significantly higher proportion of women with mild PPH (84.8%) who had a caesarean section compared to women with moderate/severe PPH (60.7%). Significantly more women with moderate/severe PPH had a lower haemoglobin concentration at the time of admission to labour ward or prior to caesarean delivery compared to women with mild PPH.

Table 12

Comparison of severity of PPH with respect to age, parity, BMI, mode of delivery, HIV seropositive status and mean haemoglobin level on admission for delivery.

	Mild PPH, <1200ml (n=1095)	**Moderate to severe PPH, 1200ml or more (n=135)**	**OR (95% CI)**	**P value**
Mean age (yrs)	27.62	28.15		0.37
Age group (yrs) Up to 35 36 or more	 965 (88.1%) 130 (11.9%)	 117 (86.7%) 18 (13.3%)	 1.14 (0.632 – 1.96)	 0.578
Parity 0 1 or more	 404 (36.9%) 691 (63.1%)	 45 (33.3%) 90 (66.7%)	 1.17 (0.79 – 1.75)	 0.238
BMI (kg/m^2): Up to 35 36 and above Unknown	 620 (56.6%) 203 (18.5%) 272 (24.9%)	 67 (49.6%) 16 (11.9%) 52 (38.5%)	 *0.729 (0.386 – 1.31)	 *0.346
Mode of Delivery: Caesarean section Vaginal delivery	 929 (84.8%) 166 (15.2%)	 82 (60.7%) 53 (39.3%)	 3.62 (2.41 – 5.38)	 0.00001
HIV seropositive HIV seronegative HIV untested	240 (21.9%) 820 (74.9%) 35 (3.2%)	30 (22.2%) 95 (70.4%) 10 (7.4%)	**0.927 (0.592 – 1.48)	**0.736
Mean Hb (g/dl)	10.95	9.58		0.00001

* Odds ratio and P value comparing BMI up to 35 and 36 or more

** Odds ratio and P value comparing HIV seropositive and HIV seronegative

Table 13 shows that a significantly higher proportion of HIV positive women suffered mild to moderate morbidity from PPH compared to their HIV negative counterparts and more HIV negative women had no morbidity from PPH compared to HIV positive women. Morbidity was classified according to the morbidity score described in chapter 4 above.

Table 13

HIV status and morbidity from PPH

	HIV positive (n=270)	**HIV negative (n=915)**	**Untested (n=45)**	***OR (95% CI)**	***P value**
None	80 (29.6%)	340 (37.2%)	17 (37.8%)	0.712 (0.52 – 0.96)	0.025
Mild to moderate	168 (62.2%)	484 (52.9%)	15 (33.3%)	1.467 (1.10 – 1.96)	0.008
Severe	22 (8.2%)	91 (9.9%)	13 (28.9%)	0.803 (0.47 – 1.32)	0.411

*Odds Ratios and P values comparing HIV positive with HIV negative group

Table 14 shows a comparison of the occurrence of morbidity from PPH in relation to maternal age, parity, BMI, mode of delivery, HIV seropositive status and mean haemoglobin level at the time of admission to labour ward or prior to caesarean section. To simplify the table, morbidity from PPH was divided into two categories of 'no morbidity' and 'mild to severe' according to the morbidity score described in

chapter 4 above. There was no difference in HIV status or parity in women with no morbidity from PPH compared to those with mild/severe morbidity.

Mean age and mean haemoglobin concentration was significantly lower in women who had mild to severe morbidity from PPH compared to those who had no morbidity. In addition, there was a significantly lower proportion of women with mild or severe morbidity who had a BMI over 35kg/m^2. Also there was a lower proportion of women who had a caesarean section delivery in women with mild/moderate morbidity compared to those with no morbidity.

Table 14

Comparison of morbidity from PPH with respect to age, parity, BMI, mode of delivery, HIV seropositive status and mean haemoglobin level on admission to delivery.

	No Morbidity (n=437)	**Mild to severe morbidity (N=793)**	**OR (95% CI)**	**P value**
Mean age (yrs)	28.45	27.25		0.001
Age group (yrs)				
Up to 35	373 (85.4%)	708 (89.3%)	0.70	0.045
36 or more	64 (14.6%)	85 (10.7%)	(0.488 – 1.01)	
Parity				
0	154 (35.2%)	295 (37.2%)	0.919	0.536
1 or more	283 (64.8%)	498 (62.8%)	(0.714 – 1.18)	
BMI (kg/m^2):				
Up to 35	101 (23.1%)	455 (57.4%)	*0.113	*0.00001
36 and above	232 (53.1%)	118 (14.9%)	(0.082 – 0.156)	
Unknown	104 (23.8%)	220 (27.7%)		
Mode of Delivery:				
Caesarean section	394 (90.2%)	616 (77.7%)	2.63	0.00001
Vaginal delivery	43 (9.8%)	177 (22.3%)	(1.83 – 3.85)	
HIV seropositive	80 (18.3%)	190 (24.0%)	**1.40	**0.024
HIV seronegative	340 (77.8%)	575 (72.5%)	(1.038 – 1.909)	
HIV untested	17 (3.9%)	28 (3.5%)		
Mean Hb (g/dl)	11.79	10.22		0.00001

* Odds ratio and P value comparing BMI up to 35 and 36 or more

** Odds ratio and P value comparing HIV seropositive and HIV seronegative

5.6 Impact of CD4 count and anti-retroviral therapy provided on the severity and morbidity of HIV positive women with PPH

Table 15 below shows the influence of the level of CD4 count on the severity of PPH in HIV positive women. 240 of the 270 HIV positive women with PPH (88.9%), were classified as having mild PPH ie had blood loss of 500 – 1200 ml. The severity of PPH was not significantly different in women with CD4 count of up to 250cells/mm^3 compared to women with CD4 count of more than 250cells/mm^3. In addition, table 16 shows that there was no difference in morbidity from PPH in women with CD4 count of up to 250cells/mm^3 compared to those with CD4 count of more than 250cells/mm^3.

Table 15

The influence of CD4 count on the severity of PPH (n=270).

	CD4 count (cells/$mm^{3)}$				
	Up to 250 (n=70)	**More than 250 (n=186)**	**No record (n=14)**	***OR (95% CI)**	***P value**
Mild	62 (88.6%)	166 (89.2%)	12 (85.7%)	0.93 (0.37 – 2.58)	0.82
Moderate to very severe	8 (11.4%)	20 (10.8%)	2 (14.3) %		
Total	70	186	14		

*Odds Ratio and P value comparing severity of PPH between women with CD4 count up to 250 cells/mm^3 and those with CD4 count above 250 cells/mm^3

Table 16

The influence of CD4 count on the morbidity from PPH (n=270)

	CD4 count (cells/mm^3)				
	Up to 250 (n=70)	**More than 250 (n=186)**	**No record (n=14)**	***OR (95% CI)**	***P value**
No morbidity	20 (28.6%)	55 (29.6%)	5 (35.7%)	0.95 (0.49 – 1.81)	1.00
Mild to severe	50 (71.4%)	131 (70.4%)	9 (64.3%)		
Total	70	186	14		

*Odds Ratio and P value comparing severity of morbidity from PPH between women with CD4 count up to 250 cells/mm^3 and those with CD4 count above 250 cells/mm^3

HIV treatment with either Zidovudine (AZT) alone or highly active anti-retroviral therapy, HAART, (mostly with Zidovudine, Lamivudine and Nevirapine) did not influence the severity of as well as the morbidity from PPH when compared with women who had not been on any form of treatment during their pregnancy. This lack of association was observed regardless of the duration of the treatment (data not shown).

Chapter 6

Discussion

The study showed that the incidence of postpartum haemorrhage was significantly higher in HIV positive women compared to HIV negative women in the two hospitals during the study period; 9.9 % of HIV positive women delivering during the study period had PPH compared to 7.5% of HIV negative women. The study had sufficient power (98.74%) to show this statistically significant difference in the incidence of PPH between HIV positive and HIV negative women ($p = 0.001$).

The severity of postpartum haemorrhage did not differ between HIV positive and negative women. However, mild to moderate morbidity from haemorrhage was significantly greater in HIV positive women with PPH compared to HIV negative women with PPH. It is important to note that according to the definition of at least 1800ml of blood loss for severe haemorrhage in this study, only 31 women fell into the categories of severe and very severe PPH. This was a small number of women to be able to meaningfully compare the severity of and morbidity from PPH between the two groups of women.

Demographic characteristics of the women such as mean age, parity, previous caesarean delivery, gestational age at delivery and mean haemoglobin level at the time of admission to labour ward or prior to caesarean section were similar in the HIV positive PPH group and the HIV negative PPH group.

Maternal age over 35 years and BMI over 35 kg/m^2 are known to be risk factors for PPH. In our study, the methodology did not allow a proper assessment of risk factors

to be made. Of note was our finding that there was a significantly lower percentage of women over 35 years of age in HIV positive women with PPH compared to HIV negative women.

Similarly, although obesity is a known risk factor for PPH, a significantly lower proportion of HIV positive women with PPH had a BMI of 36 kg/m^2 or more compared to HIV negative women. These findings on age and BMI suggest that the association between HIV infection and PPH is not due to an increased proportion of women with these risk factors for PPH (age and obesity) in the HIV positive group of women with PPH; and points to a possible direct effect of the HIV infection. However, without the knowledge of the frequency of these parameters in the whole delivery population, it is not possible to make this conclusion.

This study had several limitations. Since it was a retrospective study, some women who had PPH may not have been recorded in the labour ward and operating theatre registers and therefore may have been left out of the study. In addition, not all the required information could be found in the women's records. Information such as booking haemoglobin level, height and weight measurements and haemoglobin level at the time of admission to labour ward for delivery was particularly lacking.

Since demographic and other data on women delivering at the two hospitals during the study period who did not suffer PPH were not retrieved, the proper assessment of confounding factors for the observed association between HIV infection and PPH was not possible.

The selection of Mowbray Maternity and Groote Schuur Hospitals may have presented a biased sample with women who may have been sicker from the HIV disease compared to HIV positive women accessing care at the MOU. In addition, the aetiology of PPH in these hospitals may have been influenced by the high prevalence of conditions such as hypertension and abruptio placentae. As such, the results of this study are not generalized to the general population.

Although widely accepted, the clinical visual estimation of blood loss at the time of delivery is known to be inaccurate and prone to intra as well as inter-observer error with a tendency towards underestimation. A more accurate measure of blood loss would be more appropriate for research settings. However, this is not achievable with a retrospective study design.

Additionally, since an assessment of other haematological indices such as platelet count which may affect the rates of PPH between the two study groups is not routinely done in clinical practice, it is not possible to explain why there could be a significant difference in the rates of PPH.

The causes of haemorrhage were similar between the two groups of women with uterine trauma at caesarean section being the most common cause. This was bleeding mainly from the incision site during caesarean section. Such bleeding included that from uterine tears extending from the caesarean section incision and intentional extensions of the uterine incision due to difficult delivery of the baby among others. This finding is in keeping with the findings of the National Committee on Confidential Enquiries into Maternal Deaths (NCCEMD) in South Africa for the

triennium 2005 – 2007[72]. It is important to note that by having deliveries from Mowbray Maternity and Groote Schuur Hospitals alone, the sample may have been biased towards more caesarean deliveries due to the high rates of such deliveries in these hospitals. A sample including MOUs where normal vaginal deliveries take place may have shown a different pattern of PPH causes.

Hypertension was more frequent in the HIV negative PPH group than in the HIV positive PPH group. This may be a result of a reduced incidence of pre-eclampsia in the HIV positive PPH group due to inhibition of immune hyper-reactivity from the immune deficiency state. There are however conflicting findings from studies that have investigated the relationship between HIV infection and pre-eclampsia[73].

In this study, 60% of all the women who had post-partum haemorrhage had emergency caesarean delivery. This was the most common mode of delivery in all the three groups of women (positive, negative and untested). It is well known from literature that emergency caesarean section is a risk factor for obstetric haemorrhage[74]. The difference in mean blood loss at emergency caesarean section between HIV positive and HIV negative women with PPH was almost statistically significant (p=0.067). The impact of HIV infection on haemorrhage at emergency caesarean section therefore requires further exploration.

It is also interesting to note that a significantly higher proportion of HIV negative women with PPH (28.2%) compared to HIV positive women with PPH (21.5%) did not require any intervention to arrest bleeding (p=0.028). Uterine trauma at caesarean section was the cause of bleeding in nearly 90% of these HIV negative women. This

may suggest that these women generally have better functioning clotting mechanisms compared to the HIV positive women.

Despite having a similar mean haemoglobin level of 10.8g/dL prior to delivery and a non significantly different mean blood loss (p=0.697), more HIV positive women had anaemia with haemoglobin level of 10g/dL or less by the second or third day following the episode of PPH. The effect of HIV infection on different haematopoietic cell lines is well known[52,53].

Considering the severity of PPH, in the combined group of women with PPH (ie both HIV positive, HIV negative and untested women), the mean haemoglobin at the time of admission to labour ward or prior to caesarean delivery was significantly lower in women who had blood loss of 1200ml or more compared to those with blood loss less than 1200ml. Anaemia in HIV positive women could therefore be an important factor predisposing HIV positive women to more severe consequences of PPH.

Considering morbidity from PPH, the mean age and mean haemoglobin at the time of admission to labour ward or prior to performing caesarean section was significantly lower for women with mild to severe morbidity compared to those with no morbidity. Also the proportion of women with increased BMI (over 35kg/m^2) and the proportion of women having a caesarean section delivery was less in women with mild to severe morbidity compared to those with no morbidity. These findings are not in keeping with the literature which shows that advanced maternal age and increased BMI are known risk factors for PPH. However as indicated before, due to the lack of information regarding these parameters in the group of women who delivered in the

two hospitals during the study period and did not have PPH, it is not possible to adequately assess these risk factors for PPH. It is therefore not possible to assess whether they could be possible confounding factors for the association between HIV positive status and an increased morbidity from PPH.

Out of the 1230 cases of postpartum haemorrhage in this study, only 27 cases of hypovolaemic shock following PPH were documented. Twenty-four of these were in the HIV negative group, two in the untested group and only one in the HIV positive group. It is thought that there was poor documentation of hypovolaemic shock in the attending doctor's notes. There were many women who met the criteria for shock ie persistent severe hypotension defined as a systolic blood pressure <90mmHg with a pulse rate of at least 120 beats per minute[40]. However, where it was not clearly documented that the woman had hypovolaemic shock, the effect of anaesthesia and other confounders on these parameters could not be isolated. Therefore, where there was no mention that a woman had hypovolaemic shock, no assumption was made that they had this complication.

The level of CD4 count at booking for antenatal care, treatment of HIV with either Zidovudine alone or highly active anti-retroviral therapy as well as the duration of such treatment was not seen to have an impact on the severity of and morbidity from PPH. Once again this may be the case because the number of HIV positive women with severe PPH was very small. As a result no conclusion can be drawn from these findings.

The finding of similar results for severity of PPH and morbidity from PPH in the two treatment groups of Zidovudine alone and highly active anti-retroviral therapy may have been because the majority of patients on HAART were on a Zidovudine containing regimen of Zidovudine, Lamivudine and Nevirapine. This was the prevailing treatment guideline during the time period under study.

In this study, 3.7% of all the women with PPH were HIV untested. This group comprised women who were either unbooked for antenatal care or those that had declined HIV testing at booking. As many as 17.8% of these women had abruptio placentae as the cause of PPH. These women were not included in the statistical analysis for this study.

As shown in the introduction, the Saving Mothers reports for the triennia 2002 – 2004 and 2005 – 2007 showed that maternal mortality rate from post-partum haemorrhage was almost three times higher in HIV positive women compared to HIV negative women[2,3]. This could be due to increased incidence of PPH or increased severity of PPH in the HIV positive group.

Our study shows an association between HIV infection and an increased incidence of PPH. It also showed that the HIV positive PPH group suffered greater morbidity than the HIV negative PPH group. However, there was no difference in the severity of PPH between the two groups of women. Because of the serious limitations in the study design (place of delivery and referral bias, lack of detailed data on women without PPH and therefore failure to investigate for confounding), the weak strength of association, the sameness of the haemoglobin concentration before delivery, and

the absence of the difference in mean blood loss, we cannot conclude that HIV is an independent risk factor for PPH.

Further research which is appropriately designed and powered to investigate the relationship between HIV disease and its treatment, CD4 count and post-partum haemorrhage is required considering the burden of the disease in sub-Saharan Africa in general and South Africa in particular where maternal mortality ratio in HIV positive women is as high as 327.7 per 100,000 livebirths compared to 34.4 per 100,000 livebirths in HIV negative women[2].

The relationship between the level of CD4 count and the rate of post-partum haemorrhage needs to be investigated. This study did not have a large enough number of HIV positive women with PPH to investigate this relationship and data regarding the level of CD4 count for the entire HIV positive population of women delivering at the two hospitals in 2009 was not collected. Future research should be aimed at exploring this relationship.

Another area of future study should be the impact of the different HIV treatment regimens on the severity of PPH.

Chapter 7

Conclusion

The results of this study demonstrate a significant association between HIV infection and an increased incidence of postpartum haemorrhage at Mowbray Maternity and Groote Schuur Hospitals. HIV infection was also associated with increased morbidity from PPH in the HIV positive PPH group. However, it was not associated with increased severity of PPH.

Post-partum haemorrhage is a major cause of maternal mortality especially in low resource settings. Unfortunately, it is in these same, often rural areas that the prevalence of HIV infection is high. Such areas in sub-Saharan Africa also suffer a huge shortage of skilled health care workers and other essential resources such as blood products.

Due to the serious study limitations, our study could not establish that HIV infection is an independent risk factor for post-partum haemorrhage. More research is required to explore the relationship between HIV infection and both the incidence of post-partum haemorrhage and the morbidity associated with PPH. In order to investigate whether HIV infection independently predisposes to PPH, a comprehensive exploration of confounding factors would be necessary. If such an association is confirmed, there is need to investigate the role of other anti-retroviral treatments in increasing severity of and morbidity from PPH.

Given the apparent association between HIV infection and PPH, health care workers in high HIV prevalence areas need to be well trained in the stepwise medical and

surgical management of post-partum haemorrhage. Most of the haemorrhage will respond to the simple measures without resort to hysterectomy. It is also important that people working in lower level health facilities quickly recognise this complication and timeously refer to the appropriate level of care.

REFERENCES

1. Lalonde AB, Daviss BA et al. Postpartum haemorrhage today: Living in the shadow of the Taj Mahal. In B-Lynch C, Keith LG et al, eds. A text book of postpartum haemorrhage. Duncow, UK: Sapiens Publishing, 2006: 2 – 10
2. Saving Mothers. Fourth report on confidential enquiries into maternal deaths in South Africa 2005 - 2007. Department of Health, Republic of South Africa. 2008
3. Saving Mothers. Third report on confidential enquiries into maternal deaths in South Africa 2002 - 2004. Department of Health, Republic of South Africa. 2006.
4. Royal College of Obstetricians and Gynaecologists. Prevention and Management of Postpartum Haemorrhage. Green-top Guideline No. 52. London. RCOG; May, 2009.
5. Lewis G, editor. Why mothers Die 2000 – 2002, The Sixth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. London: RCOG Press; 2004
6. Confidential Enquiry into Maternal and Child Health(CEMACH). Saving mothers' lives. 2003 - 2005; www.cemach.org.uk. December 2007.
7. The World Health Report, 2005: Make every mother and child count. World Health Organization, Geneva. 2005
8. Mataka E. Maternal health and HIV: bridging the gap. Lancet 2007; 370: 1290.

9. McIntyre J. Maternal Health and HIV. Reproductive Health Matters 2005; 13(25): 129 – 135.

10. The provincial and district HIV antenatal survey, Western Cape 2002. Department of Health, Western Cape, Republic of South Africa; 2003.

11. Shah IH, Say L. Maternal mortality and maternity care from 1990 to 2005: Uneven but important gains. Reproductive Health Matters 2007. 15(30): 17 – 27.

12. Ronsmans C, Graham WJ, on behalf of the Lancet Maternal Survival Series steering group. Maternal mortality: who, when, where, and why. Lancet 2006; 368: 1189 - 200.

13. Graham WJ, Newell ML. Maternal deaths in South Africa: what proportion occurs at home? In Saving Mothers. Fourth report on confidential enquiries into maternal deaths in South Africa 2005 - 2007. Department of Health, Republic of South Africa. 2008

14. Countdown to 2015. Decade report (2000 – 2010). Taking stock of maternal, newborn and child survival. World Health Organization and UNICEF 2010.

15. Department of Health, Medical Research Council, OrcMacro. South Africa Demographic and Health Survey 2003. Department of Health, Pretoria, Republic of South Africa 2007.

16. Fezoui H, Garnier G, Taillan B, Cassuto JP, Pesce A. Haemostatic anomalies and Human Immunodeficiency Virus infection. Rev. Med. Interne 1996; 17: 738 – 745.

17. Side effects of Antiretroviral drugs. Drug Side Effects. http://www.drugs.com/sfx/

18. Coker A, Oliver R. Definitions and classifications of postpartum haemorrhage. In B-Lynch C, Keith LG et al, eds. A text book of postpartum haemorrhage. Duncow, UK: Sapiens Publishing, 2006: 11 – 16
19. Royston E, Armstrong S, editors. Preventing Maternal Deaths. Geneva: World Health Organization; 1989
20. World Health Organization. The prevention and management of postpartum haemorrhage. Report of a technical working group. Geneva: WHO; 1990.
21. Benedetti T. Obstetric haemorrhage. In Gabbe SG, Niebyl JR, Simpson JL, eds. A Pocket Companion to Obstetrics, 4th edn. New York: Churchill Livingstone, 2002: Ch17.
22. Khan RU, El-Refaey H. Pathophysiology of postpartum haemorrhage and third stage of labor. In B-Lynch C, Keith LG et al, eds. A text book of postpartum haemorrhage. Duncow, UK: Sapiens Publishing, 2006: 62 – 69.
23. Rogers MS, Chang AMZ. Postpartum haemorrhage and other problems of the third stage. In James DK, Steer PJ et al, eds. High risk pregnancy: Management options. Elsevier Inc. 2006: 1559 – 1578.
24. Balki M, Dhumne S et al. Blood transfusion for primary postpartum haemorrhage: A tertiary care hospital review. J Obstet Gynaecol Can 2008;30(11): 1002 – 1007.
25. Cameron MJ, Robson SC. Vital statistics: An overview. In B-Lynch C, Keith LG et al, eds. A text book of postpartum haemorrhage. Duncow, UK: Sapiens Publishing, 2006: 17 – 34.

26. Combs CA, Murphy EL, Laros RK. Factors associated with postpartum haemorrhage with vaginal birth. Obstet Gynecol 1991;77: 69 – 76.
27. Combs CA, Murphy EL, Laros RK. Factors associated with postpartum haemorrhage in cesarean deliveries. Obstet Gynecol 1991;77: 77 – 82.
28. Basu SM. Anaemia and pregnancy. In Gupta S ed. 1st Edition. Obstetric Anaesthesia. Delhi: Arya Publications, 2004: 433 – 456.
29. Guidozzi F. Blood disorders in pregnancy. In Cronje HJ, Grobler CJF eds. Obstetrics in Southern Africa. Pretoria: Van Schaik Publishers 2003: 543 – 555.
30. Hoque M, Kader SB, Hoque E. Prevalence of anaemia in pregnancy at Uthungulu Health District of KwaZulu-Natal, South Africa-2003. SA Fam Pract 2007; 49(6): 16 – 16d.
31. AbouZahr C, Royston C. Maternal mortality: A global factbook. World Health Organization, Geneva; 1991
32. Nojilana B, Norman R, Dhansay M et al. Estimating the burden of disease attributable to Iron Deficiency Anaemia (IDA) in South Africa in 2000. S Afri Med J 2007; 97(8): 741 – 746.
33. Nokes C, Van Den Bosch C, Bundy DAP. The effect of iron deficiency and anaemia on mental and motor performance, educational achievement and behaviour in children: An annotated bibliography. International Nutritional Anaemia Consultative Group, Washington, DC. 1998.

34. McCormick N. The contribution of low birth weight to infant mortality and childhood mortality. New Engl J Med 1985; 31: 82 – 90.
35. Ross J, Thomas EL. Iron deficiency anaemia and maternal mortality. Profiles 3, working notes series No 3. Washington, DC: Academy for educational development; 1996.
36. Unicef. State of the world's population 1994, New York, UNFPA; 1998.
37. Fleming AF. The aetiology of severe anaemia in pregnancy in Ndola, Zambia. Ann Trop Med Parasitol 1989; 83: 37 – 49.
38. Van den Broek NR. Anaemia in pregnancy in developing countries. Review. Br J Obstets and Gynaecol 1998; 105: 385 – 390.
39. Hoque M, Hoque E, Kader S. Risk factors for anaemia in pregnany in rural KwaZulu-Natal, South Africa: Implication for health education and health promotion. SA Fam Pract 2009; 51(1): 68 – 72.
40. Say L, Souza JP, Pattinson RC. Maternal near miss – towards a standard tool for monitoring quality of maternal health care. Best Practice and Research Clinical Obstetrics and Gynaecology 2009; 23: 287 – 296.
41. Anthony J. Major obstetric hemorrhage and disseminated intravascular coagulation. In James DK, Steer PJ et al, eds. High risk pregnancy: Management options. Elsevier Inc. 2006: 1606 – 1623.
42. Bonnar J. Massive obstetric haemorrhage. Bailliere's Clinical Obstetrics and Gynaecology 2000; 14(1): 1 – 18.

43. Karpati PCJ, Rossignol M, Pirot M et al. High incidence of myocardial ischaemia during postpartum haemorrhage. Anesthesiology 2004; 100: 30 – 36.

44. Mousa HA, Walkinshaw S. Major postpartum haemorrhage. Current Opinion in Obstetrics and Gynaecology 2001; 13(6): 595 – 603.

45. Ledee N, Ville Y, Musset D et al. Management in intractable obstetric haemorrhage: an audit study in 61 cases. Eur J Obstet Gynecol Reprod Biol 2001; 94: 189 – 196.

46. Pelage JP, Le Dref O, Jacob D et al. Selective arterial embolization of the uterine arteries in the management of intractable postpartum haemorrhage. Acta Obstet Gynecol Scand 1999; 78: 698 – 703.

47. Chanrachakul B, Chaturachinda K, Phuapradit W, Roungsipragarn R. Caesarean and postpartum hysterectomy. Int J Gynaecol Obstet 1996; 54: 109 – 113.

48. Tamizian O, Arulkumaran S. The surgical management of postpartum Haemorrhage. Curr Opin Obstet Gynecol 2001; 13: 127 – 131.

49. Engelsen IB, Albrechtsen S, Iversen OE. Peripartum hysterectomy-incidence and maternal morbidity. Acta Obstet Gynecol Scand 2001; 80: 409 – 412.

50. Wenhem J, Matijevic R. Postpartum hysterectomies: revisited. J Perinat Med 2001; 29: 260 – 265.

51. Gunther K, Dhlamini B. D-dimer levels are markedly raised in HIV related TTP. AIDS 2007; 21: 1063 – 1064.

52. Park YA, Hay SN, Brecher ME. ADAMTS 13 activity levels in patients with Human Immunodeficiency Virus-associated thrombotic

microangiopathy and profound CD4 deficiency. Journal of Clinical Apheresis 2009; 24: 32 – 36.

53. Aster J. Red cells and bleeding disorders. In Cotran S, Kumar V, Collins T eds. Robbins pathologic basis of disease, 6th ed. Pennsylvania: WB Saunders Company 1999; 601 – 643.

54. del Arco A, Martinez MA, Pena JM et al. Thrombotic thrombocytopenic purpura associated with human immunodeficiency virus infection: demonstration of p24 antigen in endothelial cells. Clin Infect Dis 1993; 17: 360 – 363.

55. Green DF, Resnick L, Bourgoignie JJ. HIV infects glomerular endothelial and mesangial but not epithelial cells in vitro. Kidney Int 1992; 41: 956 – 960.

56. Cenacchi G, Re MC, Preda P et al. Human immunodeficiency virus type-1 (HIV-1) infection of endothelial cells in vitro: a virological, ultrastructural and immuno-cytochemical approach. J Submicrosc Cytol Pathol 1992; 24: 155 – 161.

57. Ganchev RV, Ludlam CA. Acquired and congenital haemostatic disorders in pregnancy and the puerperium. In B-Lynch C, Keith LG et al, eds. A text book of postpartum haemorrhage. Duncow, UK: Sapiens Publishing, 2006: 209 – 232.

58. Cruz MA et al. Interaction of von Willebrand factor with collagen: localization of the primary collagen-binding site by analysis of recombinant vWF A domain polypeptides. J Biol Chem 1995; 270: 10822.

59. Mitchell RN, Cotran RS. Hemodynamic disorders, thrombosis and shock. In Cotran S, Kumar V, Collins T eds. Robbins pathologic basis of disease, 6th ed. Pennsylvania: WB Saunders Company 1999; 113 – 138.

60. Racoosin JA, Kessler CM. Bleeding episodes in HIV-positive patients taking HIV protease inhibitors: a case series. Haemophilia 1999; 5: 266 – 269.

61. Saving Mothers1999 – 2001: Second report on confidential enquiries into maternal deaths in South Africa. Government Printer, Pretoria 2003.

62. Clinical Guidelines: Prevention of Mother-to-Child transmission (PMTCT) of HIV, 2010. National Department of Health, Republic of South Africa. 2010.

63. Policy and guidelines for the implementation of the PMTCT programme. National Department of Health, Republic of South Africa. February, 2008.

64. Reyal F, Sibony O, Oury JF, et al. Criteria for transfusion in severe postpartum hemorrhage: analysis of practice and risk factors. Eur J Obstet Gynaecol Reprod Biol 2004; 113: 61 – 64.

65. Rouse DJ, MacPherson C, Landon M et al. Blood transfusion and caesarean delivery. Obstetrics & Gynecology 2006; 108(4): 891 – 897.

66. Stehling LC, Scottsdale A, Doherty DC et al. Practice guidelines for blood component therapy. Anesthesiology 1996; 84: 732 – 747.

67. Klapholz H. Blood transfusion in contemporary obstetric practice. Obstet Gynecol 1990; 75: 940 – 943.

68. Sherman SJ, Greenspoon JS, Nelson MJ, Paul RH. Obstetric haemorrhage and blood utilization. J Reprod Med 1993; 38: 929 – 934.

69. Fawcus S, Moodley J eds. A monograph of the management of post partum haemorrhage. National committee on the confidential enquiry into maternal deaths in South Africa. 2010. Department of Health, Republic of South Africa 2010.

70. Adams TS. A quality of care assessment of the management of obstetric haemorrhage in the Peninsula Maternal and Neonatal Service. MMed Obstets and Gynaecol Thesis, UCT 2009.

71. Ronsmans C. Severe acute maternal morbidity in low income countries. Best Practice and Research Clinical Obstetrics and Gynaecology 2009; 23: 305 – 316

72. Fawcus S, Moodley J. Haemorrhage associated with caesarean section in South Africa – be aware. SAMJ May 2011; 101 (5): 306 – 309.

73. Hall DR. Is pre-eclampsia less common in patients with HIV/AIDS? Journal of Reproductive Immunology 2007; 76: 75 – 77.

74. Brace V, Kernaghan D, Penney G. Learning from adverse clinical outcomes: major obstetric haemorrhage in Scotland, 2003 – 2005. BJOG 2007; 114: 1388 – 1396.

Appendix 1

THE EFFECT OF HIV INFECTION ON THE INCIDENCE AND SEVERITY OF POST PARTUM HAEMORHAGE

DATA COLLECTION SHEET

SECTION 1: DEMOGRAPHIC DATA

1. Age:_____ **2. Parity:**_____ **3. Gravidity:**_____

4. Folder Number: _____ **5. Hospital Code:**_____ **6. GA at delivery:**_____ **wks**

SECTION 2: PAST OBSTETRIC AND GYNAECOLOGICAL HISTORY

7. Previous Deliveries

Child No.	Year	Mode of Delivery	Birth Weight	Sex	Outcome
1					
2					
3					
4					
5					
6					

8. History of PPH Yes [1] No [2] If no go to Question 11

If yes, state cause:_____
Was transfusion required Yes [1] No [2]
Other Complications Yes [1] No [2]

If yes, outline:_____
_____
_____

9. Previous Miscarriages Yes [1] No [2]

Gestational Age _____ Weeks

Intervention: Medical [1] Surgical [2] Other [3] (Specify):_____

10. Previous Gynaecological Surgery Yes [1] No [2]

If Yes, name operation:_____

Other abdominal surgery Yes [1] No [2]

If yes, specify:_____

SECTION 3: INDEX PREGNANCY

11. Booked Yes [1] No [2]

12. Gestational age at booking _____ weeks

13. Date of booking _____

14. Weight at booking: _____ Kg

15. Height: _____ Metres

16. BMI: _____ Kg/sqm

17. Booking Hb:_____ g/dL

18. Hb on Admission:_____ g/dL **19. APH** Yes [1] No [2]

20. Blood Group: A [1] B [2] AB [3] O [4]

21. RPR: Postive [1] Negative [2] **22. Rhesus**: Postive [1] Negative [2]

23. HIV Postive [1] Negative [2]

24. CD4 count:_____ **25. Date Taken** _____

26. Treatment: Zidovudine [1] Heamatinics [2] HAART [3]
HAART state regime:_____ Date commenced:_____

27. Duration of treatment:_____ wks

28. Ultrasound Done Yes [1] No [2]

29. Gestation at 1st ultrasound: _____Weeks

30. Concurrent medical disorders: Hypertension Hypertension Yes [1] No [2]
Diabetes Mellitus Yes [1] No [2]
Thyroid Yes [1] No [2]
Bleeding disorder Yes [1] No [2]
Gestational hpt Yes [1] No [2]
Abruptio placenta Yes [1] No [2]
Other (specify):_____

31. Nature of gestation Single [1] Multiple [2]
If multiple, state order:_____

32.Mode of Delivery Elective CS [1] Emergency CS [2] NVD [3] Breech [4]
Forceps [5] Ventouse [6]

33. Indication for CS: _____

34. Anaesthetic Spinal [1] General [2]

35. Incision type Lower segment [1] Classical [2]

36. Place of Delivery Home [1] MOU [2] Level 2 [3] Level 3 [4]
Enroute to health Facility [5]
Other [6] (Specify):_____

SECTION 4: DETAILS OF PPH

37. Estimated blood loss: _____ ml

38. Lowest Hb recorded after PPH: _____ g/dL

39. Lowest BP at time of diagnosis: _____ mmHg

40. Pulse rate at time of diagnosis:_____

41. Cause of PPH: Uterine atony [1] Retained Placenta [2]
Retained products of conception [3] Trauma Vag [4]
Trauma Cer [5] Trauma Ut [6] Uterine rupture [7]
Post Abr. Placenta [8] Post Placenta Pre. [9]
Anticoagulation treatment [10]

42. Intervention Oxytocin [1] Ergometrine [2] Misopostol [3] F2 Alpha [4] MROP [5] Evac [6]
Repair of Tear [7] B-Lynch suture [8] Balloon Tamponade [9] Hysterectomy [10]
Abdominal Packing [11] Suture [11]

43. Blood products given Yes [1] No [2]
Packed cells: _____ units
Fresh frozen plasma: _____ units
Cryoprecipitate: _____ units
Other (specify):_____

44. Severity score: normal blood loss [0] Mild [1] moderate [2] severe [3] very severe [4]

45. Morbidity score: none [0] mild [1] moderate [2] severe [3] very severe [4]

SECTION 5: COMPLICATIONS OF PPH

46. Hypovolaemic shock Yes [1] No [2]

47. Disseminated intravascular coagulation Yes [1] No [2]

48. Acute renal failure Yes [1] No [2]

49. Hepatic failure Yes [1] No [2]

50. Adult respiratory distress syndrome Yes [1] No [2]

51. Other (specify) _____

SECTION 6: COMPLICATIONS ARISING FROM TREATMENT OF PPH.

52. Transfusion reactions Yes [1] No [2]

53. Fluid Overload Yes [1] No [2]

54. Need for assisted ventilation Yes [1] No [2]

55. Infection Yes [1] No [2]
If yes, state site:_____

56. Uterine perforation Yes [1] No [2]

57. Bladder injury Yes [1] No [2]

58. Ureteric injury Yes [1] No [2]

59. Bowel inury Yes [1] No [2]

SECTION 7: FINAL OUTCOME

60. Outcome of baby: Alive [1] Stillbirth [2]
Gender: M [1] F [2]
Weight _____ grams
Apgar score _____

Outcome of Mother

61. Alive and well at discharge Yes [1] No [2]

62. Disability Yes [1] No [2]
If yes, give details:_____

63. Death Yes [1] No [2]

64. Duration of hospital stay _____ **Days**

65. Admission to MK SCU Yes [1] No [2]
If yes, give duration of stay _____ **Days**

66. Admission to other ICU Yes [1] No [2]
If yes, specify location _____
Duration of Stay _____ **Days**