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Outcomes of very low birthweight babies born to HIV positive mothers

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OUTCOMES OF VERY LOW BIRTHWEIGHT BABIES BORN TO HIV POSITIVE MOTHERS

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Obstetrics and Gynaecology

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DECLARATION

I, Serilla Moodley, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Obstetrics and Gynaecology in the University of the Witwatersrand, Johannesburg. It has not been submitted before any degree or examination at this or any other University.

Signature: _____

Date: _____

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Dedication

This research report is dedicated to my late father, Yaganathan ‘Sonny’ Moodley. ‘Dad, you were and still are my inspiration’.

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ABSTRACT

Introduction

Birthweight is one of the major determinants of child survival. Very low birthweight babies are those that weigh < 1500g at birth. They constitute a major burden on a community's resources. Likewise, the effect of HIV is a major burden to bear. The effect of HIV on very low birthweight and very low birthweight on HIV has not been extensively studied in South Africa.

Objectives

To compare the perinatal outcomes of very low birthweight babies born to HIV positive and negative mothers.

Methods

This was a retrospective cross-sectional analysis of maternal and neonatal data from November 2006 until April 2007. Live infants weighing ≥ 500g and < 1500g who were born at Chris Hani Baragwanath Hospital were included.

Results

Data from 279 maternal records was analysed. Maternal HIV infection was present in 39% of women. The rate of maternal hypertension was 23% in HIV positive and 38% in HIV negative mothers. The mean gestational age was 27.7 weeks for HIV exposed and 28.6 weeks for HIV unexposed babies. The overall rate of respiratory distress syndrome was 95%. Fifty percent of these babies received respiratory support. For babies < 1000g the mortality was 60% for HIV exposed and 73% for HIV unexposed. For those babies ≥ 1000g the mortality was 19% for HIV exposed and 14% for HIV unexposed, but this was not statistically significant (p value 0.28). Mortality was 100% for babies < 750g and 10% for those more than 1249g. There was no significant difference in the rate of necrotising enterocolitis, severe intraventricular haemorrhage or chronic lung disease between HIV exposed and unexposed babies (23% vs. 22%, 13% vs. 10%, and 9% vs. 9% respectively).

Conclusion

There is no significant difference in neonatal outcomes between HIV exposed and unexposed very low birthweight babies.

ABBREVIATIONS

AIDS	- acquired immunodeficiency syndrome
APH	- antepartum haemorrhage
ARVs	- antiretrovirals
CD4	- cluster of differentiation 4
CI	- confidence interval
CLD	- chronic lung disease
CPAP	- continuous positive airway pressure
CMJAH	- Charlotte Maxeke Johannesburg Academic Hospital
ELBW	- extremely low birthweight
HAART	- highly active antiretroviral therapy
HIV	- human immunodeficiency virus
HMD	- hyaline membrane disease
IQR	- interquartile range
IUGR	- intrauterine growth restriction
LBW	- low birthweight
MTCT	- mother to child transmission
NEC	- necrotising enterocolitis
NICHD	- National Institute of Child Health and Human Development
NICU	- neonatal intensive care unit
OR	- odds ratio
PCR	- polymerase chain reaction
PPROM	- preterm prelabour rupture of membranes
PMTCT	- prevention of mother to child transmission
RDS	- respiratory distress syndrome

Rh	- rhesus
RPR	- rapid plasma reagin
RR	- relative risk
SIVH	- severe intraventricular haemorrhage
SGA	- small for gestational age
VLBW	- very low birthweight

1. **Introduction**

Birthweight is one of the major determinants of child survival. Very low birthweight (VLBW) babies are those that weigh less than 1500g at birth and extremely low birthweight (ELBW) babies are those that weigh less than 1000g at birth. These babies constitute a major financial and social burden on a community. They utilize sophisticated health care resources for prolonged periods of time and place a major demand on health care systems. Although they represent a small percentage of live births (1-2%), they account for more than 50% of overall neonatal mortality (1). This impacts heavily on resource poor countries like South Africa. At Chris Hani Baragwanath Hospital between 2000-2002, Velaphi reported the VLBW rate at 3% (2). Although this was a small proportion of total live births, this accounted for one quarter to one fifth of all admissions into the neonatal intensive care unit (NICU) and for 50% of all deaths in the unit.

The effect of HIV is also a major burden to bear. Children born to mothers infected with HIV have a higher mortality than those born to uninfected mothers, and in Africa, the mortality of these infants is higher than in the developed world (3). HIV is associated with high rates of prematurity, low birthweight (LBW) infants (<2500g), small for gestational age (SGA) and miscarriage (4). The effect of maternal HIV on infant birthweight has substantial significance because LBW has a strong influence on neonatal morbidity and mortality (3). The influence of HIV on VLBW, and VLBW on HIV has not been extensively studied in South Africa.

1.1. **Risk factors associated with VLBW babies**

Maternal Risk Factors

HIV positive mothers are at greater risk of having a LBW baby than their seronegative counterparts (5). In New York, Markson *et al*. found 29% of HIV positive women and 9.3% of HIV negative women had LBW babies (4). They found that when compared to women in the general population without any medical risk factors, HIV positive women had 2.2 times higher adjusted odds of a LBW baby. Although the adjusted odds ratio of 1.9 for LBW was also increased in women in the general population with medical risk factors, this was still not as high as for HIV positive women. In these women antiretroviral usage reduced the LBW rate, but a CD4 count below 200/µl and advanced HIV disease were risk factors for LBW. Similarly in Zaire, Ryder *et al*. found higher LBW rates in women with advanced HIV disease (6). The LBW rate was 32% for women with AIDS, 16.9% for HIV-infected women without AIDS, and 9.8% for uninfected women. In that study no distinction was made between LBW and VLBW infants.

A study in Georgia, USA, showed the best predictor of VLBW was a history of a previous VLBW delivery (7). The authors found that the VLBW rate remained unchanged from 1994-1996 to 2003-2005. There was a decrease in the rate of first VLBW deliveries, and a significant increase in subsequent VLBW deliveries. Recurrent VLBW accounted for up to 16% of all VLBW deliveries.

Antenatal care or rather lack thereof may also be associated with a risk of VLBW babies. In the developing world, studies carried out in Turkey and India found VLBW rates to be 11.3% and 44% respectively in unbooked mothers (8, 9). Similarly

in a case control study in Chiawelo, Soweto, Ndiweni and Buchmann looked at 91 unbooked mothers and compared them to 91 booked mothers matched for birthweight and 67% of these infants weighed < 1500g (10).

In general, other maternal factors associated with LBW include preterm prelabour rupture of membranes (PPROM), hypertensive diseases, antepartum haemorrhage (APH), intrauterine growth restriction (IUGR), cardiac or respiratory disease, smoking, alcohol abuse, and maternal infections such as intestinal parasites and malaria (11, 12). In South Africa, Odendaal *et al.* found that among 227 mothers who delivered VLBW babies at Tygerberg Hospital between March 1997 and August 1997, the primary obstetric causes for delivery were hypertensive disease, preterm labour, PPROM, intrauterine death, APH and congenital abnormalities (11).The authors did not elaborate on the HIV status of the patients or the impact of maternal HIV on VLBW babies.

Wei *et al.* found LBW to be the most important predictor of neonatal mortality(13). In this randomized trial, LBW and not in utero HIV infection was associated with increased neonatal mortality. In utero infection with HIV was however the foremost risk factor for post neonatal mortality. Among 823 singletons, LBW was strongly related to neonatal mortality (relative risk 5.14; 95% confidence interval 2.31-11.39). The large sample size and frequent testing for HIV transmission gave this study a power to detect the association between LBW and infant mortality. LBW was associated with a two fold increased risk of infant mortality (RR = 2.4; 95% CI 1.45-3.95). This is similar to a follow up study of a cohort of over 4000 pregnant women in

rural Uganda where the most important determinant of child survival was found to be maternal HIV status and low birthweight (14).

Fetal risk factors

In utero infection with HIV may be of significance (15, 16). Some studies have shown that infants who are HIV-infected in utero may be more likely to have low birthweight, as HIV may be associated with IUGR (4). In Tanzania it was shown that a positive infant HIV status at birth as measured by polymerase chain reaction (PCR) was associated with a significantly lower birthweight (12). Fetal HIV infection appeared to contribute to poor intrauterine growth independent of maternal disease progression. In this study maternal confounders such as stage of HIV disease and immunological disease progression were accounted for, and HIV infected neonates weighed 178g less after adjustment for risk factors.

It is not clear whether in utero infection leads to poor fetal growth or if fetal growth impairment predisposes the fetus to increased risk of HIV infection. While some studies from industrialized countries have found an inverse relation between HIV infection and birthweight, others report no association. In Malawi, Taha *et al.* in a prospective study of 1385 children born to HIV positive and negative mothers found no significant difference in the mean birthweight between HIV infected and uninfected infants (2956.1g vs 2864.8g for infected and uninfected children respectively; t=-1.6, p=0.11) (3). However, these finding may be biased as infants who seroconverted in the first 12 to 18 months of life were compared to seronegative infants. No clear distinction was made between in utero transmission and postnatal transmission. In Zimbabwe, Marinda *et al*. looked at infants born to 4495 HIV positive women (17). They found the risk for in utero HIV transmission to be

inversely related to birth weight. 16% of these infants were LBW. Of these, 24 % were infected in utero, 22 % intrapartum and 14 % tested negative at 6 weeks.

Other infections that have been shown to be associated with low birthweight include intrauterine bacterial infections, malaria and helminthic infections (11).

In North Carolina in the USA, Dolfus *et al.* found over a 5 year period, congenital abnormalities accounted for 4.7 % of all VLBW deliveries (18). In the Tygerberg study 1.3% of all VLBW infants had congenital abnormalities (11). This was less than expected but could be explained by the fact that the South African study was a smaller cross sectional descriptive study and congenital abnormalities were only diagnosed in 3 patients, of which there were 2 singletons and 1 twin pregnancy.

1.2**. Maternal HIV and prematurity**

Taha *et al*. found the incidence of prematurity in HIV exposed babies to be 12.5% vs. 3.8% in unexposed babies (3). According to the European Collaborative Study, mothers with CD4 counts below 200/µl are at increased risk of premature delivery (19). The prematurity could be as a result of maternal HIV itself, or due to associated chorioamnionitis. There has been well documented evidence of a higher incidence of chorioamnionitis in HIV positive mothers (3,20). In utero infection with HIV is also associated with a higher risk of prematurity (21). HIV-associated prematurity thus contributes to LBW.

1.3. **Maternal HIV and infant mortality**

Mortality rates of infants born to HIV infected mothers are high. In the Malawian study, significant differences in mortality rates for normal birthweight and LBW infants between seropositive and seronegative mothers were shown (3). The mortality rates for normal birthweight infants were 23% and 8% in HIV positive and HIV negative women respectively. For LBW infants the corresponding rates were significantly higher, 42% vs. 18% for HIV positive and HIV negative women respectively. Again, no distinction was made between LBW and VLBW infants.

Bourne *et al.* in the Western Cape, South Africa, looked at infant mortality for the period 1997- 2002 (22). They noted an increased risk of infant mortality at 2-3 months of age in HIV exposed infants. They attributed this risk to either intrapartum or in utero infection with HIV. This is similar to a finding by Chopra *et al.* who showed a mortality risk of 10% for infants born to HIV positive mothers and 4% for infants born to HIV negative mothers (RR 2.25, 95% CI 1.34-5.62) (15). In the Chopra study, the baseline HIV test on infants was done at 3 weeks. A positive HIV result at this time was found to be one of the strongest risk factors for infant death.

In Zimbabwe, Marinda *et al.* found that infants born to HIV positive mothers were 16 times more likely to die compared to non-exposed infants (17). But, unlike Chopra *et al.* they found that uninfected infants of infected mothers have twice the mortality risk of infants born to uninfected mothers (15). The two year mortality was 67.5%, 65.1%, 33.2% for those infected in utero, intrapartum, and postnatally respectively.

Some studies have shown that mothers of HIV infected babies are more likely to have AIDS, and that those with AIDS are at a higher risk of having a VLBW baby (14,17). Furthermore, babies born to mothers who are at an advanced stage of the disease are at increased risk of death, regardless of the status of the infant (23). This could be because these mothers are unable to take care of their children due to their poor physical condition.

Brocklehurst and French found that HIV positive women are at increased risk of LBW infants, preterm delivery and IUGR (24). These adverse pregnancy outcomes have been associated with vertical transmission of HIV and increased mortality among infected children (3,12).

1.4. **VLBW rates**

The rate of VLBW babies born to HIV positive mothers has been reported at 3.3% in a study in the USA (21). The Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection Study Group looked at 600 live-born infants of HIV-infected mothers. The rate of prematurity was 19%, LBW 18.3% and VLBW 3.3%. This rate was noted to be high for that population. In South Africa, at Chris Hani Baragwanath Hospital, between 2000 and 2002 Velaphi found a VLBW rate of 3% (2), while the group at Tygerberg Hospital (11) found a rate of 8.8%. At a peripheral facility in Kwa Zulu Natal, Bondi found that VLBW babies accounted for 3.7% of all admissions to that NICU (25). Chris Hani Baragwanath Hospital, Tygerberg Hospital and Madadeni hospital all served as referral hospitals for the surrounding areas. None of these studies distinguished between HIV exposed and unexposed babies.

1.5. **Transmission of HIV**

According to the South African National Antenatal Survey 2010, the local prevalence of HIV infection in pregnant women was 29.4% (26). The World Health Organisation has reported that the mother-to-infant transmission rate prior to PMTCT in developing countries is 21-43% (27).The majority of transmission occurs late in pregnancy, during labour or delivery. Marinda *et al.* have reported higher intrapartum than in utero transmission rates (508/4495 vs 382/4495) (28). In Kenya, Mwanyumba *et al.* found that LBW is a significant risk factor for HIV transmission during the peripartum period (15). Here it was shown that the rate of intrauterine transmission was 5.1%, with 20.1% of the exposed infants becoming infected during the intrapartum period.

In South Africa, in the Western Cape, Kirsten *et al.* looked at 141 VLBW infants born to 122 HIV positive mothers. During the study period the overall mother to child HIV transmission rate in the Western Cape was 6% (31). They tested infants at 14 weeks and concluded the HIV transmission rate for HIV exposed VLBW infants was 15%. This is lower than 22% found in Malawi (3) but higher than the overall 6% noted in the Western Cape.

In a prospective study in Baltimore, Nair *et al.* looked at 134 infants born to HIV positive mothers to determine factors associated with vertical transmission HIV (20). The authors found that LBW, IUGR, maternal chorioamnionitis and neonatal infections were significantly associated with vertical transmission of HIV. LBW had the strongest association, and multiple logistic regression analysis showed that LBW had the highest risk for HIV transmission (OR 3.26, 95% CI 1.40, 7.58). Maternal

chorioamnionitis was found in 16.2% of infected infants and 5.8% of uninfected infants. Landesman *et al.* in the Women and Infants Transmission study found a similar association between LBW and vertical transmission of HIV (31). This was a prospective multicentre observational study of HIV infected women. They noted that HIV transmission was significantly associated with low CD4 count (less than 225/µl), prematurity, low birthweight and chorioamnionitis.

This is similar to the trend in industrialized countries. In the USA in the 1990s (21) it was found that there was a significant association between gestational age at delivery and infant HIV infection. In their study population of 600 live-born infants to HIV infected mothers, the rate of prematurity was 19%. These infants had a high rate of HIV infection (30.7%), and this rate decreased as gestation increased.

1.6. Neonatal outcomes

With the advent of better neonatal care and ventilation, the survival of VLBW babies has steadily been improving, with rates of 85% being reported in the USA (32). However, survival of VLBW babies in developing countries is low, with rates varying between 43% - 70% (9, 33). This is mainly due to a lack of resources and neonatal care available for VLBW babies. At Chris Hani Baragwanth Hospital between 2000-2002, 12% of admissions to NICU died and VLBW babies constituted 53% of these deaths (2). Among the VLBW infants the overall survival rate was 70%. Due to resource constraints infants weighing less than 1000g were not offered mechanical ventilation. After excluding infants less than 1000g the survival rate was 82%. At Charlotte Maxeke Johannesburg Academic Hospital, Ballot did a retrospective record review and looked at 474 records of VLBW babies born between July 2006 and June 2007 (34). The overall survival rates of VLBW babies was 70.5%; 70% of HIV

exposed babies and 80% of HIV unexposed survived to discharge (p value 0.057, OR 0.61). Similar rates were found in Tygerberg, where 80% of HIV exposed VLBW babies survived to discharge (30).

At a level 2 nursery in Madadeni, Bondi *et al.* reported that the survival rate of VLBW babies born between 1993 and 2005 to be 28.7% (25). The authors noted an increase in the survival rates in the 2002-2005 cohort compared to 1993-2001 group (40.8% vs 21.1% respectively), following the implementation of various intervention programmes. The low survival rates, compared to facilities in tertiary care centres, could be related to the lack of ventilator support and only nasal CPAP being offered in the nursery.

However, with better survival of VLBW babies comes an increase in morbidities. The causes of major morbidity include severe intraventricular haemorrhage (SIVH), chronic lung disease (CLD) and necrotising enterocolitis (NEC). The minor morbidity includes respiratory distress syndrome (RDS) and neonatal sepsis. Morbidity is influenced by variables such as antenatal steroid use, surfactant use, mode of delivery and ventilatory support (35, 36). This morbidity could also be related to the interventions used to prolong the survival of VLBW babies. Little is known about these morbidities in VLBW babies born to HIV positive mothers. The Ballot study found the incidence of HMD to be 68%, with 41% requiring ventilatory support, but HIV infected and HIV negative babies were not distinguished (34). In the USA 30% of VLBW infants that survived to discharge had major complications with 22% having CLD (33). The Tygerberg group followed up VLBW babies to 12 months (33). At discharge 18.8% had IVH and 19.6% had CLD. At 12 months only 3% had

severe motor developmental abnormalities. Again, no distinction was made between HIV infected and HIV negative babies.

1.7. Implications of HIV

What is known?

HIV infection on its own is a serious condition and difficult to manage. HIV infection in pregnancy is associated with risks of miscarriage, preterm birth, low birthweight, small for gestational age and increased incidence of genital tract infections (21, 37).

What is not known?

There have been studies showing outcomes of LBW babies in both developing and developed countries. Some studies have examined the outcomes of VLBW babies, but few have shown outcomes in VLBW babies born to HIV positive mothers in South Africa.

The Objective

The objective of this study was to highlight the effect, if any, of maternal HIV infection on neonatal outcome. This included any effect on morbidity as well as any differences in mortality rates.

2. METHODS

2.1. Design

This was a retrospective cross-sectional analytical study.

2.2 Ethics approval

The study was approved by the Ethics Committee of the University of the Witwatersrand for research on human subjects.

Ethics number MO61121 (Appendix A)

2.3. Setting

This study was conducted at Chris Hani Baragwanath Hospital in Johannesburg. This is a secondary and tertiary level hospital that serves as a referral centre for the surrounding regions. There were 23 511 deliveries in 2007. The VLBW rate for 2007 was 3.3%. The maternity ward is equipped to handle any complication of labour and delivery.

The neonatal intensive care unit (NICU) has 12 beds with equipment for mechanical ventilation. There are 33 high care beds with facilities for continuous positive airway pressure (CPAP). The NICU and high care areas are able to provide surfactant treatment and care for preterm babies. At the time of the study there was a minimum weight limit of 1000g for ventilation, although babies between 900 and 1000g were considered on an individual basis. Babies are admitted to the NICU regardless of the maternal HIV status.

2.4. Study population

Maternal and neonatal data was extracted from patient records from November 2006 to April 2007. Only live births less than 1500g but more than or equal to 500g were considered. Babies born outside Chris Hani Baragwanath but brought to the labour ward nursery were not considered eligible.

2.5. Data abstraction

The names of eligible babies were obtained from the labour ward-nursery register. Maternal files were then obtained from the onsite file storage room in the maternity department. Neonatal files were obtained from the paediatric record room. The necessary information was entered onto a data collection form which was then used for analysis. The neonates were followed up until death or discharge.

2.6. Sample size

A sample calculation was made based on an HIV seropositivity rate of 40% in women who gave birth to VLBW babies. To show a difference in neonatal death rate of 38% vs. 22% for HIV positive and HIV negative mothers, a sample of 290 infants was needed, assuming a statistical significance of 0.05 and a power of 80%.

2.7. Patient information

Patient information included sociodemographic variables. Maternal and neonatal data were collected according to common definitions as described in standard texts.

The following maternal data was recorded:

- Antenatal care status. A patient was defined as unbooked if she did not receive any antenatal care
- Rh (rhesus) status, RPR status, HIV status and CD4 count
- Best estimate of gestational age. This was obtained by a combination of early ultrasound (before 24 weeks), date of last menstrual period, and palpation
- Parity, presence of cardiac disease, diabetes, epilepsy, or AIDS-defining condition
- Preterm prelabour rupture of membranes (PPROM) was defined as rupture of membranes before the onset of labour, at less than 37 weeks gestation
- Maternal hypertension, taken as hypertension (SBP $\geq$ 140 or DBP $\geq$ 90 mmHg $\geq$ 4 hours apart) occurring at any gestation. It was not further classified into chronic hypertension or pre-eclampsia
- Intrauterine growth restriction (IUGR), diagnosed clinically by palpation or by ultrasound scan
- Genital tract infection, diagnosed if there was any such infection that was recorded on the antenatal card and required treatment. This included both bacterial vaginosis and candidiasis
- Antepartum haemorrhage (APH), smoking, drug or alcohol use
- History of previous preterm labour, defined as any birth that occurred before 34 weeks gestation
- Mode of delivery recorded as either normal vaginal delivery, vaginal breech delivery, or caesarean section. Complications occurring during the delivery were recorded. These included problems encountered during the second stage of labour, or at the time of delivery at caesarean section

- Antenatal corticosteroids, with the number of doses given

The neonatal profile included the following:

- Birthweight and sex
- Apgar scores, recorded at 1, 5 and 10 minutes
- The use of nevirapine and the HIV-PCR results, if applicable or available
- Duration of stay until discharge or death
- Chronic Lung disease (CLD), defined as oxygen dependence after 28 days of life
- Necrotising enterocolitis (NEC) of any grade
- Severe intraventricular haemorrhage (SIVH) grades 3 or 4, detected after ultrasound examination of the brain.
- Respiratory distress syndrome (RDS) including any baby that was clinically distressed at birth and still required supplemental oxygen 24 hours after delivery
- Ventilatory support either the need for ventilation or CPAP
- Infection occurring in the first 3 days of life, taken to be early onset infection and after the first 3 days taken to be late onset infection, usually with positive blood cultures
- The use of surfactant together with the number of doses given
- Jaundice, defined as any bilirubin level that necessitated the baby receiving phototherapy or exchange transfusion as per American Association of Paediatrics guidelines
- Anaemia, defined as a haemoglobin level $\leq$ 12g/dl, that required the baby receive a blood transfusion

- Fundoscopy was not routinely performed on babies during their stay in hospital. If retinopathy of prematurity was suspected, the babies were sent to the ophthalmologists upon discharge

2.8. Data analysis

The data was analysed using the Epi-info 6 statistical package. Frequencies with percentages, means ± standard deviations, medians with ranges and interquartile ranges (IQR) were recorded. Comparisons of outcomes were done using Student's t-test and Mann-Whitney test for continuous variables and the Chi-square test and Fischer's exact test for discrete variables. Statistical significance was accepted at p-values less than 0.05.

3. RESULTS

Three hundred and twenty six maternal records were collected. Data from 47 records was not included as these neonatal files could not be located. Two hundred and seventy nine maternal records were analysed with 308 infants weighing less than 1500g at birth (this included births from multiple pregnancies). 16 infants were not included, either due to birthweight ≥ 1500g or being stillborn. The overall distribution of gestational ages is shown in Table 1. Half of mothers (50%, 131/263), were between 25 and 28 weeks pregnant and 6% (17/263) were more than 32 weeks pregnant. The mean gestational age was 28.2 weeks. The mean birthweight was 1095± 238g. Sixteen mothers who arrived in hospital being unbooked, or lacking information on gestational age could not be included on this table.

Gestational age (weeks)	Distribution (n=263)
22	1
23	6
24	16
25	24
26	34
27	37
28	38
29	36
30	39
31	5
32	14
33	9
≥34	4
Unknown	16

Table.1 **Distribution of gestational ages**

Table 2 shows the maternal profile. Sixteen percent (45/279) of women did not receive any antenatal care. Thirty-nine percent were HIV positive (108/279), 57% were HIV negative and 4% were not tested. Only one woman received highly active antiretroviral therapy (HAART). Seventy five (27%) women had CD4 counts tested. The mean CD4 count was 379.5±263 (range 4-1088/µl) and 21% had a CD4 count less than 200/µl. Only 36% (39/108) of HIV positive mothers received nevirapine before delivery.

Amongst the unbooked women, 24/45 tested HIV negative, 17/45 tested HIV positive and 4/45 had unknown HIV status. Only 5/17 women who were HIV positive received nevirapine.

The mean maternal age was 27.5±6.9 years. The median parity was 2 (range 1-8, IQR 1-3). There were 116 primiparous and 163 multiparous patients. Twenty-six percent (42/163) had a previous preterm delivery. There were no patients with recorded drug abuse. Fifty-nine percent of mothers had steroids; 35% of these had 1 dose and 65% had 2 doses. The steroid used was betamethasone given at a dose of 12mg intramuscularly, 12 hours apart. There were 45 multiple pregnancies, all being twin deliveries.

Table 2. **Demographic and obstetric data for mothers**
(n=279 maternal records, n=308 neonatal records)

Maternal profile	N	%
Unbooked	45/279	16
HIV positive	108/279	39
Rh positive*	263/278	95
RPR positive*	3/278	1
Highly active antiretrovirals†	1/108	1
$CD_4 < 200/\mu l$†	23/108	21
Maternal nevirapine use†	39/108	36
Cardiac disease	2/279	0.7
Diabetes mellitus	2/279	0.7
Epilepsy	4/279	1.4
AIDS defining condition†	10/108	9
Preterm rupture of membranes*	41/234	15
Spontaneous preterm labour	150/279	54
Maternal hypertension	88/279	32
Antepartum haemorrhage	24/279	9
Intrauterine growth restriction	32/279	11
Previous preterm delivery‡	42/163	26
Sexually transmitted disease	15/279	5
Smoking	4/279	1
Alcohol	3/279	1
Use of recreational drugs	0/279	0
Caesarean section	126/308	41
Complications during delivery at caesarean section*	7/124	6
Received steroids	164/279	59
Twin pregnancy	45/279	16

Footnote * Incomplete denominators due to missing data
† The denominator denotes HIV positive mothers only
‡ The denominator refers to multiparous women only

Forty-nine percent (152/308) of babies were born by normal vaginal delivery, 10% (30/308) by vaginal breech delivery, and 41% (126/308) had caesarean sections. The vaginal breech deliveries had the most complications at delivery 20%; 6/30 while 2%; 3/127 of the vaginal vertex deliveries and 6%; 7/124 of the caesarean sections had complications. The complications refer to difficulty during delivery of the newborn as documented in the maternal records. The HIV status did not impact on the mode of delivery. Forty two percent (75/179) of HIV unexposed babies and 40% (47/118) of HIV exposed babies were delivered by caesarean section. Babies weighing ≥ 1000g had a higher rate of caesarean section than those less than 1000g (106/197; 54% vs 33/100; 33% respectively).

Table 3 shows the neonatal profile. Sixty-six percent (203/308) of VLBW babies survived to discharge. Fifty-one percent (157/308) of babies were male, and 49% (151/308) were female. One hundred and eighteen babies were exposed to HIV. Seventy three percent (86/118) of HIV exposed infants had nevirapine at birth. Seventeen did not (14%), and in 15, (13%) there was insufficient information. PCR results from 26 infants were available, and 5/26 (19%; 95% confidence interval 7-40%) babies were found to be HIV infected. Twenty-seven were not eligible for PCR, due to demise before 6 weeks. Sixty-five HIV exposed babies were lost to follow up and PCR results could not be obtained.

Fifty percent of babies (153/305) received respiratory support (mechanical ventilation and/or CPAP). Sixteen percent received ventilation only, and 16% had both ventilation and CPAP. The babies who were ventilated had a median duration on the

ventilator of 5 days (IQR 2-8) and those who received CPAP, had a median duration of 2 days (IQR 1-3).

One hundred and eighty one babies received steroids (181/301) and of these 53 (29.3%) died. One hundred and twenty babies did not receive steroids of which 51 (42.5%) died (p=0.02). Twenty-one percent (66/305) of babies received surfactant, 57(19%) had 1 dose and 6 (2%) had 2 doses. Twenty-one (31.8%) of those babies that received surfactant died and of those who did not (n=239), 84 (35.1%) died (P=0.61). Twelve percent (37/308) had early onset infection and 44% (134/308) had late onset infection. Ballard scores and assessment of IUGR/SGA was not consistent. Initial assessment of neonates was carried out by different health care professionals all at different levels of training.

Table 3. **Neonatal outcomes** (n=308)

Neonatal profile	n	%
Male infant	157/308	51
Apgar <7 at 1 min	132/273*	48
Apgar <7 at 5 min	46/226*	20
HIV exposed neonates	118/308	38
Nevirapine	86/118†	73
PCR-HIV positive (n=26)	5/26*	19
Chronic lung disease	28/308	9
Necrotising enterocolitis	68/308	22
Severe intraventricular haemorrhage	34/308	11
Jaundice	171/308	56
Anaemia	71/308	23
Early onset infection	37/308	12
Late onset infection	134/308	44
Death	105/308	34
Respiratory distress syndrome	293/308	95
Ventilation only	49/305*	16
CPAP only	55/305*	18
Both ventilation & CPAP	49/305*	16
Surfactant	66/305*	21

* Incomplete denominators due to missing data

† Denominator refers to HIV exposed babies only

The maternal profile of HIV negative and HIV positive women is shown in Table 4. The HIV negative women were on average a year younger than the HIV positive women. Although the rate of PPROM was slightly higher in the HIV positive group, this was not statistically significant. In HIV negative women the incidence of maternal hypertension was 38%, significantly higher than in the HIV positive group (p=0.015). The caesarean section rate was similar in both groups with 42% of HIV negative and 40% of HIV positive mothers having operative deliveries. The mean gestational age at delivery was significantly lower in the HIV infected group (27.7±2.4) than the HIV negative group (28.6±2.6) (p=0.006).

Table 4. **Demographic and obstetric data of mothers according to HIV serostatus** (n=268, mothers whose HIV results are known)

	HIV -	**HIV +**	p-value
Unbooked	(22/160) **14%**	(17/108) **16%**	0.65
Age (yr)	**27.1** ± 7.2	**28.6** ± 6.2	0.08
Preterm prelabour rupture of membranes	**(**20/159)* **13%**	(20/106)* **19%**	0.16
Spontaneous preterm labour	(86/160) **54%**	(57/107)* **53%**	0.93
Maternal hypertension	(60/160) **38%**	(25/107)* **23%**	0.015
Gestational age(wks)	**28.6** ± 2.6	**27.7** ± 2.4	0.006

* Incomplete denominator due to missing data

The neonatal profile does not show any significant differences between HIV-unexposed and HIV exposed babies (Table 5). The mean birthweight was similar in the two groups (1098±247.2g and 1085±224.4g respectively). The median duration of stay in hospital for the survivors was 37 days for HIV unexposed and 40 days for HIV exposed babies (p=0.13).

There were no significant differences in rates of major neonatal morbidities. SIVH was more frequent in the HIV exposed group (15/116; 13% vs 17/117; 10%) but this was not statistically significant. The incidences of respiratory distress and ventilatory requirements were high in both groups. The frequency of early and late onset of infection was slightly higher in the HIV exposed group but this difference was not statistically significant. There was 34% (60/177) mortality in the HIV unexposed and 33% (39/117) in the HIV exposed group.

Table 5. **Profile of HIV unexposed and HIV exposed babies**

	HIV-unexposed		**HIV-exposed**		p-value
Chronic lung disease	(16/177)	**9%**	(11/117)	**9%**	0.92
Necrotising enterocolitis	(39/177)	**22%**	(27/117)	**23%**	0.83
Severe intraventricular haemorrhage	(17/177)	**10%**	(15/116)*	**13%**	0.31
Respiratory distress syndrome	(169/177)	**95%**	(112/117)	**96%**	0.92
Ventilation	(55/177)	**31%**	(37/117)	**32%**	0.92
Continuous positive airway pressure	(62/177)	**35%**	(41/117)	**35%**	1
Early onset infection	(21/177)	**12%**	(16/117)	**14%**	0.65
Late onset Infection	(75/177)	**42%**	(55/117)	**47%**	0.43
Death	(60/177)	**34%**	(39/117)	**33%**	0.92
Surfactant	(40/177)	**23%**	(25/117)	**21%**	0.8
Jaundice	(101/177)	**7%**	(67/117)	**57%**	0.97
Anaemia	(41/177)	**23%**	(29/117)	**25%**	0.75

*Missing information due to incomplete data

Mortality rates for the newborns decreased with increasing birthweight. Mortality was 100% (24/24) for babies < 750g, 58% (46/80) for babies of 750-999g, 24% (25/103) for babies of 1000-1249g and 10% (10/98) for those ≥ 1250g, (Figure 1).

It was also shown that the duration of stay for the survivors decreased as the weight increased (from 750g). The median duration of stay for those < 750g was only two days (all demised) and infants > 1250g, 28.5 days (Figure 2).

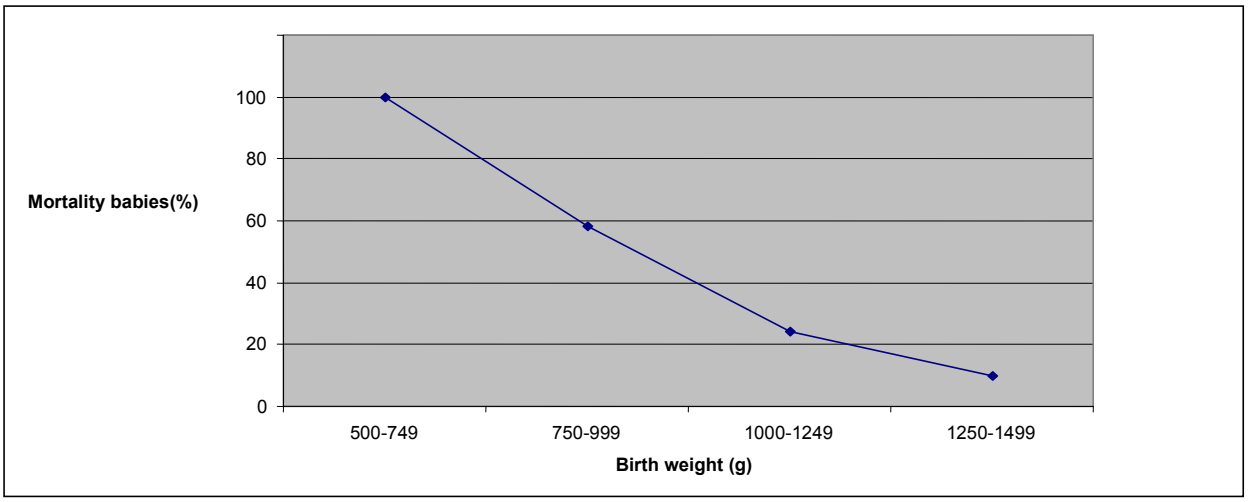


Fig.1 **Percentage of mortality of newborns according to birthweight categories**

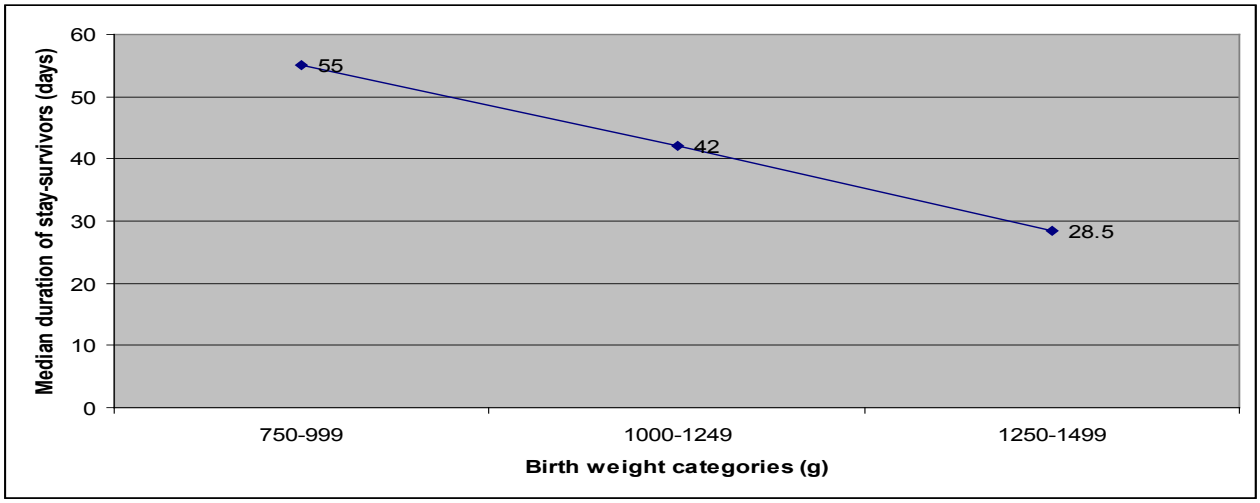


Fig. 2 **Relationship between duration of stay and weight of surviving infants**

When comparing the outcomes of HIV unexposed and HIV exposed babies, two weight categories were selected : <1000g and ≥1000g.

For babies < 1000g (extremely low birthweight) there was no significant difference in outcomes (Table 5). Both HIV exposed and HIV unexposed babies had similar gestational ages and birthweights. The average length of hospitalisation of survivors was similar (58.5 days for HIV unexposed and 55.5 days for HIV exposed babies). The rates of NEC and SIVH in HIV unexposed and HIV exposed babies were 12% vs. 15%, and 5% vs. 15% respectively. The incidence of CLD was 7% in HIV unexposed and 13% in HIV exposed. Late onset infection was slightly more frequent in the HIV exposed than unexposed group (17/40; 43% vs 23/60; 38%) respectively. The mortality rate was slightly higher in the HIV unexposed group. None of these differences were statistically significant.

In the group with babies ≥ 1000g, the only statistically significant difference was the recorded gestational age at birth (Table 7). The gestational age for babies born to HIV exposed mothers was 7 days less than those born to HIV unexposed mothers. This difference did not extend to a difference in birthweight. The median duration of stay in hospital for the survivors was similar. There was no difference in the incidence of CLD, NEC or SIVH. HIV exposed babies had more early and late onset infection but this difference was not statistically significant. They also had a higher mortality rate (19% vs. 14%) but this difference was also not statistically significant.

Both groups had high rates of respiratory distress. There was no statistical difference between the HIV unexposed and HIV exposed groups. More of those babies ≥ 1000g received mechanical ventilation than those < 1000g. Forty percent and 36% of the

HIV unexposed and HIV exposed respectively (p-value=0.59), in the group ≥ 1000g; and 13% and 23% respectively (p-value=0.23) in the group less than 1000g received mechanical ventilation. The opposite was true for CPAP requirements. There was no difference in the duration of ventilation or CPAP for HIV unexposed and HIV exposed babies in both groups. Thirteen percent of the babies < 1000g had surfactant and twenty-five percent of babies ≥ 1000g received surfactant.

Table 6. **Neonatal outcome with birthweight < 1000g according to HIVexposure**

		HIV unexposed (n=60)	HIV exposed (n=40)	p – value
Gestational age	n=100	Mean 26.5±4.1 (n=54)*	Mean 26.4±3.3 (n=38)*	0.9
Birthweight	n=100	1094±244	1077±221	0.58
Duration of stay of survivors	n=32	Median 58.5 Range 25-81 IQR 44.5-66 (n=16)	Median 55.5 Range 35-216 IQR 48-59.5 (n=16)	0.72
Chronic lung disease	n=100	4(7%)	5(13%)	0.26
Necrotising enterocolitis	n=100	7(12%)	6(15%)	0.63
Severe intraventricular haemorrhage	n=100	3(5%)	6(15%)	0.15
Early onset infection	n=100	3(5%)	2(5%)	1.00
Late onset infection	n=100	23(38%)	17(43%)	0.68
Jaundice	n=100	21(35%)	16(40%)	0.62
Anaemia	n=100	13(22%)	8(20%)	0.84
Caesarean section	n=100	20(33%)	13(33%)	1.00
Respiratory distress syndrome	n=100	60(100%)	38(95%)	0.16
Continuous positive airway pressure	n=100	29(48%)	19(48%)	0.93
Death	n=100	44(73%)	24(60%)	0.16

* Incomplete denominators due to missing data

Table 7. **Neonatal outcome with birthweight ≥ 1000g according to HIV exposure**

		HIV unexposed	HIV exposed	p-value
Gestational age	n=163*	Mean 29.6±2.5 (n=100)	Mean 28.6±2.4 (n=63)	0.01
Birthweight	n=197	1242±148	1213±144	0.18
Duration of stay of survivors	n=162†	Median 34 Range 2-92 IQR 25-45 (n=101)	Median 35 Range 9-96 IQR 28-46 (n=61)	0.36
Chronic lung disease	n=194*	12/117(10%)	6/77(8%)	0.56
Necrotising enterocolitis	n=194*	32/117(27%)	21/77(27%)	0.99
Severe intraventricular haemorrhage	n=193*	14/117(12%)	9/76(12%)	0.98
Early onset infection	n=194*	18/117(15%)	14/77(18%)	0.61
Late onset infection	n=194*	52/117(44%)	38/77(49%)	0.5
Jaundice	n=194*	80/117(68%)	51/77(66%)	0.76
Anaemia	n=194*	28/117(24%)	21/56(38%)	0.76
Caesarean section	n=197	62/119(52%)	44/78(56%)	0.55
Respiratory distress syndrome	n=194*	109/117(93%)	74/77(96%)	0.39
Continuous positive airway pressure	n=194*	33/117(28%)	21/77(27%)	0.89
Death	n=194*	16/117(14%)	15/77(19%)	0.28

* Incomplete denominators due to missing data

† Denominator refers to survivors only

4. DISCUSSION

This study has shown the outcomes of VLBW babies born to HIV positive mothers from November 2006 till April 2007, at Chris Hani Baragwanath hospital. Thirty-nine percent of pregnant women giving birth to these infants were HIV positive. This was somewhat higher than the prevalence of HIV (30%) in the pregnant population in South Africa at the time of the study. It is known that HIV positive mothers are at a higher risk of prematurity and LBW babies (4). As this study was carried out only on VLBW babies, it is not surprising that the population of women studied had a relatively high HIV seroprevalence.

4.1. Perinatal risk factors

Sixteen percent of the study population did not receive any antenatal care. Fourteen percent of HIV negative and 16% of HIV positive mothers were unbooked. This lack of antenatal care is high but in keeping with findings from other developing countries (8,9). Lack of antenatal care may not necessarily lead to poorer neonatal outcomes as shown by Ndiweni and Buchmann (10). Although the authors found the incidence of VLBW babies to be high among unbooked mothers, they also noted that birthweight adjusted perinatal mortality rates of babies born to booked and unbooked mothers were similar. Unbooked patients were of low risk, often presenting because of preterm complications before their intended first antenatal visit.

In my study the consequence of being unbooked is that many mothers did not know their HIV status prior to delivery and were not able to receive prophylactic nevirapine. This may impact on the transmission of HIV to the neonates (27)

and ultimately the neonatal outcome. High rates of transmission in VLBW babies can be confounded by failure to book and to receive NVP before delivery. Unfortunately, no solid inferences in this regard can be made from the data as a large number of babies did not have PCR results.

Many mothers who presented in preterm labour often presented in the late stages of labour and missed out on the opportunity for steroids. This explains the low rate of antenatal steroid use (59%). This could contribute to the high rate of respiratory distress (38).

The rate of multiparous women (26%) who had had a previous preterm delivery was not influenced by HIV status but was higher than the 15.2% found in New Delhi and the 16% in Georgia (9,7). This high rate could impact on the VLBW rate in this study, similar to the Georgian study which found the strongest risk factor for a VLBW birth to be a previous VLBW birth (7).

The overall rate of maternal hypertension (32%) is comparable to previous findings (8). The rate of maternal hypertension was significantly higher in HIV negative than positive mothers (38% vs. 23%, p-value = 0.015). This begs the question whether HIV is protective against gestational hypertension. In a study at Chris Hani Baragwanath hospital Frank *et al.* found that HIV infected mothers less than 37 weeks at delivery had lower rates of proteinuric hypertension (8.4%) than their HIV negative counterparts (15.3%) (39). This could be related to the fact

that some mothers give birth before pre-eclampsia can develop. In HIV infected women the contribution of spontaneous preterm labour to VLBW rates is greater than the contribution of hypertension.

The high rate of spontaneous preterm labour was similar in both HIV negative and positive mothers, but is higher than that reported in a Pretoria study (40). It may be that in my study population there was a high rate of underlying infection which could have resulted in spontaneous preterm labour but which was not detected clinically and hence not documented in the notes. The rate of PPROM was slightly higher in the HIV infected group, but this difference was not statistically significant. The Pretoria study looked at babies less than 2000g and the rate of spontaneous preterm labour was 20%. The authors did not distinguish between HIV positive and negative patients.

4.2. HIV and antenatal risks

The average gestational age was lower in the HIV infected mothers by almost one week. This is similar to a finding by Kumar *et al.* where the mean gestational age was 9 days less in HIV infected mothers (41). This outcome could be related to the higher rate of preterm birth in HIV infected mothers (3, 4). There are conflicting reports on the mean birthweights of babies born to HIV infected mothers (21). In this study there was no statistical difference in the mean birthweights between HIV exposed and unexposed babies.

Among the HIV infected women one was on HAART. Twenty three had CD4 counts less than 200 and should have been on HAART. Some of the mothers who were unbooked only had their HIV status disclosed to them after delivery. Also, with late

booking many mothers may only get ARVs in the third trimester and present in preterm labour before this can happen. None of the patients with an AIDS-defining condition were on ARVs. Many of the HIV exposed babies did not receive nevirapine at birth. As mentioned previously this could be because many mothers did not know their HIV status prior to delivery. More effort should be placed into finding out the mothers' status so that the babies could benefit from the use of nevirapine (27). At the time of the study the ARV rollout programme was not fully implemented.

The overall caesarean section rate in this study was 41%. It is possible that the method of delivery could confound the neonatal outcome. A study by Muhuri *et al.* found mixed results for neonatal outcome of babies delivered by caesarean and vaginal delivery (42). They found that VLBW babies who had a caesarean section for breech presentation had decreased neonatal mortality risk. Babies between 500 and 749g with vertex presentation who had a caesarean section also fared better. Babies between 1250 and 1499g with vertex presentation had an increased neonatal mortality risk when a caesarean section was done. In this study complications at delivery of a breech was highest with vaginal breech deliveries. This could have an influence on neonatal outcome, similar to the Brothwood study, which found breech deliveries and birth asphyxia to be of important prognostic significance for poor neurodevelopmental outcome in ELBW infants (35). Here, low 5 minute apgar scores, the need for ventilation and IVH occurred more frequently in babies who subsequently died.

The overall transmission rate (of HIV) is 19% but this figure is based on the results of only a small number of babies and has a wide 95% confidence interval. Many mothers did not come back with their infants for follow-up, as a result HIV-PCR results were

only obtained for a few infants. Because of these limitations this study can make no conclusions about MTCT of HIV in VLBW infants.

4.3. Neonatal outcomes

Among major morbidities, the slightly higher rates of NEC (any grade) and SIVH in HIV exposed babies were not statistically significant. The overall incidence of CLD (9%) was less than the 28% reported in the USA and less than the 19% reported from Tygerberg (21, 33). This could be related to that fact that more preterm babies in the developed world survive long enough to develop CLD, whereas in this study there was a high mortality in the VLBW babies.

The overall rate of respiratory distress was high (95%) with no difference between HIV unexposed and exposed babies. Fifty percent of all distressed babies received respiratory support, either mechanical ventilation or CPAP support. Bigger babies (more than 1000g) received more mechanical ventilation and less CPAP than the smaller babies. In our institution smaller babies are not prioritised for respiratory support because there is an undersupply of NICU beds. Preference is given to those babies who are expected to have a better outcome. And as bigger babies are better candidates for ventilation, those less than 1000g were provided with the next best option, CPAP.

Babies were not discriminated whether to receive ventilation on the basis of their mothers' HIV status. Both groups (HIV negative and positive) had a similar duration on the ventilator or CPAP support, and had a similar duration of stay in hospital. This is in keeping with a finding by Martin *et al.* where the incidence of neonatal distress

was not higher than expected in HIV-exposed infants (when prematurity and birthweight were adjusted for) (21).

Twenty-one percent received surfactant with no difference between the HIV exposed and unexposed babies. This is similar to that in the Turkish study where 24.8% received surfactant (8). This could have improved neonatal outcomes for those babies whose mothers did not receive antenatal steroids.

Hyperbilirubinaemia and sepsis were the commonest minor morbidities. Early onset of sepsis (12%) was less than in the Turkish study and less than would have been expected taking into account the rate of HIV exposed (8). Late onset of sepsis (44%) was higher than that reported in Turkey. Ahmed *et al.* in Bangladesh found that the commonest reason for mortality in VLBW to be neonatal infections (43). They found the mortality to be 71.4% in neonates diagnosed with sepsis. The high incidence of late onset sepsis in my study could actually be erroneous, in that it is actually early onset of infection that was just not recognised timeously. Another possible explanation could be overcrowding in the NICU. If it is a true reflection of the sepsis present then it is quite disturbing that there is such a high incidence of nosocomial infection present. There was no significant difference in the rates of sepsis between HIV exposed and HIV unexposed infants.

4.4. Survival of VLBW babies

Sixty-six percent of VLBW infants survived to discharge with no difference between HIV exposed and unexposed babies. The survival of VLBW babies ranged from 0% (500-749g) to 90% (1250-1499g). Compared with statistics from the National

Institute of Child Health and Human Development Neonatal Research Network (NICHD) this rate is low (46). This rate is slightly higher than the 56.7% found in the Bangladesh study.

At Chris Hani Baragwanath the reason for the poor outcome of infants < 750g is attributed to the fact that only minimal resources are allocated to ensure the survival of these infants. At the time of the study these infants were not prioritised for ventilation and babies less than 900g generally did not qualify for ventilation. Rather, they were provided with supportive treatment such as headbox oxygen and intravenous fluids. It must be noted though, that each case was considered individually and this would explain why a few of the babies less than 750g received CPAP. The trend of increasing survival with increasing birthweight is similar to that seen in other studies (8, 9, 44). This is because at higher gestational ages the neonatal organs are more mature and better equipped to deal with extrauterine life.

The ELBW survivors had a longer duration of stay in hospital than babies more than 1000g. In New Delhi, India, it was found that ELBW constituted less than 1% of all live births but exhausted a large amount of hospital resources in terms of bed occupancy and duration of stay (9). When taking into account the strained resources available at our institution, it is possible that putting any effort into ensuring the survival of babies less than 750g is futile. And since babies between 750-999g have a 43% survival rate, careful consideration should be given into putting more effort into ensuring their survival.

VLBW babies are not just an immediate problem in terms of their ventilation and survival, but thought has to be given to the consequences of ventilation or the insults they are exposed to during the neonatal period. They are prone to many complications including, CLD, SIVH and NEC, and as a result of this have prolonged hospital stays. In this study these complications were prevalent in both the HIV exposed and unexposed babies.

5. LIMITATIONS

The results of this study are limited by the fact that there was missing data for many of the variables. Many of the maternal and neonatal records did not contain all the required information. Data for three neonates was incomplete as they were transferred out to other institutions. All VLBW babies born at Chris Hani Baragwanath hospital were not followed. Forty seven neonatal records could not be located and only those with available data were included in the study. The large number of PCR results that are not available makes it difficult to comment on the transmission rate of HIV to the neonates. The small number also makes it difficult to infer information on neonatal outcomes of HIV exposed babies born to mothers with low CD4 counts.

6. CONCLUSION

There is a paucity of information regarding the outcomes of VLBW babies born to HIV positive mothers in developing countries. This study confirmed the high mortality rates in babies less than 750g but did not elicit any major differences in

morbidities or mortality between HIV exposed and unexposed neonates. Further research is required to illustrate the effect of maternal HIV on neonatal outcome.

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APPENDIX A

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Moodley

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER MO61121**
PROJECT	Outcomes of very low birthweight babies born to HIV positive mothers
INVESTIGATORS	dr S Moodley
DEPARTMENT	Obs & Gynaecology
DATE CONSIDERED	06.11.24
DECISION OF THE COMMITTEE*	APPROVED UNCONDITIONALLY

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

DATE 07.01.26 **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof EJ Buchmann

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 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 B

Data capture sheet Date of delivery:

Record no.			
Age		Parity	
Rh		RPR	
RVD	Yes	No	Unknown
ARV'S		Start date	
CD_4		No. completed mnths RX	
NVP given	Yes	No	Unknown
Medical condition Cardiac diabetes epilepsy AIDS defining dx		Pregnancy complxns PROM SPTL PET APH IUGR	
STD		Prev hx prem	
Smoking Drugs Alcohol		Mode of delivery	
Complications during delivery		Use of steroids	
Gestational age	LMP	U/S	HOF

Neonatal outcomes			
Birthweight		Sex	
Apgars		NVP	
Date of admission		Date of discharge	
HIV-PCR			
Chronic lung disease		NEC	
Severe IVH		RDS	
Ventilator support		ROP	
Early onset infection		Late onset infection	
Outcome/Death		Surfactant	