EFFECT OF MATERNAL HUMAN IMMUNODEFICIENCY VIRUS STATUS ON OUTCOMES OF VERY LOW BIRTH WEIGHT INFANTS AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree of Master of Medicine in Paediatrics.

Johannesburg, 2014.

DECLARATION

I, Mayowa M. TIAM declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Paediatrics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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16 May 2014

DEDICATION

In memory of my late mother Busurat Ayotomi HASSAN

ABSTRACT

Background

Human immunodeficiency virus (HIV) sero-prevalence rate during pregnancy was 26% in 2009 in Gauteng. HIV exposure is associated with high morbidity and mortality in infants. Few studies have assessed the effect of HIV exposure on morbidity and mortality in very low birth weight (VLBW) infants.

Aim

To determine the infant characteristics at birth, morbidity during hospital stay and mortality at hospital discharge of VLBW infants according to maternal HIV status.

Methods

This was a retrospective cross sectional descriptive study. Hospital records of VLBW infants admitted at the Chris Hani Baragwanath Academic Hospital, Division of Neonatology from 1st January 2011 to 30th June 2011 were reviewed. Data were collected in an Excel spread sheet and imported to STATA version 12 for analysis.

Results

302 hospital records of VLBW infants admitted from January to June 2011 were retrieved and reviewed. About a third (34.1%) of VLBW infants were born to mothers who were HIV positive. There were more babies who weighed <1000 grams in the HIV-exposed infants compared to HIV-unexposed infants (p-0.001). HIV exposed infants had a smaller head circumference (p-0.003), a shorter body length (p-0.006) and significantly more severe grades of IVH (p <0.001) compared to HIV unexposed infants. The overall mortality rate in VLBW infants was 27%, with HIV exposed infants having a mortality rate of 38.6% compared to 21% in the HIV-negative infants (p-0.002). Multivariate analysis showed that the main predictor of mortality was birth weight (p<0.001).

Conclusion

Though on univariate analysis maternal HIV status was associated with mortality in VLBW infants, this effect was not found on multivariate analysis. Therefore the final conclusion from this study is that maternal HIV status has no independent effect on outcomes to hospital discharge in VLBW infants. Birth weight was the predictor of survival in VLBW infants.

ACKNOWLEDGEMENTS

First, I would like to thank God Almighty for giving me the strength and good health to be able to conduct this research.

My special thanks to my supervisor, Professor Sithembiso Velaphi, for his guidance throughout this work. I also like to thank Dr David Moore in research department of CHBAH, for his tremendous contributions at the beginning of this work.

I also wish to acknowledge and thank my dear husband, Appolinaire (Appolo Dear), for his understanding and support during this project. Thanks also to our children Fotie and Megne for cooperating with daddy through these years that I was away.

My father, Hassan and siblings Moturayo, Gani, Biodun, Sherifat, Fali, and Bukky. My in-laws: Fotie, Alexis, Antoinette, Norbert, Gisele, and Tagne.

A special thank you to a friend and a colleague, Dr Oladoyinbo, Clinical epidemiologist and Dr. Akintade, for assisting me with data analysis.

I am also thanking Dr R. Familoni, Dr and Mrs Ajayi, Olumide and Refiloe Benedict, Dr Biodun and Ekaite Benedict, Professor and Mrs Benedict, Dr and Mrs Oluwatimilehin, Pastor and Mrs Oyinloye, Pastor and late Mrs Ajiboye, Pastor and Mrs Martins.

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ACRONYMS

AIDS: Acquired immunodeficiency syndrome

ANC: Antenatal Care

ART: Antiretroviral therapy

ARV: Antiretroviral drugs

CRP: c - reactive protein

GA: Gestational age

LBW: Low birth weight

LR: Likelihood ratio

NICU: Neonatal intensive care unit

PTD: Preterm delivery

PMTCT: Prevention of mother-to-child transmission

VLBW: Very low birth weight

VLBWI: Very low birth weight infants

CHAPTER 1: INTRODUCTION

Human immunodeficiency virus (HIV) is a major cause of infant and childhood morbidity and mortality in sub-Saharan Africa[1]. The antenatal HIV sero-prevalence in Gauteng Province was estimated to be 26% in 2009[2], implying that more than one quarter of infants born in the province are HIV-exposed [2]. Pregnancies in which HIV features as a complicating factor are at increased risk for premature delivery[1,3,4], and other life-threatening outcomes (including infection) in mothers and exposed infants[3,5]. There are limited studies which explore the extent to which HIV exposure impacts on outcomes in very low birth weight (VLBW) infants. The aim of this study was to determine the characteristics, morbidity and mortality in HIV-exposed compared to HIV-unexposed VLBW infants at Chris Hani Baragwanath Academic Hospital.

CHAPTER 2: LITERATURE REVIEW

2.1 HIV infection and pregnancy

Over thirty years have elapsed since the first case of HIV infection was reported[6]. During this period, HIV has evolved from a fatal condition to a manageable chronic disease[7,8]. In 2012, 35.3 million people were living with HIV; 3.3 million of whom were children with more than 90% of them from Sub-Saharan Africa[6]. Although the number of new paediatric infections has reduced significantly from 350,000 in 2010 to 260,000 in 2012; more than 90% of these infections are through vertical transmission with over 95% of new paediatric infections occurring in Sub-Saharan Africa[7,8,9].

HIV infection can be transmitted through the following routes; unprotected sexual intercourse with an infected partner, injection or transfusion of contaminated blood or blood products (infection, through artificial insemination, skin grafts and organ transplants is also possible), sharing unsterilized injection equipment that has been previously used by someone who is infected, maternal-fetal transmission (during pregnancy, at birth, and through breastfeeding). In Sub-Saharan Africa, most infections among adults are through sexual contact while over 95% of pediatric infections are through vertical transmission from mother to child during pregnancy, delivery or breastfeeding period[6,7,10]. Without any intervention to prevent the transmission of HIV from mother to child, 15-30% of infants will get infected in utero or during delivery. An additional 10-15% of infections will occur during breastfeeding period[7,9,10].

Biologically, women are at higher risk of contracting HIV during sexual intercourse with an HIV infected male partner[11]. In addition, HIV prevalence among women of reproductive age has been linked to several socioeconomic and cultural factors[12]. Low financial income makes

women vulnerable by contributing to trans generational relationship and sex for money practices[6,12]. Migration within or across borders separates families; thereby making multiple concurrent partners common practices[12,13]. In Southern Africa where men leave their wives and spend several years in mines has been known to be one of the key factors in high HIV prevalence in South Africa and other Southern African countries[13]. Furthermore, in recent times there has been a surge of migration of women from rural to urban area of South Africa looking for jobs[13]. Social conditions in townships where these women live fueled by poverty further contribute their vulnerability in acquiring HIV infection[13]. Cultural practices that promote inequality between women and men make women vulnerable to acquiring HIV. In additional, sexual violence especially rape has been known to contribute to increase prevalence among women[6,12,13].

The HIV epidemic among adolescents and adults has stabilized in several African countries including South Africa[6]. Despite effort in preventing mother to child transmission of HIV, there is still a lot that needs to be done. Most especially to ensure pregnant women access antenatal care services during which interventions can be offered to those who are found to be HIV infected. In addition, there is need for male partner involvement considering the high number of sero-discordant relationships and the number of women who sero-convert during pregnancy[6,14]. With success in prevention of mother to child transmission of HIV, the number of children with HIV infection has been reduced, but the number of children who are exposed to HIV will remain high as long as the prevalence of HIV infection in women at reproductive ages remains high.

2.2 Perinatal outcomes in HIV infected Mothers

In developing countries one of the infections that is at epidemic level is HIV infection. HIV infected pregnant women are at increased risk for their own health and that of the foetus/new born infants[14]. Among women of reproductive health, HIV is a recognized leading cause of death[14,15]. In Sub-Saharan Africa, maternal mortality has continued to rise proportional to HIV prevalence in ANC attendees in recent years[15,16,17]. There are several hypotheses on how HIV and pregnancy interact. Whatever the case, there is immunological progression of the disease during pregnancy period and introduction of antiretroviral therapy before or during pregnancy has been shown to contribute positively to pregnancy outcomes[16,17,18].

In different studies, the excess risk of pregnancy-related mortality attributable to HIV among women who were HIV-infected (attributable risk) ranged from 174 per 100 000 pregnant women in South Africa[19] to 28386 per 100 000 pregnant women in Zimbabwe[20]. In a meta-analysis, Calvert et al found that overall, the pooled attributable risk from all the studies was 994 per 100 000 women (95% CI 677–1310)[21, 22, 23].

Different studies have given variable outcomes for infants born to HIV infected women. In a study in Botswana, Reitter et al, found that 36.5% of deliveries of HIV exposed infants were preterm[24]. Many studies in sub-Saharan African countries have shown that infants born to HIV-infected women have a significantly increased risk of low birth weight, preterm birth, neonatal mortality and infant mortality[25,26,27]. Kim and colleagues found that maternal HIV was associated with pregnancy loss and perinatal mortality[28]. They reported that maternal HIV disease affected infant health and survival directly via the risk of HIV transmission and indirectly via low birth weight and prematurity[28]. The effect of intrauterine HIV infection in

the infant was apparent by 70 days but excess neonatal mortality was primarily attributed to low birth weight and preterm birth independent of infant HIV status[28].

Global rates of mother-to-child HIV-1 transmission vary from region to region, depending on the infrastructures available to prevent vertical transmission of HIV; estimates range from 14 to 48% in the absence of appropriate prevention of mother-to-child HIV transmission (PMTCT) programmes[5,28,29,30]. In non-breastfeeding populations, in the era before optimised PMTCT activities, the risk of perinatal HIV transmission was in the region of 15–25%[29,30]. The variation in the rate of transmission may be due to maternal viral loads (mothers with elevated viral loads tend to transmit virus more effectively to their infants through the placental barrier in utero, or during the birth process)[30], or to the viral type (certain clades of HIV are more virulent, and more easily transmissible)[29,31,32]. Mock et al observed that one-third of infants infected in utero were *V*LBW deliveries, and report that VLBW is associated with in utero transmission of HIV[32]. Maternal HIV infection has been shown to be associated with a number of adverse perinatal outcomes, including preterm delivery and VLBW[32,33]. Brocklehurst and French, in a systematic review, reported that adverse perinatal outcomes related to maternal HIV infection include: IUGR, VLBW, and preterm delivery[33]. Laar et al found that maternal HIV infection status was associated with a VLBW prevalence of 23% among neonates born to HIV-positive women, compared to 14% among those born to HIV-negative women[34]. Comparatively, pre-term delivery was higher among HIV positive mothers (24% versus 14%)[34]. In a Cochrane review, Sturt et al demonstrated that VLBW was associated with use of antiretroviral therapy (ART) in HIV infected women[35]. Furthermore, Ekouevi et al conducted an observational study in a breast feeding population in the Ivory Coast, to determine the efficacy of highly active ART compared to a short-course prophylactic ART regimen in preventing vertical transmission of HIV from mothers to their

infants[36]. The risk of giving birth to a VLBW infant was significantly higher in the prolonged ART arm (31/139; 22%) compared to the short course ART arm (21/170; 12%), (Relative Risk [RR] 1.81; 95% Confidence Interval [CI], 1.09 - 3.0)[36]. Similarly, Tonwe-Gold et al, deriving their data from the Ivory Coast cohort mentioned above, demonstrated that VLBW occurred significantly more frequently in the ART arm (26%) than in the short course ART group (9%), (RR 2.17; 95% CI 1.23 - 3.81)[37].

2.3 Morbidities in infants born to HIV positive mothers

HIV is a major cause of infant and childhood morbidity and mortality especially in Sub-Saharan Africa[38]. HIV exposed infant is an infant born of HIV infected mother[38,39]. In a study, comparing HIV exposed to HIV unexposed infants, there was a 1.5-fold higher prevalence of anemia at 1 month of age among HIV exposed infants (20%, 32 of 160) compared with infants born to HIV-negative women (13.8%, 71 of 514)[40].

HIV co-infection with other infections are common in women living with HIV[40,41]. This increases the risk of such infections in HIV exposed infants e.g. syphilis, TB, and CMV[41,42,43]. Effect of HIV exposure on immune function in the foetus could result to immunosuppression, therefore increased risk of infection at birth, and during hospital stay (nosocomial infections). Immune response has been demonstrated in HIV exposed infants who are not infected. CD8+ immune responses to HIV-1 Env, Gag, and Nef proteins are present in peripheral blood of these infants shortly after birth[44]. De Maria and Rowland-Jones and colleagues demonstrated in separate studies that HIV-1-specific CD8+ IFN-γ responses have been detected in the peripheral blood of 25% of exposed uninfected infants between 15 to 50 months of age as well as in an uninfected infant using virus-specific stimulation[45, 46]. In addition, Legrand et al, showed that HIV exposed uninfected infants had higher levels of

CD4+, CD25+, CD1272 T-regulatory cells in neonatal cord blood, decreased T-cells activation levels thereby leading to increased risk of infection[47]. Further, they found that, there was augmented HIV-1 Gag, CD8+, IFN-*c*, CD4+ and IL-2 immune response in exposed-uninfected neonatal cord blood upon the removal of T-regulatory cells neonatal cord blood[47]. VLBW infants are more likely to be preterm, therefore at risk of developing NEC. HIV exposure has been implicated in development of NEC[40, 41, 42].

2.4 Infant mortality and HIV exposure

In Sub-Saharan Africa, HIV infection accounts for a significant mortality and morbidity in childhood especially in countries with a generalized epidemic[43]. Naniche et al, showed in a study in Mozambique that overall infant mortality was 2.3-fold higher in babies born to HIV-positive women than those born to HIV-negative women (p-0.002)[40]. Considering the timing of deaths, it was with post-neonatal deaths that differences were noted between HIV-exposed and unexposed infants. Infants born of HIV-positive mothers had a higher post neonatal mortality rate (7.8%, 15 of 193) than those born to HIV-negative mothers (1.9%, 12 of 623) ($p < 0.001$)[40]. However, Monebenimp et al found mortality to be similar between HIV exposed and HIV unexposed infants in a case control study in Yaoundé Cameroon[48].

2.5. Morbidity and mortality among VLBW infants

By definition, very low birth weight infants are those who have a birth weight less than 1500 grams[3,49]. Very low birth weight can be caused by preterm birth, intrauterine growth restriction, or a combination of both[49,50]. Ngoc, et al, reported that preterm delivery contributed up to 61% of children with low birth weight in six developing countries[51]. Considering determinants of low birth weight, small for gestational age and preterm delivery in Indonesia, Sebayang et al found constitutional, demographic and psychosocial factors,

toxic exposure, maternal nutrition and obstetric history and maternal morbidity during and prior to pregnancy to be key determinants[52]. Infants who weigh 2000-2499 g at birth have a four-fold higher risk of neonatal death than those who weigh 2500-2999 g, and a ten-fold higher risk than those weighing 3000 - 3499g[35,53].

VLBW infants are more susceptible to hypoglycaemia and to birth asphyxia[33]. In a substantial number of studies they suffered more diarrhoea and pneumonia for a few months after birth, explaining in part why LBW is also a risk factor for post neonatal death[1,33,54]. During the first weeks of life, wasted, LBW new-borns experienced more morbidity whereas stunted new-borns were more likely to die during this time [35,36].

Very low birth weight infants are prone to disease conditions ranging from infections to metabolic imbalance[39]. Infections associated with VLBW can be bacterial, fungal or viral. Up to a quarter of VLBW suffer from nosocomial infections with rates higher in lower weights and younger gestational age[54,55]. Staphylococcus species account for more than half of bacterial nosocomial infections[55]. Sepsis is associated with increased rate of intraventricular hemorrhage, periventricular leukomalacia, neurodevelopmental impairment, chronic lung disease, increased number of days on ventilator support[54,55,56]. These conditions occur as a result of the immature organs and immunological system of the VLBW infants[55,56].

In terms of fungal infections, they account for major cause of morbidity among VLBW and preterm infants. Aydemir et al demonstrated in a randomized clinical trial that prophylactic treatment of fungal infection among VLBW was associated with reduced mortality[57]. Viral infections can be acquired during intra-uterine period or peri-natally. In a systematic review and meta-analysis, Lanzieri et al demonstrated that VLBW infants are at increased risk of

perinatally acquired cytomegalovirus infection which leads to hepatopathy, respiratory distress syndrome, sepsis like syndrome, low white cell count, thrombocytopenia[42].

In a meta-analysis describing mortality among infants in East Africa, preterm delivery and low birth weight accounted for 52% of deaths[58]. In an audit of disease and mortality in neonatal ward in Johannesburg hospital, Ballot and colleagues reported extreme mulitorgan immaturity, hyaline membrane disease (HMD), asphyxia, necrotizing enterocolitis (NEC), nosocomial sepsis, septicaemia, congenital infection, intraventricular haemorrhage (IVH), congenital abnormality, pulmonary haemorrhage as leading causes of deaths among VLBW[59]. In a study in Iran, Nayeri reported a mortality rate of 33% in their ward. Some of the factors associated with mortality were respiratory distress syndrome, neurological complications, intraventricular hemorrhage, need for resuscitation at birth, low Apgar score and need for a ventilator[59].

CHAPTER 3: METHODOLOGY

3.1 Aim and Objectives

3.1.1 Aim

The aim was to determine the infant characteristics at birth, morbidity during hospital stay and mortality at hospital discharge of VLBW infants according to maternal HIV status.

3.1.2 Objectives

1. To describe demographic characteristics, clinical presentation and laboratory findings at birth of HIV-exposed and unexposed VLBW infants.
2. To determine the mortality rate in HIV-exposed VLBW infants.
3. To determine mortality rate in HIV-unexposed VLBW infants.
4. To compare the mortality rates between HIV exposed and unexposed VLBW infants.
5. To determine predictors of mortality in VLBW infants.

3.2 Methods

3.2.1 Study design

This was a retrospective cross sectional descriptive study.

3.2.2 Site of study

The study was carried out at Chris Hani Baragwanath Academic Hospital (CHBAH) Neonatal Unit. CHBAH is a tertiary health institution located in Soweto, Johannesburg in South Africa. The neonatal unit is made up of four wards, neonatal intensive care unit (level 3 nursery); transitional care unit or high care (level 2 nursery); ward 66 (a combination of level 1 and 2 nursery), and ward 40 (kangaroo mother care unit – level 1). The neonatal unit had

120 authorized beds but 160 usable beds (12 – NICU, 43- High care, 80- Ward 66, and 25 – KMC) during the period studied.

3.2.3 Study population

The hospital conducts about 22 000 live births per year, of which 3-5% were estimated to be VLBW (660 - 1100 infants). The study population was made up of all VLBW infants (infants born with a weight less than 1500 g) who survived and were admitted to the Neonatal Unit from 1st January to 30 June 2011.

3.2.4 Sample size

The primary outcome I focussed on was mortality rate. Assuming that the mortality rate in VLBW infants at CHBAH was 25% with a margin of error of 5% and confidence level of 95%, we needed to have a sample size of 245 VLBW infants. In order to accommodate for charts with missing outcome (mortality) I decided to enrol about 300 VLBW infants which required that I collected charts over a time period of 6 months (1st January to 30 June 2011).

3.2.5 Data collection

Variables were then extracted from patients' files and entered into an Excel spread sheet. Each file was given a code (numbered in order of folder review) and this code was linked to the data entered into the Excel sheet and the study participant anonymously so as to maintain confidentiality of study participants. A special form was designed to extract data from the hospital records. The data collected included maternal and infant demographic characteristics, maternal HIV-related laboratory results, clinical presentation and diagnosis at birth, laboratory findings in those who had blood tests done and outcomes (comorbidities and survival) to hospital discharge (data collection sheet in Appendix 1).

3.2.6 Data management and analysis

Data checking was done on all categorical and continuous variables captured for values that were not within plausible range and attempt was also made to check for missing values to authenticate that these values were actually missing. Data was collected in an Excel spread sheet and imported to STATA version 12 and Epi info version 7 for analysis.

Data was described using means and standard deviation for parametric continuous variables, and medians and ranges for non-parametric continuous variables. Categorical variables were described using percentages. Comparison of continuous measurements was done with a Student t-test where measurements were normal distributed and Mann-Whitney test where measurements were not normal distributed. Comparisons of categorical variables measurement were performed using a chi-square test. Statistical significance was set at 0.05. Univariate analysis was used to compare different variables between HIV-exposed and unexposed infants. Multivariable logistic regression was used to detect predictors of mortality in VLBW infants.

3.2.7 Ethics

Data collected was treated with confidentiality and anonymously using a coding system. The latter was a serial number allocation made of 4 digits preceded by the first alphabet of the ward to which the infant was first admitted to the CHBAH Neonatal Unit (for example if the first patient is from NICU the code was N0001, if from TC or High care the code was T0001, and if from Ward66 the code was W0001). Each file selected was given a code/identity number that links the file to the Excel data sheet. Only the principal investigator had access to the linked file. Application for ethics approval was made and obtained from the Human

Ethics Research Committee (HREC) of the University of the Witwatersrand (Appendix 2). Institutional approvals were obtained from the Chief Executive Officer of CHBAH, by application to the institution's Medical Advisory Committee (Appendix 3). As this was a retrospective record review, informed consent was not required from parents or caregivers.

CHAPTER 4: RESULTS

There were 546 VLBW infants admitted in the neonatal wards of CHBAH from 1st January to June 2011. The first 306 patient's records found were analyzed, 4 of these records did not have maternal HIV results, therefore were excluded. In total 302 VLBW infants had maternal HIV results and outcome recorded and therefore were included and analyzed for this research report.

4.1 Maternal characteristics

Out of the 302 infants included in this study, 103(34.1%) were born to mothers who were HIV positive (HIV-exposed). Maternal age ranged from 16 to 43 years with the median age of 26 years. Twelve (3.9%) women were aged less than 18 years with ten of them being HIV negative and two of them being HIV positive (p-0.1935). Mothers who were HIV positive were significantly older than HIV negative mothers, with a median age of 29 compared to 24 years ($p<0.001$) in HIV-negative mothers as shown in Table 1. Most mothers (72.5%) had more than 1 previous pregnancy with more HIV positive mothers having more than 1 previous pregnancy than HIV negative mothers ($p<0.001$). Eighty three percent of mothers attended antenatal care, and 51% delivered by caesarean section. There were no statistically significant differences in number of mothers who attended antenatal clinic during pregnancy, and those who delivered by caesarean section between HIV positive and HIV negative women ($p>0.05$). Among the 103 mothers who were HIV positive, 67 (65%) had recorded CD4 counts. The mean CD4 count was 323.4 (±186.3) cells/mm^3, with 59.7% of them having a CD4 count <350 cells/mm^3. Seventy nine mothers were on antiretroviral drugs, with 38 (48%) of them receiving HAART and the rest getting ARVs for PMTCT.

Table 4.1: Characteristics of mothers of very low birth weight infants admitted at CHBAH over the 6 month period

Variable	Total (N=302)	HIV-Positive (N=103)	HIV-Negative (N=199)	p-value
Median Maternal Age	26 (16-43)	29 (16-42)	24 (16-43)	<0.001
- Mothers <18 year old	12	10 (83%)	2 (17%)	0.1935
Gravidity**				<0.001
1	76 (27.1%)	10 (10.8%)	66 (35.1%)	
≥2	205 (72.9%)	83 (89.2%)	122 (64.9%)	
Antenatal Care***				0.5591
Yes	225 (83.3%)	70 (81.4%)	155 (84.2%)	
No	45 (16.7%)	16 (18.6%)	29 (15.8%)	
Mode of delivery****				0.4151
Vaginal	134 (48.6%)	41 (45.1%)	93 (50.3%)	
Abdominal	142 (51.4%)	50 (54.9%)	92 (49.7%)	

Note:
**Ten HIV positive and eleven HIV negative women did not have records of their gravidity
***Seventeen HIV positive and fifteen HIV negative women did not have records of antenatal booking status.
****Twelve HIV positive and fourteen HIV negative women did not have records of mode of delivery

4.2. Infants demographics and clinical characteristics of the study population

Table 2 shows the infant characteristics and clinical profile of the study population (for both HIV exposed and unexposed babies). Overall, almost all the infants were born before 36 weeks gestational age. There was no significant difference between HIV exposed and HIV unexposed infants in terms of gestational age (p-0.224). Fifty four percent of infants were females. About gender, there was no statistically significant difference between the HIV exposed and unexposed infants.

The median birth weight was 1220 grams. There were more babies with birth weight less than 1000 grams in the HIV exposed infants compared to HIV-unexposed (p-0.001). The mean head circumference and length at birth were 27.5±2.3 and 37.5±3.9 cm, respectively. HIV exposed infants had statistically significant smaller head circumference (p-0.003) and shorter length (p-0.006) at birth than HIV unexposed infants.

The median Apgar scores at 1 and 5 minutes were 7 and 9 respectively. There were more infants with Apgar score <7 at 1 minute (p-0.015) and at 5 minutes (p-0.030) in the HIV exposed infants. Sixty three percent of VLBW infants were exclusively breast fed. The HIV exposed infants were more likely to be exclusively formula fed (63.1%) than HIV unexposed infants 30.5% (p<0.001).

Table 4.2: Demographic and clinical characteristics of very low birth weight infants admitted at CHBAH over a 6 month period.

Variables	**Total (n=302)**	**HIV exposed n = 103**	**HIV unexposed n = 199**	**p-value**
Mean Gestational age (weeks)*		29.4 ±2.9	29.82 ± 2.7	0.224
<28	63 (21)	28 (27.7)	35 (17.6)	
28-32	196 (65.3)	60 (59.4)	136 (68.3)	
>32	41 (13.7)	13 (12.9)	28 (14.1)	
Female	164 (54.5)	59 (57.8)	105 (52.8)	0.400
Birth Weight**				0.001
Number weighing <1000 grams	88 (29.2)	42 (41.2)	46 (23.1)	
Number weighing 1000-1499 grams	213 (70.8)	60 (58.8)	153 (76.9)	
Body length at birth (cm)	37.5 ± 3.9	36.6± 4.0	38.0 ± 3.9	0.006
Head Circumference at birth (cm)	27.5 ± 2.3	26.9± 2.4	27.7 ±2.2	0.003
Apgar score at 1 minute***				0.015
0-6	122 (45.7)	50(55.0)	72 (40.9)	
7-10	145 (54.3)	41(45.0)	104 (59.1)	
Apgar score at 5 minutes****				0.030
0-6	38 (14.9)	18 (20.7)	20 (13.4)	
7-10	218 (85.1)	69 (79.3)	149 (86.6)	

Note:
* Two HIV exposed infants did not have records of gestational age
** One HIV exposed infant did not have record for birth weight
*** Twelve HIV exposed and twenty three HIV unexposed infants did not have records of Apgar score at one minute
****Sixteen HIV exposed infants and 30 HIV unexposed infants did not have records of Apgar score at five minutes.

4.3. Laboratory profile of study population (HIV exposed and HIV unexposed babies)

Table 4.3 describes clinical and clinical profile of HIV exposed and HIV unexposed infants. Eleven (3.4%) infant had congenital abnormalities. There was no statistical difference in

prevalence of congenital abnormalities between HIV-exposed and HIV-unexposed infants (p-0.631).

The commonest diagnosis on admission was respiratory distress syndrome (RDS) 220 (72.8%), followed by a combination of RDS and congenital pneumonia 78/281 (25.9%) and congenital pneumonia 4 (1.3%). There was no statistically significant difference between HIV exposed and unexposed infants in type of diagnoses on admission (p-0.250).

The mean white blood cell count, and platelet count at birth were 10.3 x 10^9cells/mm^3, and 198 x 10^9cells/mm^3 respectively. There were no significant differences between HIV exposed and HIV unexposed infants in these full blood count parameters (p-0.734). The mean C-reactive protein (CRP) was 3.1 with more than 95% of sick infants at birth having a CRP of less than ten. There were no differences between HIV exposed and HIV unexposed infants in CRP levels. There was no statistical difference between infants with positive blood cultures at birth in the sick HIV-exposed infants (7.1%) compared to the sick HIV-unexposed infants (4.9%), p-0.27.

Table 4.3: Clinical Presentation and Laboratory findings at birth in VLBW infants

Variables	Total N=302 (%)	HIV exposed n=103 (%)	HIV unexposed n=199 (%)	p-value
Congenital abnormalities*				0.631
No	286 (96.6)	98 (97.0)	188 (95.9)	
Yes	11 (3.4)	3 (3.0)	8 (4.1)	
Admission diagnosis				0.250
Respiratory Distress Syndrome	220 (72.8)	79 (35.9)	141 (70.9)	
Congenital Pneumonia	4 (1.3)	0 (0.0)	4 (2.0)	
Both of the above	78 (25.9)	24 (30.8)	54 (27.1)	
White blood cell count (x 10^9/L)**				0.734
No. with Wcc <9 x 10^9/ L	136 (91.3)	47 (82.5)	89 (96.7)	
No. with Wcc 9-30 x 10^9 /L	3 (2.0)	0 (0.0)	3 (3.3)	
No. with Wcc >30 x 10^9 /L	10 (6.7)	10 (17.5)	0 (0.0)	
Platelets count (x 10^9/L)***				0.350
No. with platelets <150 x 10^9 /L	75 (28.2)	27 (29.0)	48 (27.7)	
No. with platelets ≥150 x 10^9 /L	191 (71.8)	66 (71.0)	125 (72.3)	
CRP******				0.934
No. with CRP <10 mg/dL	241(94.5)	80 (94.1)	161(94.7)	
No. with CRP ≥10 mg/dL	14 (5.5)	5 (5.9)	9 (5.3)	
Blood culture at birth ***+**				0.270
Negative	255 (90.7)	84 (85.8)	171 (93.5)	
Positive	16 (5.7)	7 (7.1)	9 (4.9)	
Contaminants	10 (3.6)	7 (7.1)	3 (1.6)	

Note:
* Two HIV exposed infants and three HIV unexposed infants did not have record under congenital anomalies.
** Forty six HIV exposed and one hundred and seven HIV unexposed did not have record of white blood cells count measurement.
*** Ten HIV exposed and twenty six HIV unexposed did not have records of platelets count.
****Eighteen HIV exposed and twenty nine HIV unexposed infants did not have records of CRP results.
***** Five HIV exposed and sixteen HIV unexposed infants did not have records of blood culture at birth.
+ Six patients had Group B Streptococcus, ten patients had other microorganisms and ten had contaminants of Bacillus, CNS and corynebacterium.

4.4. Morbidity and mortality in VLBW infants

Table 4.4 shows distribution of co-morbidities and outcomes in VLBW infants. Other than the diagnoses made at the time of admission, the morbidities that were recorded in the infant records were suspected infections, necrotizing enterocolitis (NEC) and intraventricular infections. Overall 62.7% of VLBW infant had episodes of suspected nosocomial infections with more than half having more than one episode of suspected nosocomial infection during their stay in the hospital. There was no statistically significant difference between HIV exposed and HIV unexposed infants in number of episodes of infection (p-0.536).

Though 19.7% of VLBW infants had a working diagnosis of suspected NEC during their stay in hospital, only 3.6% had Stage 2 and/ or Stage 3 NEC. There were no differences in incidence of NEC or severe NEC between HIV-exposed and unexposed VLBW infants (17.2 vs 21.2%, p-0.465). Of the 63 infants who had records of cranial ultrasound having been done to exclude IVH, about two thirds (70%) had abnormal findings (Grade I-IV IVH) with HIV exposed infants having significantly more severe grades of IVH compared to HIV unexposed infants (p <0.001).

In terms of survival to hospital discharge of the 302 charts reviewed, only 296 had documented outcome at discharge. 216/296 (73.0%) infants were discharged while 80/296 (27.0%) infants died. HIV exposed infants were significantly at higher risk of dying than HIV unexposed infants (p<0.001).

Table 4.4: Morbidities and survival in VLBW infants

Variables	**Total**	**HIV exposed**	**HIV unexposed**	**p-value**
Nosocomial sepsis				0.144
No	101 (37.1)	32 (36.8)	69 (37.3)	
Yes	171 (62.9)	55 (63.2)	116 (62.7)	
Number of episodes of nosocomial sepsis				0.536
1-3	133 (53.2)	44 (55.0)	89 (52.4)	
>3	38 (15.2)	11 (13.7)	27 (15.9)	
Necrotizing enterocolitis				0.464
- No	240 (80.3)	84 (82.4)	156 (78.8)	
- Stage 1	49 (16.1)	13 (12.3)	36 (18.2	
- Stage 2	7 (2.3)	2 (2.0)	5 (2.5)	
- Stage 3	4 (1.3)	3 (2.9)	1 (0.5)	
Intraventricular haemorrhage				<0.001
Normal	17 (27.0)	4 (14.3)	13 (37.1)	
Grade 1-2	26 (41.3)	8 (28.6)	18 (51.4)	
Grade 3	11 (17.5)	9 (32.1)	2 (5.7)	
Grade 4	9 (14.3)	7 (25.0)	2 (5.7)	
Alive at hospital discharge				0.012
Yes	216 (73.0)	62 (62.4)	154 (79.0)	
No	80 (27.0)	39 (38.6)	41(21.0)	

4.5. Predictors of mortality in VLBW infants

Table 4.5 shows the analysis of predictors of mortality among all the VLBWI in the study. In the univariate analysis the factors associated with mortality were maternal HIV status (p-0.001), infant birth weight (p<0.001), gestational age (p<0.001), and Apgar score at 1 (p<0.001) and 5 minutes (p<0.001), and presence of congenital abnormalities (p-0.006). In a multivariate analysis, the only predictor of mortality was infant birth weight (p<0.001). Congenital abnormalities had a trend toward significance (p-0.063).

Table 4.5: Predictors of mortality in all VLBWI

Variables	**Survivors (n=216)**	**Non-survivors (n= 80)**	**Univariate analysis**	**Multivariate analysis**
			p-value	p-value
Mean maternal age in years (±SD)	27.0 ± 6.7	27.7 ± 7.1	0.452	-
Median maternal gravidity*	2 (1-8)	2 (1-8)	0.809	-
Percent attended antenatal care	85.79%	78.57%	0.158	-
Maternal HIV status positive	28.70%	48.75%	0.002	0.342
Percent delivered abdominal	45.81%	52.86%	0.308	-
Mean birth weight in grams (±SD)	1216 ± 175	930 ± 232	<0.001	<0.001
Mean gestational age in weeks (±SD)	30.4 ± 2.5	27.8 ± 2.7	<0.001	0.106
Percent with male sex	43.52%	51.85%	0.124	-
Median Apgar score 1 minute*	7 (1-10)	5 (1-9)	<0.001	0.559
Median Apgar score 5 minutes*	9 (1-10)	7 (1-9)	<0.001	0.103
Percent with congenital abnormalities	1.9%	8.6%	0.012	0.063

* - Numbers in parenthesis are Ranges
SD – Standard Deviation

Table 4.6 shows analysis for predictors of mortality among VLBW infants who were HIV-unexposed. In univariate analysis the factors associated with mortality in the HIV-unexposed infants were birth weight (p<0.001), gestational age (p<0.001), Apgar score at 1 minute

(p<0.001), and 5 minutes (p<0.001), and congenital abnormality (p-0.043). In a multivariate analysis, predictor of mortality among this subgroup was infant birth weight (p<0.001).

Table 4.6: Predictors of mortality in HIV-unexposed VLBW infants

Variables	**Survivors (n= 154)**	**Non- Survivors (n=41)**	**Univariate analysis**	**Multivariate analysis**
			p-value	p-value
Mean maternal age in years (±SD)	26.3 ± 6.9	24.9 ± 6.5	0.268	-
Median maternal gravidity*	2 (1-7)	2 (1-5)	0.558	-
Percent attended antenatal care	85.42%	81.08%	0.610	-
Percent delivered abdominal	46.58%	61.11%	0.138	-
Mean birth weight in grams (±SD)	1218 ± 181	984 ± 264	<0.001	<0.001
Mean gestational age in weeks (±SD)	30.3 ± 2.5	28.0 ± 3.0	<0.001	0.993
Percent with male sex	44.81%	56.10%	0.198	-
Median Apgar score at 1 minute*	8 (1-10)	6 (2-9)	<0.001	0.275
Median Apgar score at 5 minutes*	9 (0-10)	7 (4-9)	<0.001	0.164
Percent with congenital abnormalities	2.65%	9.76%	0.043	0.480

* - Numbers in parenthesis are Ranges
SD – Standard Deviation

Table 4.7 shows analysis of predictors of mortality among HIV exposed VLBW infants. Univariate analysis revealed that factors that were associated with increased risk for mortality in HIV exposed VLBW infants were birth weight (p<0.001), gestational age (p<0.001), Apgar score at 1 minute (p<0.001), and 5 minutes (p<0.001), diagnosis at birth (p<0.010) and congenital abnormalities which tends toward statistically significant value (p-0.052). In multivariate analysis, the predictors of mortality in this subgroup included infant birth weight (p-0.002) and gestational age (p-0.018).

Table 4.7: Predictors of mortality among the HIV-exposed VLBWI

Variables	**Survivors (n= 62)**	**Non-Survivors (n= 39)**	**Univariate analysis** p-value	**Multivariate analysis** p-value
Mean maternal age in years (±SD)	29.0 ± 5.9	30.9 ± 6.4	0.143	-
Median maternal gravidity*	3 (1-8)	2 (1-8)	0.517	-
Percent attended antenatal care	86.79%	75.00%	0.240	-
Percent delivered abdominal	43.86%	45.45%	0.528	-
Mean birth weight in grams (±SD)	1212 ± 161	884 ± 176	<0.001	0.002
Mean gestational age in weeks (±SD)	30.5 ± 2.5	27.5 ± 2.5	<0.001	0.018
Percent male sex	40.32%	46.15%	0.353	-
Median Apgar score 1 minute*	7 (1-10)	5 (4-9)	<0.001	0.637
Median Apgar score 5 minutes*	9 (6-10)	7 (2-10)	<0.001	0.520
Percent with congenital abnormalities	0	7.89%	0.052	-

* - Number in parenthesis are Ranges,
SD – Standard deviation

CHAPTER 5: DISCUSSION

This study was carried out to determine clinical diagnosis, laboratory findings at birth, morbidity during hospital stay and outcome (discharge or dead) among HIV unexposed and HIV exposed very low birth weight infants admitted at CHBAH. Charts of very low birth weight infants were reviewed and relevant variables extracted, entered into excel data base, cleaned and uploaded into Stata and Epi info for analysis.

The major findings of this study were as follows about a third of mothers giving birth to VLBW infants were HIV positive, with about 60% of those with recorded CD4 counts having counts <350; and HIV positive mothers were more likely to give birth to ELBW infants. HIV exposed infants had lower Apgar scores at 1 and 5 minutes, and those who had cranial sonar were more likely to have severe IVHs. The mortality rate was higher in HIV exposed infants and the predictor of mortality was birth weight in all VLBW irrespective of maternal HIV status. However among HIV exposed infants gestational age significantly predicted mortality in addition to birth weight.

World Health Organisation states that in order to improve pregnancy outcomes, women must start antenatal care early in the first trimester and have at least four ANC visits in a low risk pregnancy[7]. It is important to note that women whose records were reviewed in our study, almost half attended their first ANC in the first trimester. South Africa is known with high ANC attendance which contributes significantly to the quality of care[60]. HIV prevalence among ANC attendees in South Africa especially in Gauteng has remained high over the years and our study population demonstrated this high prevalence although there is a slight drop compared to findings by Ballot and colleagues in the similar setting such as Charlotte Maxeke academic hospital[38]. The high prevalence in such settings may be explained by the

fact that being a referral hospital, most of the time other lower health institution send patients with complications among whom are HIV infected pregnant women.

Recent South African PMTCT guidelines call for the classification of advanced immunological HIV status to be CD4<350 cells/ml for which pregnant women must be initiated on ART for their own health [61,62]. These guidelines were implemented after the period of this study, therefore a large number of mothers were not on HAART. Two thirds of records of the participants, who tested HIV positive, had a CD4 count less than 350cells/ml. So the change in PMTCT guidelines implies that more patients will be put on HAART, therefore future studies will be able to look at the effect of HAART on morbidity and mortality in VLBW[62,63].

Several factors are known to contribute to the delivery of very low birth weight infants[63,64]. Of importance is prematurity which in some cases is coupled with intra-uterine growth restriction[63,64]. Of the infants reviewed in this study none were term, the peak age being between 28 and 32 weeks gestational age. Findings in this study suggest that infections play an important role as a large number of babies were diagnosed with congenital pneumonia at birth.

HIV exposure through the mother was found to be one of the factors associated with higher mortality[35,37]. This calls for more research to find out why HIV exposed infants who were known not to be HIV infected died more than HIV unexposed. It may be useful to assess the functional response of this immature immune system when it developed in the HIV environment[37]. Ballot and colleagues demonstrated that the survival rate of VLBW was 70.5% in Charlotte Maxeke Johannesburg Academic hospital in 2006/2007. In this patient

population, 36% of infants were HIV exposed although the testing rate among mothers was only 69%[38].

While comparing HIV exposed and HIV unexposed infants, of all the characteristics, there was no significant difference between the two groups of infants except the final outcome of mortality where HIV exposed infants were one and half time more likely to die compared to HIV unexposed. Despite the fact that close to one third of HIV women were on ART at the time of review, there was no difference in weight among the infants. It has been reported that intrauterine exposure to ARV especially AZT is associated with VLBW[35,36,64]. In our study there was no documentation of various regimens of women and the timing of initiation of ART as it relates to pregnancy.

The implication of this study shows that HIV exposure increases the risk of death among VLBW infants. Key factors associated with mortality are birth weight and gestational age. Considering the high HIV prevalence among ANC attendees, it is important to put in place systems that will retain HIV positive pregnant women in care with appropriate documentation to facilitate monitoring. There may be need to carry out a prospective study to understand causes of mortality among VLBW infants. Unavailability of quality data in the clinical records on important variables such as HIV status, DNA PCR results, CD4 and antiretroviral regimen calls for concern on the quality of documentation.

This study had several limitations. I used retrospective data which were not initially designed for research purpose. As such there were several data elements missing in the records. In addition, this was a cross sectional study which was unable to give the overall picture of the management of VLBW infants. Furthermore, this study was carried out only in one hospital which, being a tertiary institution makes the findings not generalizable.

In conclusion, HIV prevalence among women of reproductive age remains high. This calls for more strategies in improving primary prevention which is the first pillar of comprehensive prevention of mother to child transmission of HIV. Though on univariate analysis maternal HIV status was associated with mortality in VLBW infants, this effect was not found on multivariate analysis. Therefore the final conclusion from this study is that birth weight is the main predictor of survival in VLBW infants, not the maternal HIV status.

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Appendix 1: Data collection form

	1	2	3	4
Study Number				
DOB				
1 = Female, 2 = Male				
Birth weight (g)				
Birth head circumference (cm)				
Birth length (cm)				
APGAR Score at 1, 5, 10 minutes				
Gestational Age (weeks)				
Admission diagnosis: Respiratory distress at birth, 1 = Hyaline membrane disease, 2 = Congenital pneumonia,3 = Other (specify)				
Ever Ventilated in NICU? 0 = No, 1 = Yes				
Date of NICU admission				
Date of NICU discharge				
Length of mechanical ventilation (days)				
Surfactant administered? 0 = No, 1 = Yes				
Number of doses of surfactant				
Congenital abnormality: 0 = No, 1 = Yes				
Type of congenital abnormality				
STORCH infection: 0 = Not investigated for, 1 =Yes, 2 = No				
Type of STORCH infection				
Congenital sepsis/pneumonia 0 = No, 1 = Yes, 2 = Suspected				
Birth blood culture result				
Birth WCC				
Birth Plt count				
Nosocomial sepsis: 0 = No, 1 = Yes				
Number of courses of antibiotics during hospital stay				
Date of NVP start				
Date of HIV PCR test				
HIV PCR Result: 0 = Negative, 1 = Positive				
Date of start of cotrimoxazole prophylaxis				
Discharge Diagnoses: 1 = HMD, 2 = Congenital pneumonia,3 = Other (specify)				
Outcome: 1 = Discharged, 2 = Died, 3 = Refused hospital treatment				
Discharge weight (g)				
Discharge head circumference (cm)				
Discharge length (cm)				
Mother's hospital number (for purposes of retrieval of results)				
Maternal HIV status: 0 = Negative, 1 = Positive				
Maternal CD4 count				
Date Maternal CD4 Count				
Maternal Viral Load				
Feeding choice: 1 = Exclusive breastfeeding, 2 = Exclusive formula feeding, 3 = Mixed feeding				
Maternal PMTCT: 0 = No, 1 = Yes, 2 = Not applicable				
Maternal ART (for HIV-infected mother only): 0 = No, 1 = Yes				

Appendix 2: Ethic clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Tiam Myowa

CLEARANCE CERTIFICATE	**M120142**
PROJECT	Effect of Materal Human Immunodeficiency irus Status on Outcomes of Very Low Birth Weight Infants at Chris Hani Baragwanath Academic Hospital
INVESTIGATORS	Dr Tiam Myowa.
DEPARTMENT	Department of Paediatrics/Neonatal Unit
DATE CONSIDERED	27/01/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 27/01/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof Sithe Velaphi

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix 3: Approval Letter from Hospital CEO

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 10 February 2012

TITLE OF PROJECT: Effect of maternal human immunodeficiency virus status on outcomes of very low birth weight infants at Chris Hani Baragwanath Academic Hospital

UNIVERSITY: Witwatersrand:

Principal Investigator: Dr MM Tiam

Department: Paediatrics

Supervisor (If relevant): Prof S Velaphi

Permission Head Department (where research conducted): Yes

Date of start of proposed study: April 2012

Date of completion of data collection: May 2012

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

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Recommended

(On behalf of the MAC)

Date: 10 February 2012

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Dr. P. LINGHAM.
Dep CEO,

Approved/~~Not Approved~~

Hospital Management

Date: 14 FEB 2012.