# Transmission rates of HIV-1 and the mortality rate in high risk infants exposed to HIV, in the PMTCT programme, at the Neonatal unit, of King Edward VIII$^{th}$ Hospital, Durban, South Africa

**Submitted to:**

**NELSON R. MANDELA SCHOOL OF MEDICINE**

**UNIVERSITY OF KWAZULU-NATAL DURBAN**

**SOUTH AFRICA**

For:

Submitted in partial fulfilment of the academic requirements for the degree:

**Master of Medical Science in Clinical HIV/AIDS Management in the Department of Enhancing Care Initiative, University of KwaZulu-Natal.**

The dissertation contributes 50% of the qualification.


**BY**

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**As the candidate's supervisor I agree to the submission of this dissertation.**

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- Post Grad. Ref No. : 973119099 Date Approved: 18 October 2011
- BREC Ref No. : BE 254/010 Date Approved: 18 October 2011

21 October 2012

# ABSTRACT / SUMMARY


## Introduction

Previous studies have established that infants born to mothers with advanced HIV disease and co-infections are smaller, premature and have rapidly progressive HIV disease and an early death. King Edward VIII$^{th}$ Hospital, in Durban, admits many sick mothers and manages a large proportion of low birth weight and ill newborns. On discharge and follow-up, the mortality and morbidity of these infants are known to be high and are related to the prematurity. How much is related to being HIV exposed is still uncertain.

## Aim

To determine the perinatal transmission rate of HIV-1 and mortality at 12 months in HIV exposed infants that were admitted to and discharged from the Neonatal Unit, in Durban, South Africa.

## Methods

In this observational study, data from the outpatient charts of HIV exposed infants that required specialised neonatal care and subsequent follow up, between the period November 2007 and December 2009, were collected. Perinatal transmission rates and mortality of these infants were compared with maternal and infant risk factors.

## Results

Data on 463 HIV exposed, predominantly low birth weight infants are presented. The median maternal CD4 count was 309cells/mm$^3$ with 16.8% of mothers commenced on HAART. Maternal co-infection with TB was found in 19.2% of the cohort.

Early HIV transmission occurred in 11.5% of infants and was influenced by the type of ARV exposure (None, 20%; single dose NVP, 14.3%; dual therapy, 10.6%; maternal HAART, 8.5%). The dual therapy regimen for 7 days was more protective than that for 28 days (p=0.045). HIV infection was associated with higher risk of neonatal sepsis (RR 1.6; 95% CI, 1.1-2.3; p=0.015).

The mortality for the cohort at 12 months was 10%. Maternal HAART was associated with a lower mortality: 2.95% vs. 10.2% (RR 3.0; 95% CI, 0.4-20.5). There was a higher mortality rate in those that were low birth weight (RR 4.2; 95% CI, 1.02-18.8; p=0.037); those that were HIV infected (RR 4.8; 95% CI, 1.9-11.6; p=0.002) and those that were breastfeeding compared to formula feeding (RR 2.7; 95% CI, 1.1-6.8; p=0.038).

## Discussion

Rates of HIV transmission within the PMTCT programme were similar to that reported by the Department of Health. Early maternal ARVs for PMTCT prophylaxis, prevents HIV transmission. The coverage of maternal HAART was sub-optimal. Breastfeeding was associated with a higher HIV transmission rate and was most likely associated with non-exclusive breastfeeding during neonatal admission.

## Recommendations

Maternal HAART or ARV prophylaxis should be commenced early in the pregnancy for the best benefits. Meticulous attention should be paid to the feeding practices of high risk HIV exposed infants admitted for specialised neonatal care.

# DECLARATION

I, Dr Nadia Nair, declare that,

I. The research reported in this dissertation, except where otherwise indicated, is my original research.

II. This dissertation has not been submitted for any degree or examination at any other university.

III. This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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October 21, 2012

# ACKNOWLEDGEMENTS

I wish to acknowledge the following people, without whose assistance, this thesis would not have been possible.

| | |
|---|---|
| Prof. Miriam Adhikari | My supervisor, for her motivation and assistance in the development of the ideas. |
| Prof. Anna Coutsoudis | My facilitator, for her tireless academic support and for her generous nature. |
| Mrs. Reshmi Dayanand | My friend and colleague, for her advice, support and encouragement. |
| Mrs. Nosipho Makhanya | My colleague, for her energetic assistance with the clinical administration |
| Dr. Radhika Singh & Dr. Noxolo Mbadi | My colleagues, for all their clinical assistance. |
| Miss Alesha Sewnath | My colleague, for advice on statistical analysis and for taking all my questions. |
| Mrs Tonya Esterhuizen & Mr Stephan van der Linden | For their assistance with the statistical analysis. |
| Department of Health – KZN | For granting me the permission to continue with the study. |
| King Edward VIII$^{th}$ Hospital | For granting me the permission to continue with the study. |
| Mr & Mrs Nair | My parents, for teaching me the importance of self education. |

# PUBLICATIONS OR PRESENTATIONS

The following presentations and publications have arisen from the thesis.

- 5th International Aids Society: 2009. Electronic Poster. Throwing a lifeline to HIV exposed babies at King Edward VIII$^{th}$ Hospital in Durban.
- 26th International Pediatric Association: 2010. Poster Presentation. Transmission rates of HIV in the PMTCT programme at King Edward VIII$^{th}$ Hospital, Durban
- Paediatric Day of Excellence – Department of Paediatrics and Child Health, Nelson R Mandela, School of Medicine, University of Kwa-Zulu Natal: 2010. An audit of the outcomes, with respect to transmission rates and mortality of HIV in infants in the dual therapy programme for the prevention of perinatal transmission of HIV 1 at King Edward VIII$^{th}$ Hospital, Durban, South Africa: Preliminary findings.
- Adhikari, M., Jeena, P., Bobat, R., Archary, M., Naidoo, K., Coutsoudis, A., Singh, R. & Nair, N. 2011. HIV-Associated Tuberculosis in the Newborn and Young Infant. Int J Pediatr, 2011, 354208.

# ACRONYMS AND ABBREVIATIONS

| | |
|---|---|
| AIDS | Acquired Immune Deficiency Syndrome |
| ANC | Ante-natal clinic |
| AFASS | Acceptable, feasible, affordable, sustainable and safe. |
| ART | Antiretroviral therapy |
| ARV | Antiretroviral |
| AZT | Zidovudine |
| DBS | Dried Blood Spot |
| DOH | Department of Health |
| EBF | Exclusive breastfeeding |
| ELBW | Extremely low birth weight (<1000) |
| ELCS | Elective caesarean section |
| EMCS | Emergency caesarean section |
| ENMR | Early neonatal mortality rate |
| HAART | Highly Active Antiretroviral Therapy |
| HTEBM | Heat treated expressed breast milk |
| IMR | Infant Mortality Rate |
| IUGR | Intra-uterine growth retardation |
| KEH VIII$^{th}$ | King Edward VIII$^{th}$ Hospital |
| KZN | KwaZulu Natal |
| LBW | Low birth weight (<2500) |

| | |
|---|---|
| NEC | Necrotising enterocolitis |
| NRMSM | Nelson R Mandela School of Medicine |
| PACTG | Paediatric AIDS Clinical Trials Group |
| PEP | Post exposure prophylaxis |
| (P)MTCT | (Prevention)of Mother to Child Transmission |
| PNMR | Perinatal mortality rate |
| RSA | Republic of South Africa |
| SGA | Small for gestational age |
| sdNVP | Single dose Nevirapine |
| VLBW | Very low birth weight (<1500) |
| VTR | Vertical Transmission Rate |
| UKZN | University of KwaZulu Natal |
| WHO | World Health Organization |

# OPERATIONAL DEFINITIONS

**Antiretroviral Therapy**

The type of maternal antiretroviral drug used according to the national recommendations at the time.

**Dual Therapy**

This describes the use of both Nevirapine and Zidovudine in the mother and infant for the prevention of MTCT of HIV.

**Early Vertical Transmission**

Early vertical transmission implies the transmission of HIV-1 before (ante partum) or during (intra-partum) birth.

**Exclusive breastfeeding**

The infant receives only breast milk and no other liquids (including water) or solids, but may receive drops or syrups that consist of vitamins, mineral supplements or medicines that are deemed necessary or essential for the infant.

**Exclusive formula feeding**

The infant receives no breast milk, and is given a breast milk substitute that provides adequate nutrients until the age that they can be fully fed on family foods. During the first 6 months formula feeding should be with a suitable commercial formula, thereafter complementary foods can be introduced.

**Feeding Practices**

This describes the method of infant feeding that was reported by the mother.

**High Risk Neonates/Infants**

These are neonates with problems of the newborn who need specialized neonatal care and are at risk of immediate and long term morbidity and mortality. The American Academy of Pediatrics describes four categories: the preterm infant; the infant who requires technological support; the infant primarily at risk because of family issues; and the infant whose irreversible condition will result in an early death.

**HIV-1 Exposed**

This is an infant born to an HIV-1 positive woman.

**HIV-1 Negative**

For the purpose of the study, infants were classified as HIV-1 negative if they had a negative HIV DNA PCR at 4- 8 weeks. This implied that they did not have perinatal HIV-1 infection but were still at risk for postnatal infection via breastfeeding.

**HIV-1 Positive**

Infants were classified as HIV-1 positive if the 4-8 week HIV DNA PCR was positive. This implied perinatal HIV-1 infection.

**HIV status unknown**

This is the result of an undetermined HIV test, or a test that had not been done.

**Low Birth Weight**

These are neonates born with a weight that is less than 2500 grams (g).

**Monotherapy**

This describes the use of one antiretroviral drug (in this study it was single dose Nevirapine) as prophylaxis to prevent mother-to-child transmission of HIV in the neonate.

**Mixed Feeding**

This is the combination of breastfeeding together with other liquids or solids.

**Post Neonatal Mortality**

Post neonatal mortality is defined as deaths after 28 days of life but before one year of life.

**Preterm**

This is defined as a birth that occurs before 37 weeks of gestation.

# TABLE OF CONTENTS

# TABLES

# FIGURES

# 1 CHAPTER I: INTRODUCTION

*"We need bold initiatives to prevent new infections among young people, and large-scale action to prevent mother-to-child transmission. In the face of the grave threat posed by HIV/AIDS, we have to rise above our differences and combine our efforts to save our people. History will judge us harshly if we fail to do so now and right now."* – Nelson Mandela, July 2000, Durban, South Africa.

The above closing statement made at the 13th International AIDS Conference still rings true over a decade later. Globally, large scale changes are taking place, and the face of the HIV/AIDS epidemic is certainly altering.

A concise summation of the 30 years of effort made since the discovery of HIV, was presented at the 65th United Nations General Assembly (New York, 2010): the incidence of HIV has declined by 20%, and Sub-Saharan countries are seeing a 25% decrease in HIV infection rates.

The vertical transmission of HIV in the first world has been virtually eliminated. In addition, a multitude of effective interventions are in existence, with the prospects of a vaccine not far away.

New goals have been formulated: "Zero new infections, zero discrimination, and zero AIDS-related deaths"- within the decade.

Many Sub-Saharan countries have not been able to achieve the strides made by first world countries. South Africa continues to face a set of very difficult and unique challenges that extend from economic to social factors, which go beyond the scope of this dissertation. PMTCT is an area that can be targeted and there can be an elimination of vertical transfer of the virus from mother to child.

The effects of global initiatives are being described all over the world and HIV/AIDS is undergoing a process of transition. This study describes a component of these changes in a local setting.

## *1.1 BACKGROUND AND LITERATURE REVIEW*

### 1.1.1 The prevalence of HIV-1 infection globally and in South Africa

The UNAIDS report on the global AIDS epidemic 2010, published every two years, presented the staggeringly high prevalence data of HIV in Africa. There are 33.3 million people living with HIV throughout the world, and the largest epidemic exists in Sub-Saharan Africa, with an estimated 22.5 million people (68% of the total) living with HIV in 2009.

South Africa remains one of the top five countries in the world within which the highest numbers of people are living with HIV, together with Ethiopia, Nigeria, Zambia and Zimbabwe. In fact, in 2009, South Africa was reported as having the largest population of HIV infected people in the world, with a total of 5.6 million (compared to 5.7 million in 2007). The national prevalence of HIV in 2009 was 17.8%.[1] In certain provinces in the country, HIV prevalence rates reach higher proportions.

Kwa-Zulu Natal (KZN) is the fourth largest province in South Africa and has the highest population (more than 10 million people in 2008) compared to the other eight provinces.[2] It also has the highest population under one year of age. This province has had very high prevalence rates of HIV in its general population (25% in 2009) compared to the national prevalence rate (17.8% in 2009).[1]

Women continue to comprise a higher ratio of the total population infected in Sub-Saharan Africa and this is similar in South Africa, where the total female population infected was 3.3

million in 2009. Furthermore in this country, the highest prevalence of HIV exists amongst women aged between 15 and 49 years, attending ante-natal clinics (ANC). The national prevalence of HIV in this population has been estimated to be 29.4% in 2009.[1]

At a provincial level, since the early 1990's, KZN has had consistently higher and increasing prevalence rates of HIV, in women attending ANC, when compared to other provinces in the country. In 2008, the prevalence rate in these women was 38.7% and the most recent estimates places it at 39.5%.[1]

At a district level, the prevalence rates are high and variable. Importantly, the Ethekwini district, from which this cohort is derived, has the second highest antenatal prevalence rates (41.4%), after the neighbouring Uthukela district (46.4%) in the country, and therefore presents an ideal environment for research.

With regards to the paediatric population, globally, there are approximately 2.5 million children living with HIV – and 2.3 million of these are living in Sub-Saharan Africa.[3]

The transmission of HIV between mother and child, in developed countries has become virtually nonexistent .[3] The United States of America (USA) and Western Europe together reported less than 500 new infant infections in 2008, compared to the 390 000 new infections in Sub-Saharan Africa in the same year.[4] In 2009, 370 000 children in Sub-Saharan Africa contracted HIV either perinatally or via breastfeeding, however even though these figures are high, there has been a decline since 2001, when there was an estimated 500 000 new infections.[3]

This global decrease in new HIV infections amongst children can be attributed to many factors, including the scale up of programmes implemented for the prevention of mother to child transmission (PMTCT) of HIV. Southern Africa alone, has seen a 32% decrease in new child infections from 190 000 in 2004 to 130 000 in 2009.[3]

The rates of transmission and new HIV infections in children, within an operational setting in South Africa, have been difficult to establish. A decade ago, in 2001, South African studies estimated the risk of vertical transmission to range between 19% and 36% depending on various factors including the maternal baseline health status, mode of delivery and type of feed.[5] With the scale up of PMTCT over the last few years these rates are estimated to have decreased and the incidence of HIV in children has dropped by 34% between 2007 and 2008.[6]

However, the prevalence of HIV in children in KZN is still very high compared to the rest of the country. Nationally, in 2008 it was estimated that 3.8% of children under 15 years were infected with HIV (this equated to 598 000 children).[7] KZN, at the time, was estimated as having a provincial prevalence of 5.9% and an incidence of 95 new infections per 1000 births. The major cause was mother to child transmission.

### 1.1.2 The PMTCT programme in South Africa

Prevention of mother-to-child transmission of HIV (PMTCT) refers to the interventions utilized to prevent an infant from acquiring HI virus from the mother, whether it is during the pregnancy, at the time of labour and delivery or during the process of breast feeding, hence preventing infection of the infant. Vertical transmission is the most common mode of HIV transmission in children.

The vertical transmission of HIV-1 from infected mothers to their infants remains a significant area of concern in developing countries, particularly in South Africa as it has a high antenatal prevalence of HIV.[8] KZN and the Eastern Cape are two of the most concerning provinces.[9]

Several researched methods of preventing mother to child transmission have been advocated by the South African Department of Health over the years. Of note was the implementation of the principles set out by the World Health Organization (WHO) in their four pronged "Strategic Approaches to Prevention of Paediatric HIV Infection".

This includes prevention of HIV infection among pregnant women and the youth; the prevention of unintended pregnancies in HIV infected women; the prevention of mother to infant transmission of HIV; the provision of antiretroviral therapy (ART) and treatment of opportunistic infections; and the care and support to HIV infected women, infants and families.[10] This summarizes well how mother and child HIV is approached in the country.

Over the years, there has been a decline in HIV-1 transmission rates and improvement in the rates of HIV free survival.[11] This can be attributed to the development of many effective interventions such as early identification of the HIV positive pregnant women; early ART for those who are in the late stages of HIV or have low CD4 counts; treatment of opportunistic infections; antiretroviral (ARV) prophylaxis for those positive but healthy pregnant women; cautious obstetric practice; ARV post exposure prophylaxis in the infant; and attention to infant feeding.

During the period of this study, many changes in the antiretroviral regimens used in South Africa, have been made. Single therapy guidelines changed to dual therapy guidelines in February 2008. (These are elucidated further on.) In April 2010, the PMTCT guidelines were again revised and greater emphasis was placed on issues around breast feeding and vertical transmission.

The 2010 guidelines are currently being used in the country and recommend the use of daily AZT antenatally in the mother from 14 weeks gestation, sdNVP and three hourly AZT during labor until delivery and a stat dose of Tenofovir and Emtricitabine.[12] The infant receives 6 weeks of daily NVP if replacement feeding or if breast feeding and the mother is on HAART; alternatively, the infant is continued on daily NVP if breast feeding for the duration of exposure to the breast milk.

Studies have shown that if a maternal CD4 count is $\leq 350$ cells/mm$^3$ then treatment with HAART decreases the rate of HIV-1 transmission to the infants.[13] In the current guidelines,

the infected mother is put on antiretroviral (ARV) treatment if her CD4 count is ≤350cells/$mm^3$ or is WHO stage III or IV.

In all the PMTCT guidelines, infants are required to test for HIV at 6 weeks of age, via a heel prick and a dried blood spot. This is then tested for HIV DNA using the polymerase chain reaction. (HIV DNA PCR)

The uptake of PMTCT interventions can be measured at various steps in the programme and in general it has been improving. Recent data from the UNAIDS Global Report on HIV, published in 2010, indicated that South Africa achieved a 90% national coverage of PMTCT and that the transmission rates prior to 2010 had shown a decreasing trend.[3]

However, the Health Systems Trust reported that the uptake of PCR testing at 6 weeks in KZN was 42.3% and lower (39.2%) in the Ethekwini district between 2008 and 2009.[14] Hence, with better coverage of PMTCT but sub-optimal levels of HIV DNA PCR testing, there has been some difficulty in ascertaining the transmission rates in infants who have benefitted from the PMTCT prophylaxis, in this particular province.

### 1.1.3 The transmission of HIV-1 from mother to infant

The transmission of HIV-1 from mother to infant may occur during pregnancy (in-utero), during delivery or postnatally via breastfeeding.

The risk factors associated with perinatal HIV-1 transmission include maternal CD4 count, maternal plasma HIV-1 RNA viral load at delivery, administration of perinatal ART, mode of delivery, and the duration of rupture of membranes prior to the delivery of the infant.[15-16] Other associations are low levels of Vitamin A in the mother and sub-clinical mastitis in those that are breastfeeding. Infant factors also influence the rates of infections. These include invasive fetal monitoring, prematurity, breastfeeding, and mouth sores.

The rates of vertical transmission vary depending on the associated risk factors. In the absence of interventions, the rates of transmission are between 15 – 45%, with transmission rates of 35% in those mothers that breastfeed for a prolonged period.[17-19] Cooper et al. reported transmission rates of 20.0% in the Women and Infant Transmission Study (USA), where neither mother nor newborns received ARVS. [20]

The administration of maternal ARVS decreases vertical transmission. In an observational study conducted in 1997, Simpson et al. reported an 18% risk of transmission to infants of mothers who received no ARVs, while the transmission decreased to 5.5% in those infants whose mothers received zidovudine.[21]

But, as early as 1994, Connor et al. in the PACTG 076 randomised control trial showed a 67.5% (95% CI, 40.7–82.1) relative reduction in the risk of HIV transmission in a zidovudine receiving group compared to a placebo group. (Z= 4.03, p=0.00006) The Kaplan-Meier estimates, revealed an 8.3% transmission rate in the zidovudine group and a 25.5% rate in the placebo group, at 18 months. [22]

In 1996, Sperling et al., from the PACTG 076 trial, went on to demonstrate that the transmission rate in the zidovudine group was significantly lower, than the placebo group, 7.2% compared to 22.6%, regardless of the maternal HIV RNA viral load or the maternal baseline CD4 count.[23]

Maternal ARV therapy alters the role that these risk factors play in the transmission of the virus. Cooper et al. described factors that were individually associated with transmission, in mothers that were not receiving ART, which included: a maternal age <30years, CD4 percentage less than 29%, Centers for Disease Control and Prevention CDC Class C events before or during pregnancy, any HIV-1 RNA copy number at delivery, prenatal use of illicit drugs, duration of rupture of membranes >4 hours, preterm and low birth weight delivery.[20] Amongst mothers that were receiving ART, the additional factors associated with transmission were the type of caesarean section, gestational age of the infant, birth weight of the infant and neonatal ARV use for 2 months after birth.

### 1.1.4 The role of antiretroviral drugs in the PMTCT of HIV-1 in South Africa

The role of ART in the pregnant infected woman to prevent the vertical transmission of HIV has been shown to be an effective method of prevention and is the current standard of care. Various studies have been conducted since the early 1990's to ascertain the efficacy of the different drugs used, the appropriate duration of use, and the appropriate CD4 counts thresholds to start therapy.

#### 1.1.4.1 The role of single antiretroviral drug therapy in the prevention of mother-to-child transmission of HIV-1

Since 1994, various combinations of short course antiretroviral regimens have been researched to establish which is the most efficacious and effective intervention to reduce HIV-1 transmission. The PACTG 076 trial incorporated the use of zidovudine (AZT) and in 1997 HIVNET 012 trial, incorporated the use of single dose Nevirapine (sdNVP) administered to both the mother and infant - these interventions decreased the transmission of HIV significantly (up to 47% reduction in transmission in the HIV NET 012 trial).[22, 24]

In the latter study, the transmission rates of HIV were reported from two randomised groups - one that received a sdNVP regimen (to mother and baby) and the other that received an AZT based regimen (which included peripartum AZT to the mother and 7 days of AZT to the infant). It was found that the difference in transmission rate was insignificant at birth (8.2% and 10.4%; p=0.354), but a significant difference was seen at 6-8 weeks, favouring the sdNVP group (11.9% and 21.3%; p=0.0027). This was a predominantly breastfeeding cohort. [24] Thus,

a short course of NVP was shown to be more effective than a long course of AZT, in this setting.

South Africa piloted its first PMTCT programme in 2001, which, amongst other interventions, included the use of sdNVP. It was a monotherapy based regimen and involved the use of sdNVP in the mother 2 -24 hours prior to the delivery of the baby and administration of sdNVP to the baby not more than 72hrs after birth.

The use of sdNVP resulted in a significant overall decrease in the rates of vertical HIV-1 transmission in the country, compared to the higher rates associated with the absence of ARV usage. Sherman et al., in 2004 looked at the operational effectiveness of the national NVP based regimen in Coronation Hospital in Johannesburg. HIV transmission to infants had decreased, and was 8.7% at 6 weeks, and 8.9% at 3 months, in a predominantly formula fed group.[25]

Similarly, in 2007, Rollins et al. reported 4-8 week infant transmission rates of 15% (95% CI, 11.9%-18.6%) in mothers using sdNVP based regimen, in a predominantly breastfeeding community, in a study that performed anonymous, unlinked prevalence testing at 7 primary health care facilities in KZN. [26]

Further evidence for this decrease was seen in an earlier multicenter prospective cohort study, looking at the early transmission rates of HIV between mother infant pairs receiving sdNVP, as described by the South African National PMTCT Guidelines between 2002 and 2004. The three sites were Paarl, in the Western Cape, Rietvlei, in the Eastern Cape and Umlazi in KZN.

These 3 sites represented areas of different prevalence rates, socio-economic environments and availability of health resources. There was no statistical difference in the individual transmission rate between the three centres: 8.6%, 13.7% and 11.9% respectively. However, there was an overall decrease in the transmission rate amongst those that received the regimen appropriately (9.9%), compared to those that received the regimen outside of the recommendation (13.4%).[27]

Similarly, in other parts of Africa, in 2003, Ayouba et al. reported a decrease in transmission rate, to 10.9%, using the same Nevirapine based ultra short course regimen, in a public health Pilot Programme in Yaounde, Cameroon.[28] This PMTCT regimen mirrored the first South African one, and used sdNVP given to the mother at the onset of labor and 2mg/kg NVP given to the infant within 72 hours of birth.

Though the rates of transmission differ in different parts of the continent, all the above studies confirmed that the use of sdNVP resulted in significant decreases in transmission rates, independent of other interventions.

However, in 2005, operational and research reports reflected a growing concern regarding NVP resistance. A meta-analysis published by Arrive et al, reported NVP resistance in up to one third of women and half of the infants who had received NVP as part of prevention of MTCT interventions.[29]

### 1.1.4.2 The role of dual antiretroviral drug therapy in the prevention of mother-to-child transmission of HIV-1

Multidrug combinations and the durations of the usage for the prevention of HIV transmission in infants vary widely between studies and it is often difficult to compare the outcomes when the regimens used differ between studies.

Randomised controlled trials looking at the efficacy of short course perinatal multidrug combination ARVs have shown a decrease in transmission rates of HIV compared to single drug use. Also, the use of more than one ARV, over the antepartum, intrapartum and postpartum period has been shown to be most beneficial.

Lallemant et al. in 2004, in a double blinded three armed trial, reported transmission rates of 1.9% in exclusive replacement fed infants whose mother received AZT from the third trimester (28 weeks) and sdNVP in labor, with sdNVP in the newborn. The transmission rates in the AZT and sdNVP to mother only, had similar rates, however in the AZT and placebo arm (where mother and infant received no NVP) the transmission rate was significantly higher at 6.3%, so much so that enrolment into this arm was stopped in the interim analysis.[30] The addition of a second ARV had resulted in a marked decrease in the transmission rates compared to a single agent.

In 2004, in accordance to international recommendations, the Western Cape started a dual therapy regimen. Mothers received AZT from 34weeks (this changed to 28 weeks in 2006) and sdNVP at the onset of labour, infants received sdNVP after birth, and a week of NVP

thereafter. If a mother had a CD4 <200cells/$mm^3$ (in 2006 it changed to <250cells/$mm^3$) she was started on HAART.

In a report released by the DOH in 2009, on the operational plan for accelerating the scale up and improving the quality of services for PMTCT in RSA, the executive summary referred to the results of the above implementation. During that period, the Western Cape reported that more than 95% of pregnant women were being tested for HIV, while approximately 95% of those that were positive were receiving dual therapy and that the rate of transmission had decreased to 5%.[6] A study from Tygerberg Hospital, also in the Western Cape, reported on this regimen between 2007 and 2008, from a predominantly formula fed population. They described transmission rates of 10.1% in the dual therapy group (the majority of the transmissions occurred in those mothers who had CD4 <250).[31]

The South African National PMTCT guidelines were changed in February 2008, two years after the release of the dual therapy guidelines by the WHO. The guidelines incorporated the use of multidrug combination ARVs during the antenatal, intrapartum and postnatal periods.

It included the use of 300mg AZT twice a day, antenatally, from 28 weeks and sdNVP and 3 hourly oral AZT at the onset of labour.[32] This PMTCT regimen was intended for pregnant women that did not qualify for highly active antiretroviral therapy (HAART), to reduce the maternal viral load prior to delivery.

Women that were eligible for HAART included those with a CD4 count ≤200 cells/mm $^3$ or those classified as WHO stage IV disease. They were prioritized on to HAART at any stage antenatally, to decrease the progression of their disease.

The newborn received sdNVP at birth and thereafter, seven or twenty-eight days of AZT, depending on the duration of maternal antenatal ARV therapy. If the mother received the optimum duration of four weeks or more of AZT or HAART antenatally, then the infant only required seven days of AZT, but if the duration of maternal ARV exposure was sub-optimal then the infant was required to continue the AZT for 28 days.

The overall transmission rates reported by the National Department of Health (SA) in the National Strategic Plan, was 10% in 2009,which was during the dual therapy period.[33] The rates of transmission varied across provinces and across the country.

#### 1.1.4.3 The role of triple antiretroviral drug therapy in the prevention of mother-to-child transmission of HIV-1

Countries that are well resourced have been able to implement more complicated ARV regimens. In these countries, triple ARV drug therapy is used for PMTCT in infected pregnant women who may not require the ARVs for their own health. In contrast, poorly resourced countries need to balance the risk of transmission with the type of resources that are available in the country.

Studies from resource limited settings have reported on the effectiveness of triple combination ARV drugs as therapy or prophylaxis for the prevention of MTCT. The Mitra Plus study in Tanzania, an open labelled, non randomised cohort study, reported on transmission rates in infants whose mothers where started on HAART (AZT, Lamivudine (3TC), NVP) at 34 weeks gestation. Newborns received AZT and 3TC post delivery. Transmission rates of 4.1%, 5%, and 6% were reported at 6 weeks, 6 months and 18 months respectively, in a predominantly breastfed cohort.[34]

Other African studies like the BAN (Malawi) and Kesho Bora (Kenya, South Africa and Burkino Faso) which incorporate antepartum, intrapartum and postpartum interventions, have also demonstrated reductions in transmission rates with the use of triple therapy.[11, 35]

In-utero transmission rates, from the Kesho Bora study, in the maternal HAART (for prophylaxis) group were 1.8% (95% CI, 0.8%- 3.7%) while transmission rate in the short course AZT group was reduced to 2.2 % (95% CI, 1.2% - 4.3%). Transmission rates from birth to 6 months were also found to be reduced with the use of maternal HAART (3.1%) and short course AZT (6.3%).

The cumulative transmission rates at 1 year in the maternal HAART group was 5.5 %( 95% CI, 3.6%- 8.4%) and the short course AZT group was 9.5 %( 95% CI, 6.9%-13.0%). After one year, there was a 43% decrease in transmission rates in the triple therapy group compared to the dual therapy group, when used as prophylaxis.[35] They concluded that the use of HAART for prophylaxis against vertical transmission was safe and effective.

The above study was a randomised control trial and focused on ARV's as prophylaxis rather than treatment. A local operational study, in the Eastern Cape, followed up mothers, who conceived while on HAART for their own well being, or started HAART as treatment while they were pregnant. The overall transmission rate was 2.4% but varied according to the maternal viral load (VL). Those with a high VL (>1000 copies) had a higher transmission rate of 7.8%. Transmission was also significantly higher in those that received HAART for < 10 weeks (4.2%) and in premature births the transmission rate was at its highest at 8.6%.[36]

### 1.1.5 The association between HIV-1 and the low birth weight infant

HIV infected women have a higher risk of delivering LBW infants (whether the infants are infected or uninfected). A systematic review of 31 studies involving HIV infected and uninfected women and the outcomes in their infants was done in 1998. The results showed that there was a positive association with maternal HIV and spontaneous abortion (OR 4.05; 95% CI, 2.75-5.96) and stillbirth (OR 3.91; 95% CI, 2.65-5.77), prematurity (OR 1.83;95% CI, 1.63-2.06), IUGR (OR 1.7; 95% CI, 1.43-2.02) and LBW (OR 2.09; 95% CI, 1.86-2.35).[37] HIV infected women are more prone to chorioamnionitis and this may result in preterm labor.

HIV infected infants are at a higher risk of being born LBW. A prospective study, done in Baltimore, USA, in 1990 described how a larger proportion of infected infants were LBW (48.4% vs.22.3%) The cohort comprised of 134 exposed infants with an overall transmission rate of 23.1%. The majority of infected infants were also small for gestational age.[38]

Babies that are born with LBW, and are not infected in-utero are at a higher risk of acquiring HIV peripartum. Mwanyumba et al., in a study from Kenya, were able to show this in LBW infants (RR 1.95; 95% CI, 1·18–2·87; P<0·01)[39] They described a positive association with infant HIV infection and LBW and suggested, along with other studies, that LBW infants are more at risk for transmission because of immunological and biological immaturity.[38, 40-41] Further research is still required in this field.

### 1.1.6 The significance of feeding practices on HIV-1 transmission and mortality

There are numerous benefits to breastfeeding in infants and there is a great deal of literature to support breast feeding in both resource types of settings. However, there is a significantly higher risk of HIV transmission in HIV positive women who breast feed their infants. Devoid of any interventions, the risk of transmission is 35% in infants who are breastfed compared to 25% transmission in those that are replacement fed.[42]

Furthermore, most HIV infected mothers that breastfeed do not practice exclusive breast feeding.[43] Studies have shown that there is a greater risk of transmission in those mothers that mix feed their infants when compared to those that exclusively breastfeed.[5]

Nevertheless, owing to socio-economic factors and resources available, replacement feeding to avoid HIV transmission cannot be advocated in certain settings (South Africa included). Breastfeeding remains an important form of nutrition in infants and this is threatened by replacement feeding which can be unsafe and unsustainable in a population were many are

unemployed. There is a high risk of gastroenteritis and malnutrition associated with replacement feeding in this setting.

Breastfeeding protects against diarrhoeal disease and malnutrition. In a diarrhoeal outbreak in 2006, in Botswana, the investigators found that the majority of children who got diarrhoea were not breastfeeding. And the majority of children that had died or developed kwashiorkor were replacement feeding.[44]

In the HIV positive mothers, breastfeeding with ARV prophylaxis in the infant is able to afford more protection against mortality compared to formula feeding. The MASHI study showed that early mortality was significantly higher in a formula fed group than in a breastfed (with AZT) group, even though the HIV transmission rates in the breast fed group were higher.[45]

Furthermore, Coovadia et al., in a 2008 review of breastfeeding in HIV infected populations in Africa, it was found that by 2 years of age the risk of HIV transmission and survival in the breastfed child was similar to that in the formula fed child, in some settings.[46]

### 1.1.7 The impact of HIV/AIDS on infant mortality

There are many factors that can affect the accuracy of infant mortality rates and it is difficult to report on, in even the most organized of settings. Generally, in poorly resourced countries, there is suboptimal documentation of cause of death, under registration and misclassification

of deaths. Not all births and deaths are documented, and in 1998 Nannan et al. in assessment of vital registration, showed that the extent of completeness of the birth registration was only 19%.[47] Studies and surveys play an integral part in informing us more evidently on the state of infant and child mortality.

South Africa is one of the few countries in the world where the maternal and child mortality rates are actually increasing. The South African national mean infant mortality rate (IMR) between 2005 to 2010 reported by the United Nations in 2011, was 55 per 1000 live births.[48]

The District Health Information System in South Africa reported in 2003, that the national IMR was 42.5 per 1000 live births, with a rate of 30.4 in KZN. Using mathematical models the Actuarial Society of South Africa predicted that the national IMR would remain at 42.8 in 2010 but would increase in KZN to 55.8 per 1000 live births.[9]This increase may be attributed to the HIV/AIDS epidemic in the province.

The IMR in the HIV infected population is higher. In a systematic review of 31 studies comparing the perinatal outcomes of HIV infected and non-infected women, it was found that neonatal mortality rate was not affected. However, the perinatal and infant mortality rates were significantly higher, with the IMR having an odds ratio of 3.69 (95% CI, 3.03-4.49). [37]

It is well recognised that HIV infection increases mortality rates in infants and children, with the majority of HIV positive children dying before their fifth birthday. In the absence of the HIV epidemic, the trend observed would be a decrease in mortality as age increases in the first year.

In a review of the vital registration data in South Africa, between 1997 and 2002, it was found that the number of post neonatal deaths less than one year of age was increasing over time more especially in the 2-3 month age group. This was observed in all cause mortality and in the mortalities associated with HIV/AIDS. Thus as the HIV/AIDS epidemic developed in the country, there was an increase in the post neonatal deaths.[49]

Mortality rates are higher in exposed (infected and uninfected infants) compared to unexposed infants. In particular, a study carried out in Rakai, Uganda measured mortality rates in exposed but uninfected, infected and unexposed infants. They reported a two year mortality rate of 166 (exposed, uninfected) and 547 (exposed, infected) per 1000 live births respectively. While infants of negative mothers had a lower two year mortality rate of 128 (unexposed) per 1000 live births.[50] This showed that HIV infected infants have a higher mortality as compared to HIV exposed and uninfected infants. It also highlighted that those that were exposed and uninfected were at higher risk than the unexposed.

A pooled analysis of the mortality of infected and uninfected HIV exposed infants in Africa further supported these findings. Here it was found that the mortality at 1 year was significantly higher (35.2%) in the infected group than the uninfected group (4.9%); and that mortality in the infants was strongly associated to maternal mortality, maternal CD4 counts less than 200cells/$mm^3$, the geographical region and early HIV transmission in the infant. [51]

HIV exposed but uninfected infants have higher mortality rates when compared to HIV unexposed infants.[52-54] This maybe due to general factors like the associated loss of an

infected parent, or the absence of breast feeding. More specifically, it has been correlated to the transfer of immunity from an infected mother to her infant, and some studies have suggested that this process is inferior due to abnormal placental transfer or lower maternal immunoglobulin levels.[55]

Infants born to mothers with advanced HIV disease have increased rates of mortality. Kuhn et al., found that in the HIV exposed and uninfected infant, the early mortality rates and the risk of severe morbidity were at least double when the mother had a low CD4 count and this could not be accounted for by low birth weight of the infant or maternal mortality.[56] In this cohort 29.1% of the CD4 counts in mothers who had it available were below 200cells/$mm^3$.

Mortality in HIV exposed infants is affected by the type of ARV prophylaxis taken by the mother. In a multi-centred study done in Africa, the investigators looked at the effect of different ARV prophylactic regimes on the transmission rates and death rates. They found that the type of antenatal ARV prophylaxis used in the mother and infant significantly affected both HIV transmission and mortality. The cumulative 12 month mortality, in a triple ARV group was 6.2 %( 95% CI, 4.2-9.1%) and in the AZT and sdNVP group it was 9.8% (95% CI, 7.2-13.2%). [35]

With regards to the outcomes of the sick newborn, a prospective cohort study in KEH VIII$^{th}$ between 1996 and 1998, reported on rapidly progressive HIV-1 infected newborns with co-infections, and observed that 19 of 23 infected infants (83%) died before 9 months, with the mean age of death being 3.5 months. These data also reflected the difference in the survival rates of the HIV exposed and infected compared to the HIV exposed and uninfected.[57]

### 1.1.8 The association between low birth weight infants and mortality

The globally reported low birth weight rate is 15.5%.[58] The South African District Health Information System (DHIS) and Perinatal Problem Identification Programme (PIPP), in 2006, reported a low birth weight rate of 9% and 15.4% respectively.[59-60] In the Western Cape, in 2005, the PIPP reported that LBW (500g-2500g) contributed a PNMR of 161.6 per 1000 live births and an ENMR of 44.3 per 1000 live births, compared to 30.2 and 7.8 per 1000 live births in all births above 2500g. Thus, LBW contributes a large proportion of both PNMR and ENMR.

Low birth weight contributes heavily to neonatal morbidity and perinatal, early neonatal and neonatal mortality in general. However these factors are seldom the focus of studies with regards to HIV and literature with regard to this was difficult to find.

In one such study, involving a West African cohort, the investigators looked at the mortality outcomes of HIV exposed infants at 15 months, born to HIV positive women randomised to receive benzalkonium chloride disinfection intrapartum. The mortality at that age was not found to be associated with maternal CD4 count, maternal age, prematurity, or LBW.[61]

A Ugandan study on polygyny (i.e. the most common form of polygamy) and child mortality, found no association between LBW and child mortality in the HIV exposed or HIV unexposed infants.[62]

A study conducted by Wei et al., in Tanzania, found that in HIV exposed infants, the lower the birth weight the higher the risk of death. This is a reflection of a trend seen in unexposed infants as well. LBW was strongly associated with neonatal mortality, because of the immaturity of the infants, the increased risk of prematurity related disease, and underlying pathology related to growth restriction.[63]

After adjustments for HIV transmission, maternal CD4 counts, maternal ARV therapy, and infant morbidities, Wei et al. were able to associate LBW with more than a 2 times risk of infant mortality. They further found that in those infants that were HIV negative or had an unknown HIV status, LBW further increased the risk of mortality by 3 times.[63]

Early HIV transmission was associated with an increase in post neonatal and infant mortality rather than an increase in the neonatal mortality rate. And this can be explained by the immunological manifestations of HIV infection that occur after the neonatal period, resulting in death after that period. More importantly, what this study showed was that the exposed but uninfected infant who was low birth weight had an increased risk of death, more than an HIV unexposed infant.

### 1.1.9 King Edward VIII$^{th}$ Neonatal Unit statistics

It is important to put into perspective the survival rates of infants that are admitted to the KEH VIII$^{th}$ neonatal unit. In 2008, unpublished data of the annual number of admissions was 2766, of which 1230(44.5%) were low birth weight. There were 118 deaths that year, of which 91(77.1%) were low birth weight. Similarly, in 2009, the annual admission was 2157, of which 985(45.7%) were low birth weight. There were 113 deaths, of which 86(76.1%) were low birth weight. Low birth weights constitute less than half the admissions into the unit but result in more than two thirds of the mortality in the study setting.

### 1.1.10 Outcomes of infants admitted for specialised neonatal care

The American Academy of Pediatrics (AAP) defines high risk neonate in four categories: infants that are premature; any infant who needs technological support; any infant primarily at risk due to family issues; and any infant with an irreversible condition that will result in an early death.[64] All the infants in this cohort fell under the category of high risk as per the AAP guidelines, because the majority of the infants were premature and those that were not required some type of technological support.

When compared with age appropriate infants that are born healthy, many studies have shown that those that required NICU care and specialized neonatal services have a higher rate of readmission, and death in the first year of life. [65-66] Neonatal ICU graduates are known to have more developmental difficulties as they get older.[67]

### 1.1.11 Research needs in a local setting

There is an extensive body of empirical literature that exists on neonatal and paediatric HIV. It has established the modes of vertical transmission, the associated factors affecting HIV transmission, the outcomes of infected infants and use of ARVs and other preventative methods to combat infection and disease. The evidence comes from different geographical areas and from populations with different demographical profiles, allowing us benchmarks to work from and experiences to compare.

The UNAIDS call for the "virtual elimination of MTCT of HIV by 2015". With current methods of prevention healthy pregnant mother can be easily targeted. This may be more difficult in the sicker, co-infected mother, with advanced HIV disease. Those born to mothers with advanced maternal disease have worse mortality and transmission outcomes.[51]

It is essential to determine the outcome in infants born to mothers that have a greater severity of illness, infants born with LBW and infants born to mothers that required emergency obstetric care, since these babies are at higher risk for future mortalities and morbidities. HIV infected babies with a low birth weight have a worse outcome then if they were just LBW or HIV infected independently. These infants should be targeted to further the goal of virtual elimination of HIV.

Much of the research on PMTCT and HIV-1 transmission has looked specifically at how the disease manifests in term babies and how this affects their mortality and morbidity. Low birth weight (LBW) as an outcome of HIV infected pregnancies has been well documented, however during this literature review, it was difficult to identify studies that had focused on the low birth weight HIV exposed infants and their transmission outcomes.

There is also a paucity of information on low birth weight infants and their outcomes in our local setting. LBW infants comprise a smaller proportion of the total number of infants exposed to HIV and less emphasis is placed on the study of these infants. However, they do constitute a large proportion of admissions in certain settings, particularly tertiary and regional facilities. The percentage of LBW admitted to King Edward VIII$^{th}$ Hospital in 2008 was 44.5%.[68]

Kwa-Zulu Natal has a high prevalence of antenatal HIV and hence high numbers of HIV exposed infants. A large proportion of infants admitted to the KEH VIII$^{th}$ neonatal unit are HIV exposed (42% in 2009) and are born with LBW.[69] HIV infected babies are known to have poor mortality and morbidity outcomes. The same can be said for LBW babies. It seems logical that the combination of these factors worsens those outcomes. Their outcomes in a local setting have not been described in the recent literature.

Audits that have been done previously at the neonatal unit and at the follow up clinic did not give a clear idea of the effect of HIV exposure and infection on the outcomes of the babies that were managed. A literature search done during the development of this study revealed that there was a lack of detailed information on the consequences of HIV exposure on the low birth

weight infants. This needs further investigation in light of the province in which this cohort is based, the prevalence rates of HIV in the geographic area and the burden of disease associated with type of patients treated. In particular we need to know:

- The rate of the perinatal transmission of HIV-1 in this setting.
- The contribution of perinatal HIV infection and HIV exposure to the infant mortality.
- If the perinatal transmission and infant mortality in this setting is similar to previously and currently published data and in keeping with reported national trends.
- If the perinatal transmission rate and infant mortality rate are not in keeping with the reported trends, what are the responsible factors are?

### 1.1.12 Significance of the study

The study is an audit of the mortality and morbidity patterns of a specific group of infants. The importance of quantifying the transmission rates and having an idea of the mortality rate in these infants is paramount to our understanding of why their reported outcomes are so poor and it will enable goal directed interventions.

The study focuses on a group of infants that represent the bulk of severe neonatal disease. It is known that this population of infants contributes greatly to infant mortality, as described in many other settings around the world. [64] It is expected that the rates of transmission and mortality will be higher than that in the general population.

There is a public health need to report in a programmatic and operational setting, the rates of transmission and mortality, which have occurred over the last few years, across changing PMTCT regimens. This should provide a point of reference for comparison and offer important information for the budgeting and planning of HIV related neonatal health care.

Current data is available around this subject. However, much of the research stems from research settings, where the follow up of patients is better and the standard of care is of a high quality. This study focuses on a local, resource limited setting where it is possible to describe the effect of the use of the single dose Nevirapine, dual therapy, maternal HAART, or the lack of the use of any ARV's in HIV exposed infants for PMTCT. Feeding practices in these types of patients who were HIV exposed and required specialised neonatal care must be explored in terms of HIV transmission rates and mortality.

Operational data collected over a period of revision of the PMTCT guidelines is presented and allows a comparison of these interventional programmes (monotherapy and dual therapy rollout.) It provides a true reflection of the challenges faced and further intervention programmes should consider these challenges prior to applying new changes.

Early HIV transmission is associated with an increase in post neonatal and infant mortality rather than an increase in the neonatal mortality rate (NMR).[63] Hence it would not make sense to focus the study on the effect of LBW and HIV exposure on the NMR, which is generally audited monthly in the neonatal unit. HIV infection and LBW do however affect postneonatal rates and its effect has to be described in this population.

The study is expected to stimulate further interest and research in the subject; to increase the understanding of the LBW infant; and to increase the understanding of the consequences of being HIV exposed.

## *1.2 STATEMENT OF THE PROBLEM*

King Edward VIII$^{th}$ Hospital manages a large proportion of HIV positive pregnant women. The women are generally sicker; hence they are referred to the Hospital. Current literature informs that mothers that have a lower CD4 count and those that have progressive and severe disease are at higher risk of transmitting the virus to their infants. Other risk factors include the absence of HAART or the use of perinatal ARV prophylaxis. The extents of these risks are unknown in our unit.

There is, in addition, a large burden of disease associated with tuberculosis, particularly in the HIV positive pregnant women. Prevalence rates of TB in the late 1990's for HIV non-infected women in the obstetric wards were 72.9/100 000 and in the HIV infected, were 774/100 000. The relative risk of TB associated with HIV was 10.62.[70] This is a major risk factor for disease in newborn and can result in vertical transmission of TB to the newborn.

The neonatal unit admits approximately 42% (2009) of HIV exposed babies. We are concerned that these infants have a higher transmission rate of HIV then that describe in the general population of infants born to HIV positive mothers.

Research has shown that low birth weight infants are an outcome of pregnancies in HIV infected women. The LBW admissions to the nursery represent a large burden of disease that needs to be quantified in terms of the mortality and morbidity outcomes. King Edward VIII$^{th}$ Hospital serves as a referral centre for a large area of Kwa-Zulu Natal. Approximately 46% of the neonatal admissions, in 2009 were low birth weight, and this includes a group of small vulnerable, extremely low birth weight infants (2% of all admissions).[69] This is an ideal environment to study the outcomes of these infants.

Nationally, infant mortality comprises a large proportion of the total child deaths. The majority of child deaths (54%) occur between 1 month and 1 year of age.[71] On discharge and follow-up, it is found that the mortality and morbidity of these babies are related to extreme prematurity; gastroenteritis and infectious diseases. The data from the KEH VIII$^{th}$ neonatal unit show that the main causes of mortality and morbidity during admission are due to prematurity, infections and perinatal asphyxia. Post neonatal mortality in this setting is not audited.

Quantifying the rates of early HIV transmission has been a challenge in an operational setting. A study done in the Limpopo Province, looking at the effectiveness of comprehensive HIV services for the mother and child detailed some of these difficulties, which are experienced in this study site also. For example, the belief by health care workers that the HIV results cannot be written in the official patient records was one such shared problem. It was also shown that mothers did not realise that the 6 week follow up of the infant was part of the PMTCT programme and that it included infant testing, further delaying infant testing.[72]

A similar situation exists in this study population, where the infant's HIV exposure status is not documented in the immunization card due to the above mentioned beliefs and this subsequently delays the infant's testing, thus delaying the diagnosis and treatment of HIV.

Busy primary health clinics do not do the 6 week testing at 6 weeks, but schedule it for a later date; hence the results of early transmission rates are being delayed.

The problem of diagnosing HIV infection is further compounded when infants are lost to follow-up and their HIV DNA PCR results are not reviewed, so their HIV status remains unknown. Patients themselves move from province to province and continuity in their follow-up is lost.

The neonatal clinic has a high loss to follow up rate. This may be due to the fact that many patients, even though they are booked at the clinic prefer to go to their local clinics from where they were referred. Also, research has established that there is a high mortality rate in these vulnerable infants. Quantifying the rates of infant deaths has been a challenge. Currently there is no system in place that allows a review (even if it is annually) of the mortality of infants that were born and treated in the neonatal unit.

## *1.3 AIMS OF THE STUDY*

There are two aims in this study. Firstly, to quantify the transmission rates of HIV-1 at six weeks of age and to describe this early transmission rate and second, to quantify and describe the mortality rate in those infants less than one year, in the low birth weight and normal birth weight infants that required specialized neonatal care in the neonatal unit in KEH VIII$^{th}$ Hospital.

## *1.4 OBJECTIVES OF THE STUDY*

1. To report the transmission rates of HIV-1 at 6 weeks age in HIV exposed infants who are referred for specialised neonatal care.
2. To report the mortality outcome in the same high risk infants who were managed at the neonatal follow up clinic.
3. To describe the associations between maternal health factors and infants health factors that affect the vertical transmission of HIV in this cohort
4. To describe the associations between maternal health factors and infant health factors that affects the mortality after 12 months in this cohort.

# 2 CHAPTER II: METHODS

## *2.1 STUDY DESIGN*

Permission to carry out the study was granted by the Hospital after full ethical approval received from Biomedical Research Ethics Committee of UKZN. (Appendix 7.4 and 7.3 respectively)

This research is an observational, descriptive study. It is a summary of routine and available data at the follow up clinic and is a retrospective outpatient chart audit.

The type of resources available at the hospital were considered and it was felt that this design was cost effective with respect to financial and human resources, as it meant accessing patient files that were already available in the clinic. Employment of additional staff was not required.

A quantitative approach was used in the collection and analysis of the data. Exposures and disease occurrence found in the target population were measured. This method provided the ability to measure and describe the number of the perinatal HIV transmissions and deaths at 12 months of age. It enabled us to quantify the burden of HIV infection in our target population.

No interventions were introduced into the study. Data on events that occurred during the history of the infant's admission and of the maternal antenatal health were collected and analysed.

## *2.2 STUDY SITE*

The study site is limited to the neonatal unit and neonatal follow-up clinic at KEH VIII$^{th}$ Hospital, which is situated in ward 33 in the eThekwini district of the KwaZulu Natal Province in South Africa.

It is an academic teaching facility for the University of KwaZulu Natal - Nelson R Mandela School of Medicine. It also runs a Nursing College. It is an urban medical facility, quoted to be the second largest hospital in the Southern hemisphere that functions as a referral center for the provinces of KZN and the Eastern Cape. It offers both regional and tertiary services.[73]

There is a high prevalence of HIV in this geographic area. KZN and the eThekwini district, in particular, have very high antenatal sero-prevalences of HIV infection. Pregnant women who give birth at the hospital may receive their antenatal care primarily at a local clinic or a secondary health care facility and are then referred for more specialized care, or they are booked from the start at the KEH antenatal clinic if they are of higher risk pregnancy. In 2009 there were a total of 6800 deliveries in the labor ward.[69]

The neonatal unit is a 40 bedded unit that is capable of offering 3 invasive supportive ventilation and 4 non-invasive supportive ventilations. Neonates that are admitted to the unit usually require more specialised neonatal care. This includes invasive and non-invasive ventilation, specialised infant nursing, procedures like exchange transfusions, amplitude integrated electroencephalographic monitoring, and investigations like CT scans and cranial ultrasonography.

## *2.3 STUDY POPULATION*

The study population consisted of babies born to HIV infected mothers that were referred to the KEH VIII$^{th}$ Neonatal unit for medical care.

The cohort included all infants admitted to the neonatal unit for any condition that required specialized care. It included low birth weight and normal birth weight infants. It also included those infants with conditions of newborns such as prematurity, congenital pneumonias, meconium aspiration syndrome, congenital and nosocomial sepsis, intrauterine infections, antenatal tuberculosis exposure, birth asphyxias and hypoxic ischemic encephalopathies. Any infant requiring supportive ventilation was included. It is this group of infants that were usually followed up at the follow-up clinic.

A large majority of these admissions were born in the KEH VIII$^{th}$ labor ward, while a smaller percentage were referred from the surrounding referral centers. These referral centers included the local feeder clinics and other hospitals thus, these infants represented a group of sick infants that required care that could not be offered at a primary or secondary level. In some instances infants were referred from tertiary hospitals, when the KEH VIII$^{th}$ neonatal unit was used as a step down facility to care for the more complicated neonatal problems.

Mothers with gestational and non-gestation related co-morbidities and co-infections, who were too ill to deliver at local clinics and at secondary hospitals, that were subsequently delivered at KEH VIII$^{th}$, were also included in the study.

Of the babies admitted to the neonatal unit, only those who received specialised care were followed up at the neonatal clinic. It was expected that the majority of the cohort would be LBW as 46% of the admissions in that period were LBW.[69]

It was expected that the infants in the cohort would have histories of common neonatal diseases – ranging from neonatal sepsis and respiratory distress to perinatal asphyxia, because those babies admitted for minor problems were not followed up.

### 2.3.1 Sample Selection

Convenience sampling was used. The participants selected for this study, had been admitted to the neonatal unit for medical care and subsequently followed up, based on their problems and need for further assessment, at the neonatal follow-up clinic.

Selection of participants were based on the availability of records for those HIV exposed infants attending the neonatal follow up clinic, between the specified time frame.

The sample consisted of all available cases and could be classified as a random sample in time of the underlying population, as we assumed that the order in which the women presented was random.

The findings in this sample will only be generalizable to a population of HIV exposed babies admitted to a neonatal unit, with a similar level of care, in KZN.

### 2.3.2 Inclusion Criteria

All neonates that were born to HIV positive mothers were included.

The cohort included those referred between December 2007 and November 2009, for maternal or neonatal related disease and thereafter followed up at the KEH VIII$^{th}$ neonatal follow-up clinic.

This cohort comprised of infants with conditions related to prematurity, low birth weight, congenital pneumonias, meconium aspiration syndromes, congenital and nosocomial sepsis, exposure to maternal tuberculosis, birth asphyxias and hypoxic ischemic encephalopathies. Many patients within this cohort would have received some type of invasive or non-invasive ventilation.

### 2.3.3 Exclusion Criteria

Any baby born to an HIV negative mother or an infant with an unknown exposure status was excluded.

### 2.3.4 Sample Size

The sample size needed of 381 infants was calculated using Epi Info version 3.5.1 programme. It was calculated that this sample size would power the study to pick up a perinatal transmission rate of 10% with a 3% level of precision at a 95% confidence level. Sample size was based on an average of earlier published data, and used an overall transmission rate of 10%. However, data records were available for 463 infants that were followed-up during the study period, and thus, that became the sample size.

## *2.4 PROCEDURE OF NEONATAL FOLLOW UP*

With the infrastructure available at KEH VIII$^{th}$ Hospital, it is not possible for the neonatal clinic to manage the approximate 3000 sick neonates that it admits per year.[69] Instead, many of the patients are referred to their local hospitals or clinics if the problems are not severe. The remainder of the infants which constitute the high risk group are seen at the weekly clinic at regular intervals depending on the severity. On average, the clinic follows up 25 patients per week, and approximately 1250 per year. (Neonatal follow up clinic attendance register)

Neonates that are ill and admitted to the neonatal unit, are given follow up appointments at the follow up clinic if they fulfill certain unit criteria. These include the following babies:

- Who are born premature with a birth weight less than 1500 grams
- Who have graduated from the neonatal intensive care
- Who have required some respiratory support i.e. intermittent positive pressure ventilation (IPPV), continuous positive airway pressure ventilation (CPAP), biphasic continuous positive pressure ventilation (BiPAP)
- With moderate to severe birth asphyxia (Hypoxic Ischemic Encephalopathy grades 2 -3)
- With congenital abnormalities
- With exposure to maternal tuberculosis
- With suspected or proven chronic congenital infections
- Whose mother has demised
- With specific neonatal problems which require follow up for further investigation or management, for example, the baby with an abnormal cranial or CT scan; Patent Ductus

Arteriosis; other suspected or proven cardiac lesions; prolonged neonatal jaundice.

Whether babies were HIV exposed or not they would be subjected to the same follow up criteria. Follow up is usually done approximately 6 – 12 weeks after their initial admission, unless there is a more urgent problem to attend to. When at the clinic, the infants are assessed by paediatric registrars and consultants, who fill out the details of the patient on the "Neonatal Clinic Follow-up Form". (Appendix 7.1)

The demographic details of the mother are recorded together with the contact details (an address of where the mother lives and her or close other's telephone number.) A brief history of the patient's admission to the neonatal unit is documented. A history of the maternal HIV status is documented and this includes CD4 count, WHO stage and type of antenatal ARV exposure. Doctors at the clinic are routinely encouraged to collect as much relevant data as possible to ensure detail; they are further encouraged to check for outstanding data and collect this data at ongoing follow-ups.

The method of infant feeding is ascertained by a 24hr feeding recall that is done at the first follow-up visit, usually around 6 weeks of age. This is then classified into exclusive breast feeding; exclusive formula feed, mixed feeding and heat treated milk feeding and recorded as such.

As per the national guidelines at the time, all mothers were advised to take their infants to their local clinics for immunization, HIV DNA PCR testing and for the commencement of co-trimoxazole at 6 weeks of age, for the prevention of *Pneumocystis jiroveci* pneumonia. Co-

trimoxazole usage was documented and prescribed in the event that it was not commenced timeously at the clinic.

The clinics in the public sector perform a heel-prick dried blood spot (DBS), for infant HIV testing. The samples are sent to a regional virology laboratory, at Inkosi Albert Luthuli Central Hospital, Durban. Here the samples are tested for HIV-1, using qualitative HIV DNA polymerase chain reaction (PCR) methods. The infant is labelled infected if the result is reported as positive.

The majority of the HIV DNA PCR results outstanding from the neonatal clinic follow form were attainable via a search made on the intranet based laboratory result system between the Virology Laboratory in Inkosi Albert Luthuli Central Hospital and KEH VIII$^{th}$ Hospital. Any HIV DNA PCR test that was done after 8 weeks of chronological age was not included in the study.

The nurse or clerk working in the clinic telephoned those mothers who did not attend their scheduled appointments and rebooked them. Reasons for non attendance were documented on the neonatal follow up form (Appendix 7.1), including if the infant demised. If the patient was alive a new appointment date was given to the mother. No further enquiry into the cause of death or the reason for missed appointment was done.

Due to the high loss to follow up rates and the fact that many caregivers could not be contacted on the given contact numbers, it was difficult completely collect the data for the survival of infants at one year of age.

Additional follow-up information was attained by an informal practice that exists in the paediatric department in KEH VIII$^{th}$ Hospital which was, on occasion, when a neonate that was admitted to the neonatal unit, is later admitted to the paediatric wards, the paediatric team informs the neonatal team of the outcomes of these infants in the ward. Those mortalities and morbidities are then assimilated, by the neonatal team, in the patient neonatal records. Furthermore, if the patient was admitted into the paediatric ward, the paediatric team would ensure continuation of the follow up appointment by sending the patient and mother to the clinic on the allocated day.

## *2.5 DATA SOURCES*

The patient records that were accessible were paper based and not on a hospital computer data base. The practice of the neonatal clinic is to have two sets of records – one in the official hospital outpatient folder, stored at medical records department and one, more neonatal-specific in-house follow up form (Appendix 7.1), stored in the clinic filing cabinet – both of which are updated on a patient visit. The type of data that is collected in the clinic has been refined over many years. Relevant PMTCT information on both the mother and infant were found to be in existence on the neonatal follow-up forms.(Appendix 7.1)

Neonatal follow up forms were accessed from the filing cabinet in the Paediatric Outpatients department, Clinic A, where the neonatal follow up clinic is run on a weekly basis. They were reviewed and the appropriate records were selected. They were selected on legibility, infant name and hospital number being present (to avoid duplication of unidentified records) and

some maternal and infant data entered. Those HIV exposed babies seen at the clinic between the periods of November 2007 and December 2009 were extracted.

In those infants with outstanding data, the inpatient admission hospital records were requested for via the medical records department in KEH VIII$^{th}$ Hospital. Not all these requests were received as some of the inpatient records were missing. For those that were found, the records consisted of daily doctor's notes, nursing entries, fluid balance, prescription charts and laboratory results. The volume of information available was vast and only the relevant outstanding information was collected. Another data source used was the labor ward birth register to get outstanding birth weights of infants.

Included in the infant inpatient records was a brief maternal antenatal and intrapartum history, from where it was possible to supplement outstanding maternal information. Often, information like the antenatal CD4 count was not recorded. Thus, only some information about the mother that was outstanding from the outpatient notes was found in the infant inpatient records.

The final step in the attempt to completing the maternal data sets was accessing the maternal in-patients records and this was again was done via the medical records department.

All data were entered into a Microsoft Office Access (2007) database.

## *2.6 DATA ANALYSIS*

### 2.6.1 Variables

We looked at the following variables:

**1. Maternal demographics**

*1.1. Maternal Age*

*1.2. Maternal address*: address provided by the mother to the hospital

*1.3. Mode of Delivery*: emergency caesarean sections, elective caesarean section or normal vaginal delivery

*1.4. Maternal CD4 Count* : antenatal CD4 count

*1.5. Maternal Co-infection and Disease*: diagnosed antenatally

*1.6. Maternal TB*: diagnosed antenatally

*1.7. Maternal WHO Clinical Staging*: taken from antenatal records and from maternal history

*1.8. Maternal HAART*: antenatal commencement and type of ARV

*1.9. Reported Feeding Practice*: reported at the neonatal follow up clinic which included exclusive breast feeding, heat treat breast milk feeding, formula feeding only and mixed feed.

**2. Infant demographics**

*2.1. Date of Birth*

*2.2. Sex:* male or female

*2.3. Birth Weight :* in grams

*2.4. ARV Post exposure prophylaxis at birth:* missed dose, single dose Nevirapine, dual therapy

*2.5. Duration of Dual Therapy:* seven or twenty-eight days

*2.6. Infant admission history/ Infant co-morbidities*

2.6.1. Proven or Suspected Sepsis

2.6.1. TB Exposed

2.6.1. Congenital Tuberculosis

2.6.1. Necrotising enterocolitis

2.6.1. Hyaline Membrane Disease

2.6.1. Supportive ventilation with either CPAP or IPPV

2.6.1. Neonatal Jaundice

2.6.1. Perinatal Asphyxia

*2.7. 6 week HIV DNA PCR Result:* positive, negative, unknown

*2.8. HIV DNA PCR Result after 6 weeks of age:* positive, negative, unknown

*2.9. Infant follow up outcomes:* alive or demised at 12 months

### 2.6.2 Statistical analysis

Data was entered directly into Microsoft Office Access (2007) database. The data was cleaned by checking for missing values; identification and re-checking of outliers; double entries were made for HIV DNA PCR results and when compared, any discrepancies found were double checked with the raw data. This was done prior to statistical analysis. The Access Database

had to be exported to Microsoft Office Excel (2007) prior to exporting to a statistical package for coding and final analysis.

All statistical analyses were performed with SPSS version 18.0(SPSS Inc., Chicago, Illinois). The categorical data are presented as proportions together with the 95% confidence intervals (95% CI). Relative risk is reported with 95% CI.

Tests of association and the significance of association were calculated. The Fischer's exact test(two-tailed) was used to calculate the p-value when the Pearson Chi-square was insufficient i.e. when one or more of the cells had an expected frequency of five or less. The "p" value is set at 0.05.

Where comparisons of transmission rates were concerned, the p value was obtained using Fischer's exact test for comparisons between Breastfeeding and Mixed Feeding; Dual Therapy and None; HAART and None; Congenital TB; NEC; Supportive Ventilation; and Perinatal Asphyxia. For all other variables related to transmission the value of p was obtained using Pearson's chi-square test.

Where mortality was concerned, the p value was obtained using Pearson's chi-square test for comparisons between Emergency Caesarean Section and Normal Vaginal Delivery; Sex; Proven or Suspected Sepsis; and Hyaline Membrane Disease. For all other variables related to mortality, the value of p was obtained using Fischer's exact test.

Data were displayed in tables and figures using frequencies and descriptive statistics.

## *2.7 ETHICAL CONSIDERATIONS*

The ethical approval was obtained from the Biomedical Research Ethics Committee of the Nelson R Mandela School of Medicine South Africa, UKZN. (Reference number EXP003/06) (Appendix 7.3)

The identity of each patient will be confidential. All reports will only present aggregate data. No patient will be reported on individually. Patient records have been coded to their information using a unique study ID. The list that links the patient charts to the study ID will only be accessible by the researcher. Individual information will not be shared outside of the primary investigators. Data that has been collected will only be accessible to the researcher and supervisor.

None of the mother infant pairs were subjected to any physical or psychological harm and the risks associated with data collection from existing records were considered insignificant. Though the results of the study will not affect the infants and mothers in the study, it may have an influence for future public health developments.

# 3 CHAPTER IV: RESULTS

## *3.1 GENERAL COHORT CHARACTERISTICS*

The period of study was between November 2007 and December 2009. A total of 463 patients charts were selected for the review. There were only 62(13%) of 463 patients that had complete sets of data. Of the 463 patients, 275 (59%) were loss to follow up at one year of age. The analysis was done on those variables that were available.

## *3.2 MATERNAL DEMOGRAPHIC CHARACTERISTICS*

### 3.2.1 General

The addresses of 349 patients could be analysed. It was seen that the majority, 128(37%) came from the KwaMashu area, which is the routine feeder suburb. This was followed by Mayville, Cato Crest and Cato Manor, from which 15% of the mother infants pairs hailed. Lamontville, Wentworth and Bluff areas were also routine feeder areas. Patients were referred from as far off as Pietermaritzburg and Port Shepstone.

The maternal age was available for 401 mothers. The median age was 28 years (IQR 8 years) and the ages ranged between 16 to 45 years. 59% of the mothers were under 30 years of age.

### 3.2.2 Mode of Delivery

Of the 463 records, only 408 had sufficient data on the mode of delivery.

Being a regional hospital and referral centre, KEH VIII$^{th}$ performs a high number of emergency caesarean sections (EMCS), for both maternal and fetal indications. There was a total of 177 (43.4%) of EMCS, 54 (13.2%) elective c/sections (ELCS) and 177(43.4%) normal vaginal deliveries (NVD). There were equal numbers of EMCS and NVD performed in that period.

### 3.2.3 Maternal CD4 Count

Of the 463 charts that were reviewed, there was enough data to analyse 316 CD4 counts.

The distribution of the CD4 counts was asymmetrical. The median CD4 count was 309 cells/mm$^3$ (IQR 324), with a mode of 252 cells/mm$^3$. The range of CD4 counts was between 8 and 1198 cells/mm$^3$.

The majority of this cohort, 54.1% (95% CI, 48.4-59.7) were born to mothers who had a CD4 count of <350 cells/mm$^3$. When sub divided further, 89(28.2%) were born to mothers with a CD4 count less than 200 cells/mm$^3$ and 82(25.9%) were between 200 and 349 cells/mm$^3$. (See Figure 1.)

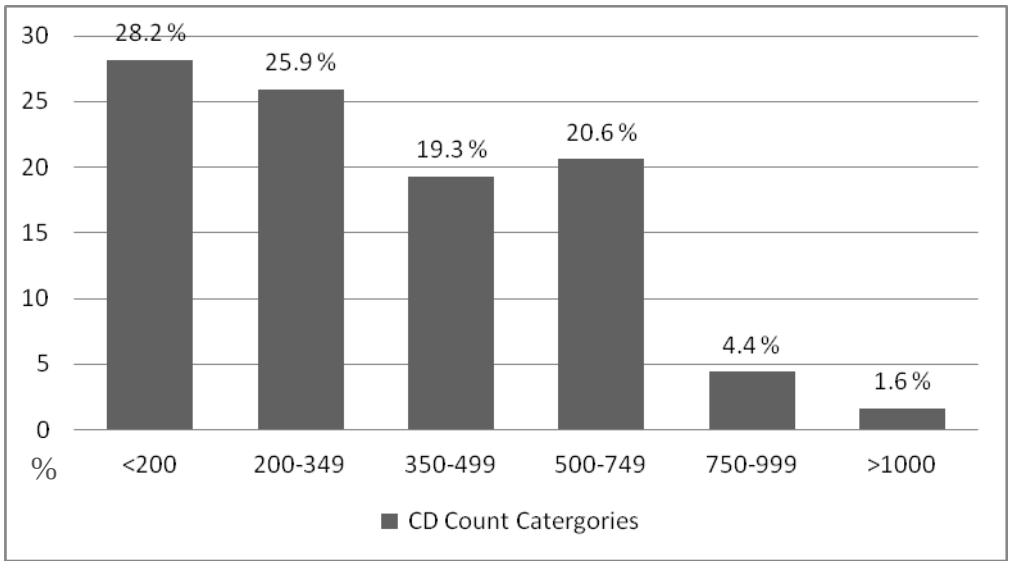


**Figure 1: Distribution of maternal CD4 count**

### 3.2.4 Maternal co-infections and severity of HIV disease

Table 1 describes the documented maternal co-infections, HIV related diseases and severity of maternal HIV reflected by the WHO clinical staging and the commencement of antenatal HAART.

The majority of the mothers had no antenatal co-infections. Pulmonary and extra-pulmonary TB was the most frequently documented co-infection. This constituted 19.12% (95% CI 15.6-23.2) of the co-infections that were documented. The group labelled "Other" constituted mainly of fungal and bacterial skin infections, dental caries and gastroenteritis.

**Table 1: Maternal co-infections and severity of HIV disease**

| Variable | Category | Frequency | %(95% CI) |
|---|---|---|---|
| **Maternal Co-Infection and HIV related Diseases (n=408)** | None | 316 | 77.45 (84.9–91.3) |
| | TB | 78 | 19.12 (15.6-23.2) |
| | Syphilis | 3 | 0.74 (0.19-2.3) |
| | Other | 14 | 3.43 (1.96-5.83) |
| | Previous TB | 2 | 0.49 (0.08-2.0) |
| | PCP | 1 | 0.25 (0.01-1.6) |
| | Kaposi's Sarcoma | 1 | 0.25 (0.01-1.6) |
| **WHO Clinical Stage (n=223)** | Stage I | 146 | 65.47 (58.8-71.6) |
| | Stage II | 18 | 8.07 (5.0-12.7) |
| | Stage III | 46 | 20.62 (15.6-26.7) |
| | Stage IV | 11 | 4.93 (2.6-8.9) |
| | Demised | 2 | 0.9 (0.16-3.6) |
| **Maternal HAART (n=417)** | No | 347 | 83.2 (79.1-86.6) |
| | Yes | 70 | 16.8 (13.4-20.8) |

It was found that only 48% of mothers were classified via the WHO clinical staging system for HIV infection and disease. Most of the mothers (65.47%; 95% CI, 58.8-71.6) were found to be WHO clinical stage 1 (asymptomatic or with persistent generalized lymphadenopathy). One fifth of the mothers (20.62%; 95% CI, 15.6-26.7) were clinically stage 3 disease followed by 8.07% (95% CI, 5.0-12.7) that were clinical stage 2 disease. WHO stage 4 disease constituted 4.93% (95% CI, 2.5-8.9).

Data from 417 mothers regarding their initiation onto HAART were analysed. The majority of the mothers, 347(83.2%; 95% CI 79.1-86.6)) were not on HAART while 70(16.8%; 95% CI, 13.4-20.8) were already initiated on HAART at the time of assessment. Of the 70 mothers who were commenced on HAART, 39 had a CD4 count <200cells/$mm^3$. The remainder had higher CD4 counts.

On examination of the cohort, it was noted that 89/316 (28.1%) required HAART based on CD4 count <200cells/$mm^3$, 39 of which had already been commenced. An additional 11 were WHO clinical stage IV and qualified on the basis of this. 9/ 11 were receiving HAART appropriately and 2 were unknown. Thus, 50/89(56.2%) additional mothers qualified for HAART but were not commenced. This resulted in the coverage of HAART, during that period of 54.8%.

## *3.3 INFANT DEMOGRAPHIC CHARACTERISTICS*

### 3.3.1 General

There were more male infants in the study than female. The ratio of male to female infants was 1.3:1.

Very little information on the gestational age of the neonate at birth could be found and the reliability of that which was found was questionable. We thus only analysed the birth weights.

### 3.3.2 Infant birth weight

There were 462 valid birth weight records that could be analysed; 1 was outstanding. The distribution of the birth weights in the study was not normally distributed. The median weight was 2015g (IQR 1420g), with a mode of 1300g. The smallest infant that was followed up at the clinic was 720g and the largest was 4960g. This is illustrated in Figure 2.

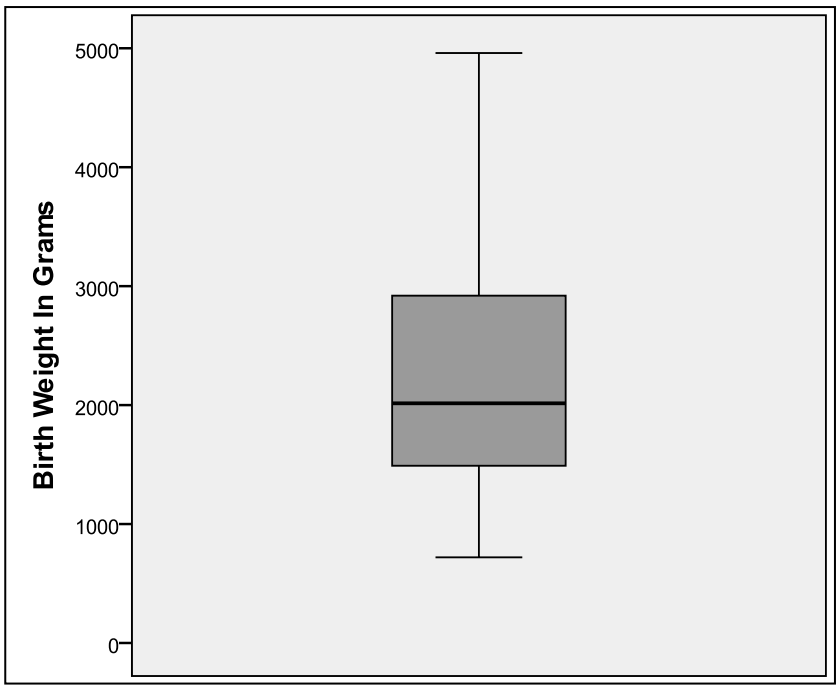


**Figure 2: Box plot showing distribution of birth weights**

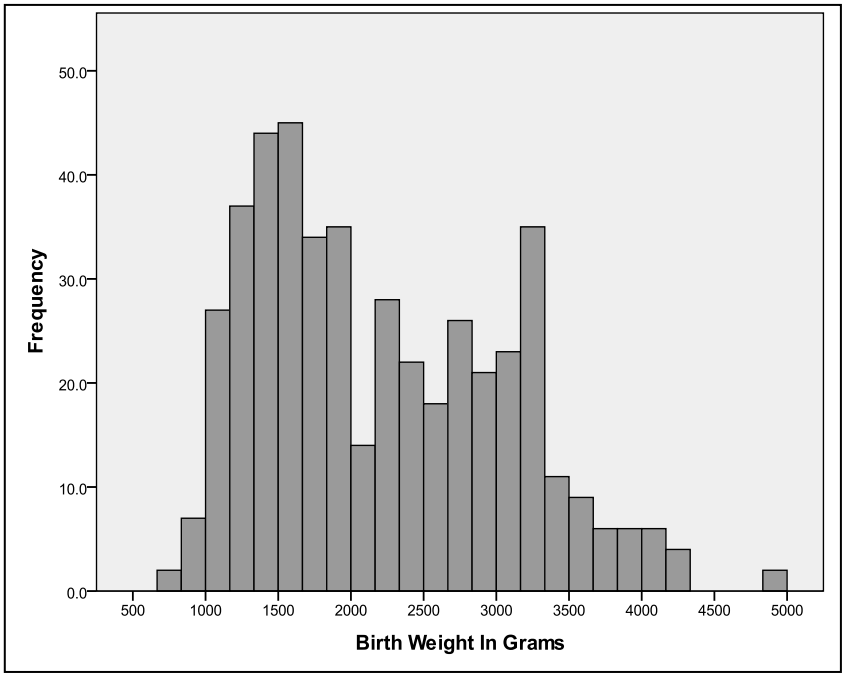


**Figure 3: Frequencies per birth weight category**

Figure 3 illustrates that the distribution of the birth weights favoured the low birth weight category. This was expected as most of the infants admitted to the neonatal unit are low birth weight and premature. 295/462 (63.9%) were LBW, 117/462(25.3%) were very low birth weight (VLBW), below 1500g and 9/462(1.94%) were extremely low birth weight (ELBW), below 1000g.

### 3.3.3 Antiretroviral prophylaxis for PMTCT

Of the 430 babies that had data on the type of antiretroviral drug prophylaxis received, 11(2.56%) did not receive any type of post exposure ARV, 60(13.95%) received single therapy and 359(83.49%) received dual therapy. (Figure 5.)

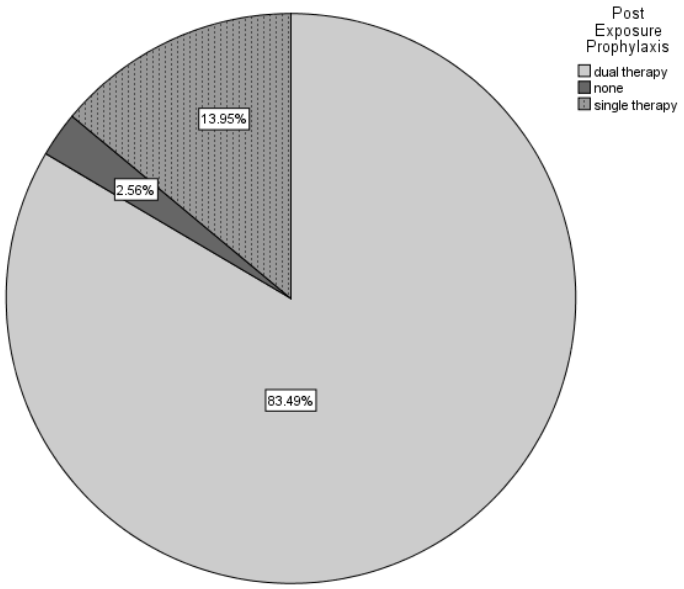


**Figure 4: Distribution of the type of post exposure prophylaxis received by the infant**

According to the dual therapy guidelines babies received sdNVP and then, either 7 or 28 days of AZT depending on the duration of maternal AZT. Not all 359 patients who received dual therapy had completed data and only 311 had sufficient data to assess whether they received 7 or 28 days of AZT. It was found that 184(59.2%) received 28 days of NVP compared to 127(40.8%) who received 7 days of AZT.

### 3.3.4 Feeding practices

Only 8% of data on feeding practices was outstanding. Mothers reported exclusive breast feeding in 127/455(29.2%) of infants and this included 6 (1.3%) of infants who were receiving heat treated breast milk, via flash pasteurization. The majority of the cohort reported exclusive formula feeding: 286/455(62.9%). There were 42/455(9.2%) that reported mixed feeding. This was a predominantly formula fed cohort.

### 3.3.5 Problems of the newborn infant

Table 2 shows the common newborn illnesses that were diagnosed during admission to the neonatal unit. Some infants may have had more than one illness while admitted. Each illness is included separately into the different categories.

**Table 2: Neonatal problems on admission to the neonatal unit**

| Diagnosis during Admission | Frequency (%) | 95% CI |
|---|---|---|
| **Proven/Suspected Sepsis** | 136/438(31) | 26.8-35.7 |
| **NEC** | 8/438(1.8) | 0.85-3.72 |
| **Antenatal TB Exposure** | 78/444 (17.6) | 14.2-21.5 |
| **Congenital TB** | 20/415(4.8) | 3.05-7.5 |
| **HMD** | 75/438(17.1) | 13.8-21.1 |
| **Perinatal Asphyxia** | 49/438(11.2) | 8.5-14.6 |
| **Neonatal Jaundice** | 75/438(17.1) | 13.8-21.1 |

It was found that 136/438 (31%) of patients in the cohort had suspected or proven sepsis on or during their admission. Also, 8/438(1.8%) of the patients in the cohort developed proven necrotising enterocolitis (NEC).

With regards to exposure to maternal TB, 78/444 (17.6%) of patients were followed up in the clinic. Not all 78 records were available for further analysis. 33% of the management data was outstanding; 41% of the TB exposed babies received TB prophylaxis; and 25.6% required full TB treatment for 6 months.

Hyaline membrane disease (HMD) was diagnosed in 75/438(17.1%) of the patients. A proportion of patients, 60/438(14%; 95% CI, 10.7-17.4) required either continuous positive airway pressure (CPAP), biphasic positive airway pressure (BiPAP) or intermittent positive pressure ventilation (IPPV), for problems related to or unrelated to prematurity.

It was noted that, 75/438(17.1%) developed neonatal jaundice while 49/438(11.2%) suffered perinatal asphyxia.

### 3.3.6 Overall perinatal transmission rate

It was found that 63 of the 6 week HIV DNA PCR test results were outstanding. Among the remaining 400 results, 46 patients were infected and the perinatal HIV-1 transmission rate for the cohort was 11.5% (95% CI, 8.6-15.1).

The data on the HIV DNA PCR results were only collected up to 8 weeks, hence late transmission rates were not reported on. Furthermore, routine testing for HIV after 6 weeks of age was not done as it was not recommended by the prevailing guidelines. Only a handful of infants had HIV DNA PCR results after 6 weeks. These constituted infants who had missed their testing at the designated period.

### 3.3.7 Overall mortality at 12 months of age

The measurement of the mortality at one year for the overall group was problematic because 275(59%) of patients were lost to follow-up. Of those remaining 19/188 (10.1%; 95% CI, 6.4-15.6) of the infants were known to have demised by 12 months of age and 169/188(89.9%) were alive.

## *3.4 PERINATAL HIV-1 TRANSMISSION RATES AND RELATED FACTORS*

### 3.4.1 Maternal Factors

#### 3.4.1.1 Maternal age

There were more infants with HIV infection born to mothers below the age of 30, 12.8% (26/203) compared to those who were born to mothers that were above the age of 30, 10.2% (15/147). (p=0.454)

#### 3.4.1.2 Mode of delivery

Of the infants who were delivered via NVD, 23/156 (14.7%) developed HIV infection within the first 6-8 weeks. EMCS was associated with an 11.8% transmission rate (18/153). There were no early HIV infections in the group of infants who required an ELCS, though of the 54 records that we had only 17 had HIV DNA PCR results that could be analysed.

There was no difference between the rate of HIV transmission between NVD (14.7%) and EMCS (11.8%). (RR 0.79; 95% CI, 0.5 – 1.5; p= 0.438) With regards to the ELCS, the numbers were very small and did not translate into significant rates, but the results do have clinical significance that needs further examination.

### 3.4.1.3 Maternal CD4 count

In general, those infants born to mothers with CD4 counts <350 had a higher transmission rate, 21/156(13.5%) compared to those ≥ 350 11/127(8.7 %). (RR 1.6; 95% CI, 0.8-3.1; p=0.200). As can be seen on Table 3 there was no significant difference between the transmission rates in those with maternal CD4 counts less than 200 and above 200cells/$mm^3$.

There were two patients of seven, born to mothers with a CD4 count above 950 that were infected. This increased the transmission rate in that group to 30%. Both mothers had no co-infections, were not on HAART, and clinically well but delivered LBW babies. One required an emergency caesarean section and breast fed while the other had a NVD and then subsequently formula fed.

### 3.4.1.4 Maternal TB co-infection

There were 78 mothers in the cohort that were recorded as having TB antenatally. Of those, 68 records had HIV DNA PCR results record. Thus it was found that 10/68(14.7%) of babies born to mothers with antenatal TB were HIV infected at 6 weeks and 35/320(10.95%) of HIV infected babies were born to mothers that were not co-infected with TB. (p=0.378)

#### 3.4.1.5 Maternal HAART

The analysis revealed that, 70/416 (16.8%) mothers were documented to have commenced HAART. Of these, 8.5% transmitted HIV to their infants (5/59). When the transmission rate in those that were commenced on maternal HAART was compared to the rate in those that were not commenced on HAART, no significant difference was found. (8.5% vs. 12.7%) (RR 0.7; 95% CI, 0.3-1.6; p = 0.359)

## Table 3: Maternal factors affecting HIV transmission

| Variable | | N | n | %(95% CI) | P Value |
|---|---|---|---|---|---|
| **Mode of Delivery** | | | | | |
| | **ELCS** | 17 | 0 | 0(0.0-22.9) | - |
| | **NVD** | 156 | 23 | 14.7(9.8-21.5) | 0.438 |
| | **EMCS** | 153 | 18 | 11.8(7.3-18.2) | |
| **Maternal CD4 Count** | | | | | |
| | **<200** | 81 | 10 | 12.3(6.4-22.0) | 0.729 |
| | **≥200** | 202 | 22 | 10.9(7.1-16.2) | |
| | **200-349** | 75 | 11 | 14.7(7.9-25.2) | - |
| | **<350** | 156 | 21 | 13.5(8.7-20.1) | 0.200 |
| | **≥350** | 127 | 11 | 8.7(4.6-15.3) | |
| **Maternal TB Co-infection** | | | | | |
| | **Present** | 68 | 10 | 14.7(7.7-25.9) | 0.378 |
| | **Absent** | 320 | 35 | 10.9(7.8-15.0) | |
| **Maternal HAART** | | | | | |
| | **Commenced** | 59 | 5 | 8.5(3.2-19.4) | 0.359 |
| | **Not Commenced** | 307 | 39 | 12.7(9.3-17.1) | |

CI, confidence interval.

N = data available, n=number that were HIV infected

### 3.4.2 Infant Factors

#### 3.4.2.1 Infant sex

It was found that 10.1% (23/228) of male infants and 13.5% (23/170) female infants were infected. The difference was not significant. (RR0.8; 95% CI, 0.5-1.4; p = 0.522)

#### 3.4.2.2 Infant birthweight

There were sufficient records to asses 399 patients for this comparison. Here we compared the infection rates in LBW and average birth weights and found that 33/255(12.9%) of LBW infants were infected compared to 13/144(9.0%) of average birth weight babies that were infected. (RR 1.4; 95% CI, 0.8-2.6; p= 0.240)

In the weight category <1000g, 1/8 (12.5%, 95% CI 1.0-53.0) were infected, which was similar to the category 1000-1499g, were 12/95 (12.6%, 95% CI 7.0-21.4) were infected. The highest rate of infection was documented in the category between 1500-1999g: 14/98 (14.3%, 95% CI 8.3-23.2). The transmission rates in the weight categories 2000-2499g and 2500-2999g, were 6/54 (11.1%, 95% CI 5.0-23.3) and 4/54 (7.4%, 95% CI 2.4-18.8) respectively. There was a peak in transmission rates in the 3000-3499g category: 7/58 (12.1%, 95% CI 5.4-23.9). The transmission rates in the 3500-3999g and ≥ 4000g, were 1/20 (5.0%, 95% CI 0.3-26.9) and 1/12 (8.3%, 95% CI 0.4-40.2) respectively.

### 3.4.2.3 Antiretroviral prophylaxis for PMTCT

In those infants who did not receive any form of antiretroviral post exposure prophylaxis the perinatal transmission rate was 20% (2/10). A proportion of infants received a single dose of NVP at birth. In this group the transmission rate was 14.3% (8/56). (RR 0.7; 95% CI, 0.2-2.9; p = 0.472) There was no significant difference.

During the dual therapy era, infants in this cohort required either 7 or 28 days of AZT after sdNVP at birth. The overall transmission in this group was 10.6% (33/309). When this rate of transmission was compared to those infants that received no ARVs and those that received sdNVP only, we found that though the rates had decreased, there was no significant difference.( RR 0.5; 95% CI, 0.1-1.9; p = 0.609 and RR 0.75; 95% CI, 0.4-1.5; p = 0.68, respectively)

On further analysis of those using dual therapy, infants that received 7 days of AZT experienced a transmission rate of 6.7%(7/104) compared to those infants that were required to take AZT for 28, that had a rate of 14.8% (23/155). (RR 0.5; 95% 0.2-1.0; p= 0.045) This tended toward being significant however the 95% Confidence Interval included 1.

Regardless of what type of prophylaxis the infant was on, if the mother was on HAART, the vertical transmission rate was 8.5% (5/59). The transmission rate was decreased but no significant difference could be shown when compared to the transmission rates in those with no maternal or infant ARV exposure (RR 0.4; 95% CI, 0.1-1.9; p = 0.582); or when compared to dual therapy. (RR 0.79; 95% CI, 0.3-1.9; p=0.603)

### 3.4.2.4 Feeding practices

The majority of the mothers in this cohort reported formula feeding, followed by breast feeding and a minority reported mixed feeding of the infants. In the breast feeding group, the early transmission rate was 18.4% (19/103), while in the formula fed group the transmission rate was lower, 8.76 % (22/251). There was a higher risk with breast feeding when compared to formula feeding in this cohort of infants (RR 2.1; 95% CI, 1.2-3.7; p =0.016). The HIV DNA PCR results included babies that were tested up to 8 weeks.

Those that were mixed feeding had a transmission rate of 11.1% (4/36). There was no significant difference found between this group and those that breast fed (p = 0.435)

### 3.4.2.5 Proven or suspected sepsis

There were 381 records that had sufficient data to do this comparison. 118 (31%) Patients had suspected sepsis or proven sepsis after birth. Of those that were HIV infected, 21/45(46.6%) had suspected or proven sepsis, compared to the 97/336(28.9%) patients that were not HIV infected and also had sepsis. (RR 1.6; 95% CI, 1.1-2.3; p=0.015) The likelihood of an HIV infected neonate having sepsis was increased.

## Table 4: Neonatal characteristics affecting HIV transmission

| Variable | | N | n | %(95% CI) | P Value |
|---|---|---|---|---|---|
| **Sex of the Infant** | | | | | |
| | **Male** | 228 | 23 | 10.1(6.6-14.9) | 0.522 |
| | **Female** | 170 | 23 | 13.5(9.0-19.8) | |
| **Birth Weight: LBW vs. Average Birth Weight** | | | | | |
| | **< 2500** | 255 | 33 | 12.9(9.2-17.8) | 0.240 |
| | **≥ 2500** | 144 | 13 | 9.0(5.1-15.3) | |
| **Neonatal Prophylaxis** | | | | | |
| | **None** | 10 | 2 | 20(3.5-55.8) | 0.472 |
| | **sdNVP** | 56 | 8 | 14.3(6.8-26.8) | |
| | **None** | 10 | 2 | 20(35.4-55.7) | 0.609 |
| | **Dual Therapy** | 309 | 33 | 10.6(7.6-14.8) | |
| | **sdNVP** | 56 | 8 | 14.3(6.8-26.8) | 0.680 |
| | **Dual Therapy** | 309 | 33 | 10.6(7.6-14.8) | |
| | **None** | 10 | 2 | 20(35.4-55.7) | 0.582 |
| | **Maternal HAART** | 59 | 5 | 8.5(3.16-19.4) | |
| | **Dual Therapy** | 309 | 33 | 10.6(7.6-14.8) | 0.603 |
| | **Maternal HAART** | 59 | 5 | 8.5(3.16-19.4) | |
| **Dual Therapy** | | | | | |
| | **7 days** | 104 | 7 | 6.7(3.0-13.9) | 0.045 |
| | **28 days** | 155 | 23 | 14.8(9.8-21.7) | |
| **Infant Feeding** | | | | | |
| | **Breastfeeding** | 103 | 19 | 18.4(11.8-27.6) | 0.016 |
| | **Formula Feeding** | 251 | 22 | 8.76(5.7-13.1) | |
| | **Breastfeeding** | 103 | 19 | 18.4(11.8-27.6) | 0.435 |
| | **Mixed Feeding** | 36 | 4 | 11.1(3.6-27.0) | |

CI, confidence interval.

N = data available, n=number that were HIV infected

### 3.4.2.6 Congenital TB

We were able to access 365 records for the above variable. It was found that 18 infants were diagnosed with congenital TB. Of the 43 HIV infected infants with sufficient information about the exposure to TB, 2(4.6%) were diagnosed with congenital TB. In infants that were uninfected (322), 16(4.9%) had congenital TB (RR 0.9; 95% CI, 0.2-3.6); p = 0.642). There was no significant difference in the vertical transmission of TB in the HIV infected infant compared to the uninfected infant.

### 3.4.2.7 Necrotising Enterocolitis

One infant, who developed NEC, had an unknown HIV result and was thus excluded from this analysis. Thus, proven NEC was found in 1.8% (7/381) of the sample.

In those that were HIV infected, 4.4% (2/45) developed NEC. While, in those that were HIV uninfected, 1.5% (5/331) developed NEC. (RR 2.9; 95% CI, 0.6-14.9; p=0.195). The lack of a significant relationship may be attributed to the small sample of patients.

### 3.4.2.8 Hyaline Membrane Disease

Within the sample, 63/381(16.5%) had HMD, of which 5/45(11.1%) were HIV infected and 58/336(17.3%) were uninfected. (RR 0.64; 95% CI, 0.3-1.5; p=0.394). The rate of HMD in HIV infected compared to the uninfected was not significantly different.

### 3.4.2.9 Supportive Ventilation

Of the 381records with sufficient data to compare these variables, 54(14.2%) babies received supportive ventilation. Of those that were HIV infected 2/45(4.4 %) required ventilation and, 52/336(15.5%) in the uninfected group required ventilation. (RR 0.29; 95% CI, 0.1-1.1; p=0.065) This tended toward being statistically significant and is likely that it is clinically significant as will be discussed further on.

### 3.4.2.10 Neonatal Jaundice

No clinical or statistical significance was expected in this comparison; however it was included so that it would offer some corroboration as to the precision of the other comparisons. Sixty-seven babies had NNJ. Of those that were HIV infected, 22.2% (10/45) were jaundiced. Of those that were uninfected, 17% (57/336) were jaundiced. (RR 1.3; 95% CI, 0.7-2.6; p=0.405) HIV infection did not significantly alter the rates of NNJ in this cohort.

### 3.4.2.11 Perinatal Asphyxia

There were 40 infants that suffered perinatal asphyxia. Of those that were HIV infected, 6.7% (3/45) were asphyxiated. Of those that were uninfected, 11.0% (37/336) were asphyxiated. (RR 0.61; 95% CI, 0.2-1.9; p = 0.451) The difference between these values was not significant.

**Table 5: Comparison of the rates of common neonatal problems in HIV infected and uninfected infants**

| Variable | | N | n | %(95% CI) | P Value |
|---|---|---|---|---|---|
| **Proven/Suspected Sepsis** | | | | | |
| | **Present** | 118 | 21 | 17.8(11.6-26.2) | 0.015 |
| | **Absent** | 263 | 24 | 9.1(6.1-13.4) | |
| **Congenital TB** | | | | | |
| | **Present** | 18 | 2 | 11.1(2.0-36.1) | 0.642 |
| | **Absent** | 347 | 41 | 11.8(8.7-15.8) | |
| **NEC** | | | | | |
| | **Present** | 7 | 2 | 28.6(5.1-69.7) | 0.195 |
| | **Absent** | 374 | 43 | 11.5(8.5-15.3) | |
| **HMD** | | | | | |
| | **Present** | 63 | 5 | 7.9(3.0-18.3) | 0.394 |
| | **Absent** | 318 | 40 | 12.6(9.24-16.9) | |
| **Supportive Ventilation** | | | | | |
| | **Required** | 54 | 2 | 3.7(0.6-13.8) | 0.065 |
| | **Not required** | 327 | 43 | 13.1(9.8-17.4) | |
| **Perinatal Asphyxia** | | | | | |
| | **Present** | 40 | 3 | 7.5(2.0-21.5) | 0.451 |
| | **Absent** | 341 | 42 | 12.3(9.1-16.4) | |
| **Neonatal Jaundice** | | | | | |
| | **Present** | 67 | 10 | 14.9(1.6-6.0) | 0.405 |
| | **Absent** | 314 | 35 | 11.7(8.0-15.3) | |

CI, confidence interval.

N = data available, n=number that were HIV infected

## *3.5 MORTALITY OF HIV EXPOSED INFANTS AND REALTED FACTORS*

### 3.5.1 General

Much of the data for the outcomes of the infants were missing. Of the total of 463 infant records that were collated, 275(59%) had not completed a year of follow up. 190 follow up records had an indication of whether the infant was alive or had demised. Only 19 deaths under one year were recorded. (10%)

### 3.5.2 Maternal Factors

#### 3.5.2.1 Mode of delivery

It was found that of the 10 ELCS, there were no recorded infant deaths. 8/65(14%) that were born via NVD had demised. 8 of 81 (9.9%) infants who were delivered via EMCS had also demised after 1 year of age. No significant difference was found when these variables were compared. On comparing the EMCS and NVD the relative risk was 0.8 (favouring EMCS) however this did not reach any significant level. (p=0.639)

### 3.5.2.2 Antenatal maternal CD4 Count

There were 145 sets of data available for this comparison. Of which, 3/39 (7.7%) of infants born to mothers with a CD4 count of less than 200 died, compared to 11/106(10.4%) deaths to mothers with a CD4 count above 200. (RR 0.74; 95% CI, 0.21-2.51; p=0.760). There was no difference in the number of deaths in those mothers that had a CD4 count less than 350 compared to those that had a CD4 count above 350. (10.8% vs. 8.06%) (RR 1.3; 95%CI 0.5-3.8; p=0.777)

The infant mortality was 18.8 %( 95% CI 4.5 – 32.6) in the category 350-499. In the category 500-649, the percentage of deaths was 4.2% (95% CI 0.2-23.1). There were no deaths in the categories above 650.

### 3.5.2.3 Antenatal Maternal HAART

There were 181 data sets available to asses this variable. 1/34 (2.9%) infants exposed to maternal HAART demised, while 15/147 (10.2%) of infants not exposed to maternal HAART demised. Infants exposed to maternal HAART, whether it was required by the mother at the time or not, resulted in fewer deaths. (RR 0.2; 95% CI, 0.04-2.1; p=0.21)

## Table 6: Maternal factors affecting infant mortality

| Variable | | N | n | %(95% CI) | P Value |
|---|---|---|---|---|---|
| **Maternal CD4 Count** | | | | | |
| | **<200** | 39 | 3 | 7.7(2.0-22.0) | 0.760 |
| | **≥200** | 106 | 11 | 10.4(5.5-18.2) | |
| | **200-349** | 44 | 6 | 13.6(5.7-28.1) | - |
| | **<350** | 83 | 9 | 10.8(5.4-20.1) | 0.777 |
| | **≥350** | 62 | 5 | 8.06(2.7-16.8) | |
| **Mode of Delivery** | | | | | |
| | **NVD** | 65 | 8 | 14(5.8-23.4) | 0.367 |
| | **ELCS** | 10 | 0 | 0(0-34.5) | |
| | **EMCS** | 81 | 8 | 9.9(4.7-19.1) | 0.591 |
| | **ELCS** | 10 | 0 | 0(0-34.5) | |
| | **EMCS** | 81 | 8 | 9.9(4.7-19.1) | 0.639 |
| | **NVD** | 65 | 8 | 14(5.8-23.4) | |
| **Maternal WHO Clinical Stage** | | | | | |
| | **Stage I** | 64 | 9 | 14.1(7.0-25.5) | 0.161 |
| | **Stages II-IV** | 30 | 1 | 3.3(0.2-19.1) | |
| **Maternal HAART** | | | | | |
| | **On HAART** | 34 | 1 | 2.9(0.15-17.0) | 0.21 |
| | **Not on HAART** | 147 | 15 | 10.2(6.0-16.6) | |

CI, confidence interval.

N = data available, n=number of infants that demised

### 3.5.3 Infant Factors

#### 3.5.3.1 Infant sex

The outcomes data for 41% of patients were available to asses this variable. More females, 74/80 (92.5%), survived compared to 97/110 (88.1%) of the males. (p=0.327)

#### 3.5.3.2 Infant birth weight

40.6% of the records were available to analyse the outcomes of the infants according to their birth weight. It was found in the LBW infant group that there were 17/125 (13.6%) deaths, compared to the average birth weight group, which had 2/63 (3.17%) of deaths. LBW was a risk factor for mortality. (RR4.2; 95% CI, 1.02-18.8; p=0.037)

The birth weight sub-classes were further examined. There were no documented deaths in the infants below 1000g. The majority of the deaths were documented in the weight categories 1000-1499 and 1500-1999. (6/45, 13.3%, 95% CI 5.5-27.5 and 11/57, 19.3%, 95% CI 10.5-32.3, respectively.) The only further deaths that occurred were in the category 3000-3499, were 2/32 infants died. (6.3%, 95% CI 1.0-22.2)

### 3.5.3.3 Antiretroviral prophylaxis for PMTCT

While most of the infants received dual therapy, followed by monotherapy, a few patients were missed and did not receive any ARV prophylaxis.

Of those that received no antiretroviral prophylaxis, 1/6 (16.7%) demised compared to 7/26 (26.9%) that received sdNVP. (RR1.6; 95%CI 0.24-10.8; p=1) The numbers that missed their NVP dose were too small to make any comparisons.

9/146 (6.2%) infants that received dual therapy demised compared to those that received no therapy. The use of dual therapy tended towards being protective but this again did not reach a level of significance. (RR 0.4; 95% CI, 0.1-2.5; p=0.34)

When the outcomes in the monotherapy group (26.9%) were compared to the dual therapy group (6.2%), it could be seen that the use of dual therapy had a significant effect on mortality. (RR 0.2; 95%CI 0.1-0.5; p=0.003)

A closer look at the dual therapy group revealed that 1/45(2.2%) that received 7 days of AZT demised compared to 7/81(8.6%) who received AZT for 28 days. (RR0.25; 95% CI, 0.03 – 2.0; p=0.257)

### 3.5.3.4 Feeding practices

The majority of the cohort had reported formula feeding. Those that were heat treating their breast milk were included in the breast feeding group. 8/45 (17.8%) of breast feeding infants demised compared to the 8/123(6.5%) formula feeding infants. (RR 2.7; 95% CI, 1.1-6.8; p=0.038)

When the deaths in the breast feeding group were compared to the 3/21 (14.3%) of deaths in the mixed feeding group, it was found that there was no significant difference. (RR 1.2; 95% CI, 0.4-4.2; p=0.112) Formula feeding tended toward being safer than mixed feeding but this did not reach a significant level (RR 0.5; 95% CI, 0.1-1.6; p=0.367)

### 3.5.3.5 Perinatal HIV-1 Infection

There were 25 infants that were infected with HIV-1, with sufficient data to compare these variables; 7(28%) demised before the age of 1 year. There were 9/153(5.9%) of infants who demised in the same period but remained uninfected infected by 6 weeks. There was a significant risk of mortality in those infants that were infected perinatally. (RR 4.8; 95% CI, 1.9-11.6; p=0.002)

## Table 7: Infant characteristics affecting infant mortality

| Variable | | N | n | %(95% CI) | P Value |
|---|---|---|---|---|---|
| **Sex of the Infant** | | | | | |
| | **Male** | 110 | 13 | 11.8(6.7-19.7) | 0.327 |
| | **Female** | 80 | 6 | 7.5(3.0-16.2) | |
| **Birth Weight: LBW vs. Average Birth Weight** | | | | | |
| | **< 2500** | 125 | 17 | 13.6(8.4-21.2) | 0.037 |
| | **≥ 2500** | 63 | 2 | 3.17(0.6-12.0) | |
| **Neonatal Prophylaxis** | | | | | |
| | **None** | 6 | 1 | 16.7(0.9-63.5) | 1 |
| | **sdNVP** | 26 | 7 | 26.9(12.4-48.0) | |
| | **None** | 6 | 1 | 16.7(0.9-63.5) | 0.34 |
| | **Dual Therapy** | 146 | 9 | 6.2(3.0-11.7) | |
| | **sdNVP** | 26 | 7 | 26.9(12.4-48.0) | 0.003 |
| | **Dual Therapy** | 146 | 9 | 6.2(3.0-11.7) | |
| **Dual Therapy** | | | | | |
| | **7 days** | 45 | 1 | 2.2(0.1-13.2) | 0.257 |
| | **28 days** | 81 | 7 | 8.6(4.0-17.5) | |
| **Infant Feeding** | | | | | |
| **Breastfeeding(incl. HTEBM)** | 45 | 8 | 17.8(8.5-33) | 0.038 | |
| **Formula Feeding** | 123 | 8 | 6.5(3.0-12.8) | | |
| **Breastfeeding(incl. HTEBM)** | 45 | 8 | 17.8(8.5-33) | 0.112 | |
| **Mixed Feeding** | 21 | 3 | 14.3(3.8-37.4) | | |
| **Formula Feeding** | 123 | 8 | 6.5(3.0-12.8) | 0.367 | |
| **Mixed Feeding** | 21 | 3 | 14.3(3.8-37.4) | | |
| **Infant HIV -1 Infection** | | | | | |
| **Infected** | 25 | 7 | 28(12.9-49.6) | 0.002 | |
| **Uninfected** | 153 | 9 | 5.9(2.9-11.2) | | |

CI, confidence interval.

N = data available, n=number of infants that demised

#### 3.5.3.6 Proven or suspected sepsis

Of the 181 infants with enough data to be analysed, 55 had either suspected or proven sepsis. In those with sepsis, 8/55(14.5%) subsequently demised while 10/126(7.9%) without this diagnosis also demised. The difference was not significant. (RR 1.8; 95% CI, 0.8-4.4; p = 0.172)

#### 3.5.3.7 Necrotising Enterocolitis

There were 181 records with sufficient data. A total of 18 infants demised, 33.3% had NEC compared to 9.6% who died that did not have NEC. (RR 3.5; 95% CI, 0.7-18.4; p=0.271) The numbers were too small for this to be significant.

#### 3.5.3.8 Hyaline Membrane Disease

In 30 infants that were diagnosed with HMD, 16.7% demised compared to the 8.6% of infants that were not diagnosed with disease who also demised. (RR 1.9; 95% CI, 0.7-5.0; p = 0.187)

#### 3.5.3.9 Supportive Ventilation

There were 29 infants that required supportive ventilation in the records that we could asses. 17.2% of these infants demised and in the group that did not require supportive ventilation, 8.6% demised. (RR 2; 95% CI, 0.8-5.2; p=0.174)

### 3.5.3.10 Neonatal Jaundice requiring treatment

Of the 34 infants that were documented to have NNJ 11.8% demised compared to the 9.5% of infants that did not receive treatment for NNJ who also demised. (RR 1.2; 95% CI, 0.5-3.0; p=0.751) There was no significant association.

### 3.5.3.11 Perinatal Asphyxia

In 21 neonates who were admitted with the diagnosis of perinatal asphyxia, 4.8% died before 1 year of age. In those neonates that did not suffer any perinatal asphyxia, 10.6% demised. (RR 0.4; 95% CI, 0.1-3.2; p=0.489) The mortality rate was not associated with perinatal asphyxia in the newborn period.

### 3.5.3.12 Exposure to Maternal TB

The analysis for this variable could only be done on 29 of the mothers that had antenatal TB. 6.9% of infants exposed to maternal TB during pregnancy demised, compared to 10.1% of infants that demised but were not exposed to antenatal TB. (RR 0.69; 95% CI, 0.2-2.8; p = 0.774) With regards to those neonates that were treated for congenital TB, 1/12(8.3%) demised compared to those who demised but did not have congenital TB, 16/164(9.8%). (RR 0.8; 95% CI, 0.12-5.9; p = 1)

## Table 8: Comparison of the rates of common neonatal illnesses with mortality

| Variable | | N | n | %(95% CI) | P Value |
|---|---|---|---|---|---|
| **Proven/Suspected Sepsis** | | | | | |
| | **Present** | 55 | 8 | 14.5(6.9-27.2) | 0.172 |
| | **Absent** | 126 | 10 | 7.9(4.1-14.5) | |
| **NEC** | | | | | |
| | **Present** | 3 | 1 | 33.3(1.8-87.5) | 0.271 |
| | **Absent** | 178 | 17 | 9.6(5.5-14.2) | |
| **HMD** | | | | | |
| | **Present** | 30 | 5 | 16.7(6.3-35.5) | 0.187 |
| | **Absent** | 151 | 13 | 8.6(4.9-14.6) | |
| **Neonatal Jaundice** | | | | | |
| | **Present** | 34 | 4 | 11.8(3.8-28.4) | 0.751 |
| | **Absent** | 147 | 14 | 9.5(5.5-15.8) | |
| **Perinatal Asphyxia** | | | | | |
| | **Present** | 21 | 1 | 4.8(0.3-25.9) | 0.489 |
| | **Absent** | 160 | 17 | 10.6(6.5-16.7) | |
| **Maternal TB Co-infection** | | | | | |
| | **Present** | 29 | 2 | 6.9(1.2-24.2) | 0.774 |
| | **Absent** | 159 | 16 | 10.1(5.9-15.6) | |
| **Congenital TB** | | | | | |
| | **Present** | 12 | 1 | 8.3(0.4-40.2) | 1 |
| | **Absent** | 164 | 16 | 9.8(5.9-15.6) | |

CI, confidence interval.

N = data available, n=number of infants that demised

# 4 CHAPTER V: DISCUSSION

## *4.1 Main discussion*

In this observational study, the perinatal HIV-1 transmission and mortality rates and their associated factors were examined in HIV exposed infants who were followed up after receiving specialised neonatal care.

This chapter summarizes the main findings of the research and compares it to current literature. The implications of negative findings are also explored.

The study period was from November 2007 to December 2009, which was a transitional period when the PMTCT guidelines were changed. The dual therapy era continued for duration of two years before changing again in 2010.

The study population was mainly from the surrounding areas in Durban. Having a large catchment area and servicing two provinces, it was expected that KEH VIII$^{th}$ Hospital would have a wider representation of patients from different geographical areas. But the furthest geographical areas were Pietermaritzburg and Port Shepstone, and only a few patients from these areas were included. Thus the study is mainly a representation of the local feeder clinics in the district.

Overall, the most common mode of delivery in the study was the caesarean section (c/section) (56.6%). Emergency caesarean section (EMCS) (43.3%) and normal vaginal delivery (NVD) (43.3%) were more common modes of delivery than elective caesarean section (ELCS) (13.2%). The EMCS rate was expected to be high in this setting, as many preterm and LBW babies are delivered via this mode.

According to the District Health Information System Database, the provincial c/section rate during 2008 and 2009 was 25.8% and 29.4% respectively.[74] This is comparable to the rate in KEH VIII$^{th}$ Hospital, which was 30% in 2007 (Department Statistics, KEH 2007). It is not uncommon for a hospital of this nature to have a high c/section rate as high risk patients are referred from feeder clinics and other hospitals for the facilities and expertise.

The role of the ELCS in decreasing the rate of HIV transmission is well documented.[16, 75-76] The International Perinatal HIV Group demonstrated this advantage in those that had ELCS before the onset of labor or prior to rupture of membranes. Once adjusted for maternal ARV's received, maternal HIV stage and the infant birth weight, the likelihood of transmission decreased by 50%.[75] In our analysis, there were no documented transmissions in the ELCS group and hence a 100% reduction in transmission; however there was insufficient data to adjust for the receipt of maternal ARV's and maternal stage of disease. No significant difference in transmission was noted in the ELCS group when compared to the other groups (EMCS 11.8% transmission and NVD 14.7% transmission) (p=0.221). This may be attributed to the small sample size. There was no demonstrable difference in transmission rates between infants delivered via EMCS and NVD either.

The majority of infants in the cohort were LBW, and were born to mothers younger than 30 years of age. This was expected because they are born to a category of women who are in their reproductive years and hence are vulnerable to HIV infection.

The mothers in this study had evidence to suggest more advanced HIV disease. The maternal CD4 count was expectedly low with a median of 309 cells/$mm^3$ and 54.1% had a CD4 count less than 350cells/$mm^3$. Feeder antenatal clinics refer sicker HIV positive mothers to the KEH $VIII^{th}$ Obstetric Unit for further management.

The study was unable to provide a more detailed evaluation of maternal health, as there was a lack of recorded data concerning the relevant factors. Assessment of maternal body weight, BMI, haemoglobin and maternal viral load would have assisted in creating a clearer picture of the antenatal environment that the infant was exposed to. So too would a history of prolonged rupture of membranes. These factors would have clearly affected the early transmission rates. And, although there were records of the WHO staging, this was neither rigorous enquiry nor was it revised as the maternal disease progressed.

The risk factors for breast milk transmission were not explored either. This would have included maternal viral load, sero-conversion during breastfeeding and subclinical mastitis. Apart from the maternal viral load, these would have predominantly affected the late transmission rates, which have not been reported in this study. But as a result of late transmission, these factors would most certainly have an effect on the infant mortality rate, which is an objective of the study.

Early infant transmission and infant mortality are indirectly proportional to the maternal antenatal CD4 count.[51] It was expected that those infants born to mothers with low antenatal CD4 counts would have had higher transmission rates and a higher infant mortality, but the study did not show this. The analysis did not demonstrate any significant differences in vertical transmission rates or infant mortality rates between CD4 counts <200cells/$mm^3$ and > 200cells/$mm^3$ or < 350cells/$mm^3$ and >350cells/$mm^3$. A confounding factor involved in this circumstance perhaps is that those mothers with lower CD4 counts had progressive disease with severe morbidities and disabilities. An inability of these mother-infant pairs to attend the clinic may result in a poor pick up rate of early transmission and mortality in the lower range CD4 counts. Improving loss to follow up rates would aid in more clearly demonstrating the differences within these groups and would correlate more closely with current literature.

A significant risk of HIV transmission exists when the maternal CD4 count is between 200 and 350cells/$mm^3$. This was demonstrated in a recent Zambian study, where 82% of postnatal HIV transmission occurred in those with maternal CD4 counts less than 350cell/$mm^3$, and approximately 47% of transmission occurred in those with maternal CD4 counts less than 200cells/$mm^3$. Thus 35% of transmissions where occurring between 200 and 350cells/$mm^3$ CD4 count range. Similarly, 84% of all maternal deaths occurred when the maternal CD4 counts were less than 350cells/$mm^3$; while 55% of maternal deaths occurred when the CD4 counts less than 200cells/$mm^3$.[11] Therefore a significant proportion of transmission and maternal deaths occur between the 200 to 350cells/$mm^3$.

During the period of this study, the criteria for the initiation of maternal HAART included a CD4 count below 200cell/$mm^3$ and/or WHO Stage IV. Those that were WHO Stage I-III and

had CD4 counts above 200cells/$mm^3$ were excluded; hence many mothers with CD4 counts within this risky category (200-350cells/$mm^3$) did not benefit from the initiation of HAART. This was explored in the data available to see what the impact of this exclusion was on transmission rates and it was found that the transmission rate in infants that were born to mothers with a CD4 count <350cells/$mm^3$ was 13.5%; while the rate of transmission in those with CD4 count <200 cells/$mm^3$ was 12.3% (p=0.806). With a 1.5% difference in transmission rates between the two groups, the infants in this study were not found to be at a higher risk of HIV infection, if born to a mother with a CD4 200-350cells/$mm^3$.

The percentage coverage of HAART in those that require it is an important health indicator. It was found that 28.1% of the mothers had advanced HIV disease and required HAART. Based on the CD4 count threshold of <200cells/$mm^3$, it was noted that 56.2% of them qualified but were not commenced. Thus, in those that qualified, the HAART coverage of 54.8% was poor, but parallel to the national average at the time(54.2%)[77].

Maternal HAART protects against vertical transmission and infant mortality.[20, 34] In the analysis it was shown that infants exposed to maternal HAART were less likely to die at 1 year of age, compared to infants who were not exposed to maternal HAART at birth (2.9% vs. 10.2%). Even though this did not reach significance, it suggests, as does current literature, that maternal HAART protects against infant mortality. Mothers that are not on HAART are at risk of disease progression and death postnatally and this is associated with increased infant mortality.[51, 56]

Maternal pulmonary TB was the most frequently documented co-infection in this cohort and this resulted in a large proportion of the mothers being classified as WHO clinical stage 3 (Pulmonary TB is a WHO clinical stage 3 disease). TB co-infection is 10 times higher in HIV infected than in HIV uninfected mothers and the case load of TB co-infection in pregnant women in Durban are reported to be very high.[78] In the current guidelines, HIV infected mothers with TB co-infection qualify for HAART, but that was not the case over the period of the study.

Congenital TB was diagnosed in 25.6% (20/78) of infants exposed to maternal antenatal TB, with no predilection toward those that were HIV infected (p=0.378). This vertical transmission rate of TB (VTRTB) is much higher than what has been previously described. Pillay et al. in a prospective study done in KEH VIII$^{th}$ Hospital, in 1999, reported a VTRTB of 16% associated with a high rate of HIV co-infection and an increased risk of infant mortality.[79] Further evaluation of why the VTRTB in this cohort is so high is required as it comes from the same setting but a decade later. The methods of diagnosis of TB in the neonates in this cohort have not been explored and will need study prior to any conclusion being made. The diagnosis of congenital TB or the exposure to maternal TB, in our study was not associated with a higher infant mortality.

The overall perinatal transmission rate in this cohort was 11.5%. The majority of the patients received dual therapy because the study was done over the dual therapy era. Only 2.56% of mother infant pairs had no exposure to either maternal ARVs or infants ARV's. These patients represented those that were unbooked and failed to initiate PMTCT antenatally. The absence

of infants ARV prophylaxis reflected a failure of the staff to administer the prophylaxis postnatally.

A study by Rollins et al., between 2004 and 2005, described an overall vertical transmission rate of 20.2%. Their study population included babies attending immunization clinics at 6 weeks and the ARV regimen used for PMTCT during that period was sdNVP to mother and baby. [26]

They reported a transmission rate of 26.0% in those mothers and infants who did not receive ARV prophylaxis. Cooper et al. reported a rate of 20.0%.[20] These rates are both similar to the rate described in our study, 20%, in those that were not on ARV prophylaxis. Single dose NVP usage in their cohort was associated with a reduction in transmission to 15% compared to the reduction seen in our cohort to 14.3%. But while their study was able to report a significant association between the use of sdNVP and the reduction of vertical transmission, this study was able to show the trend but did not reach significance. It would be important to reach a significant level in this study so as to report the rates in a cohort of predominantly LBW babies, which most other studies do not report on.

The benefits of dual therapy over single therapy are well known.[80] The provision of dual therapy in this cohort, over single therapy usage or no ARV usage was shown to decrease the vertical transmission to 10.6%. However, although, the calculated relative risk of dual therapy usage over the two older regimens reflected a benefit, the 95% CI were too wide. This is probably due to the relatively small number of infants who were infected.

The Western Cape reported that dual therapy usage resulted in vertical transmission rates of 8%, while in Tygerberg Hospital, in 2008, a higher transmission rate of 10.1% was described in a cohort with maternal CD4 counts predominantly < 250cells/mm$^3$.[31, 81] The overall transmission rates reported by the National Department of Health (SA) in the National Strategic Plan, was 10% in 2009,which was during the dual therapy period.[33] The rates of transmission varied across provinces and across the country, but the rates reported in this study are similar to the overall figures.

Babies in this study benefited significantly from receiving the regimen of 7 days of AZT (i.e. maternal AZT was received for more than 4 weeks) over the 28 day AZT regimen, where mothers received less than four weeks of antenatal AZT. (6.7% transmission vs. 14.8%) Antenatal AZT reduces the maternal viral load in-utero and perinatally and the duration of antenatal ARV exposure is also an important factor in the prevention of HIV transmission to the infant.[22, 80] Although there are known factors associated with a higher transmission, exactly when HIV transmission occurs in-utero is uncertain. By administering AZT earlier during pregnancy, a lower maternal viral load can be achieved. AZT is also transferred transplacentally, and increases to therapeutic levels in the fetus.[82] Hence, a longer antenatal AZT duration, reduces the period of fetal exposure to the virus as well as exposure during labor. In this study, the data shows that those pregnant women who had failed to be initiated on AZT more than 4 weeks prior to delivery, risked transmission in-utero and/or peripartum. Furthermore, administering AZT to the infants post delivery, even with the prolonged duration of 28 days, was not able to effectively salvage these infants. The conclusion is that more emphasis should be placed on antenatal initiation of AZT.

Maternal HAART for the improvement of maternal health was associated with the lowest transmission rate, when compared to the ARV prophylaxis used in the PMTCT programme (8.5%). However, this rate is inconsistent with other studies that report much lower transmissions. Cooper et al., in the USA, reported a transmission rate of 1.2 % in women receiving HAART.[20]

In South Africa, the transmission rates with maternal HAART are reported to be between 2.1 – 4.3%.[83-84] A local operational study, in the Eastern Cape, followed up mothers on HAART, and found that the overall transmission rate was 2.4% but varied according to the maternal viral load (VL). Those with a high VL (>1000 copies) had a higher transmission rate of 7.8%. Transmission was also significantly higher in those that received HAART for < 10 weeks (4.2%) and in premature births the transmission rate was at its highest at 8.6%.[36]

Thus in our cohort who were predominantly LBW, and most likely premature, the rate of transmission was very similar at 8.5%. This again highlights the importance of the duration of antenatal ARV exposure. Pregnancies that are at risk for premature delivery are certainly at a disadvantage as the duration of maternal HAART is shortened and hence the risk of transmission to the foetus and infant is increased. No significant benefit of the use of HAART over all the other PMTCT regimens was shown in this study, but again this maybe a function of the design of the study and the size of the cohort.

The benefit of infant antiretroviral prophylaxis with regards to infant mortality at 12 months could be seen when the mortalities in the single therapy group (26.9%) were compared to the

mortalities in the dual therapy group (6.2%): the use of dual therapy had a significant effect on mortality. This effect was not seen with any of the other regimens.

Complete elimination of breast feeding to prevent the vertical transmission of HIV-1 in our setting is not possible as there are many factors associated with replacement feeding that increase the risk of infant death. Replacement feeding carries the risks of gastroenteritis, infectious diseases and malnutrition if not used appropriately. Thus, in HIV positive mothers, where replacement feeding was considered to be a risk, exclusive breastfeeding for 6 months was advocated in the national PMTCT guidelines of that time.

Even though these were the prevailing guidelines during the period of study, 62.9% of mothers in this cohort still chose to replacement feed, while 29.2% reported breastfeeding. These feeding choices were recorded at the first follow up clinic, around 6weeks postnatally and they may have changed at a later stage.

A significant difference in early vertical transmission rates was found between the breastfeeding group (18.4%) and the formula feeding group (8.76%). This could be explained by the fact that although the PMTCT guidelines state that infant HIV DNA PCR testing, should be done at 6 weeks, this is not always the case: infants are often tested outside of that time.

The measures that were taken in this study to avoid complicating the perinatal transmission estimates were the exclusion of HIV DNA PCR results reported to be been taken after 8 weeks. However, it was not possible to not account for the way in which the results were

documented in the neonatal follow up forms; and if there was no rigorous enquiry as to when exactly the mother had taken her infant for testing, then these described transmission rates are overestimated because of the inclusion of very early transmission of HIV due to breastfeeding or mixed feeding. Thus, the rate of transmissions here represents the early vertical transmission via breastfeeding and not just in-utero or intra-partum perinatal transmission.

Early transmission within 6 weeks via breastfeeding can occur. Nduati et al., in a randomised control trial, described higher cumulative HIV-1 infection rates in breastfeeders 19.9% compared to formula feeders 9.7% at 6 weeks. There was a significant difference in cumulative HIV-1 infection rate at birth and 6 weeks between breast and formula feeders (10.2%).[85]

In our study the data on feeding practices is based on what the mother reported at the follow up clinic and may not be consistent with what was given to the infant during admission in the neonatal unit. A limitation of this study was that early feeds given in those first few days of admission, were not documented for this study and it is highly likely that many of the infants were given formula feeds in the first few days if mothers and/or infants were not able to breastfeed. This is likely to happen if the mother is immobile post c/section, or bedridden due to severity of illness. The transmission rates that were recorded in the breastfeeding infants are therefore very likely associated with non-exclusive breastfeeding which has been shown to increase transmission probably due to introduction of potential allergens or pathogens inducing gut epithelial damage.[5, 86-87]

This highlights the importance of promoting exclusive breastfeeding especially in vulnerable low birth weight infants. The South African government's new commitment to breastfeeding promotion has taken cognisance of this and recommends an integration of human milk banks into post natal wards and neonatal intensive care units so that vulnerable infants who do not have access to their mother's own breast milk can be provided with donated breast milk (Tshwane Declaration, August 2011). Furthermore it also points to the importance of infant ARV prophylaxis during breastfeeding which is addressed in the current PMTCT guidelines.

In this study, infant mortality at 12 months was significantly associated with breastfeeding compared to formula feeding (17.8% vs. 6.5%; p=0.038). This was probably mediated through the increased risk of HIV transmission due to very early formula feeding, as discussed above.

Research shows that exclusive breastfeeding is associated with late vertical transmission of HIV-1, but less so than mixed feeding.[86, 88] While infants that exclusively breastfeed to up 6 months have a similar rate of HIV transmission to replacement feeders, prolonged breastfeeding over 6 months (the age when infants are usually weaned onto soft diets thus resulting in non-exclusive breastfeeding) is associated with new infections.

The MASHI study showed that early mortality was significantly higher in a formula fed group than in a breastfed (with AZT) group, even though the HIV transmission rates in the breast fed group were higher.[45] In this particular study in spite of the AZT not being effective in reducing HIV transmission in the breastfed infants, breastfeeding afforded protection against mortality compared to formula feeding.

Birth weight is a used an indicator of both fetal and neonatal wellbeing and it is a factor that is strongly associated with infant mortality. The birth weight is affected by the gestational age of the infant and the quality of fetal growth. In this study the distinction between small for gestational age and appropriate for gestational age could not be made because there was no data available on gestational age. The use of gestational scoring tools like the New Ballard Score is not routine in this setting, and even if there were records of these scores, the accuracy would be uncertain.

HIV infected mothers deliver smaller babies. A meta-analysis by Brocklehurst et al. in 1998, to investigate the association between perinatal outcomes in HIV infected mothers, found a significant association with LBW (OR 2.09) and intrauterine growth retardation (OR 1.79).[37] Also, HIV infected infants are born smaller. A prospective study, by Nair et al., looking into the characteristics of 134 HIV infected newborns reported a significantly lower birth weight in infected compared to uninfected newborns. [38]

Only a handful of studies have looked into whether the LBW baby is at a higher risk of becoming HIV infected. They describe a positive association with infant HIV infection and LBW and suggest that LBW infants are more at risk for transmission because of immunological and biological immaturity.[38, 40-41] Mwanyumba et al., were able to show that LBW infants were at a higher risk of acquiring HIV over the peripartum period, rather than in-utero.[39]

The infants in this cohort that were infected had a relative risk of LBW of 1.4 compared to average birth weight infants. Low birth weight infants in this study did not have a significantly higher risk for vertical transmission of HIV-1; moreover in-utero transmission and peripartum transmission cannot be differentiated in this study as, HIV testing at birth was not done.

LBW in this cohort was significantly associated with infant mortality at 12 months; 13.6% of deaths were in the LBW group and 3.17 % in the average weight group. 35.9% of the LBW infants that demised were also HIV infected. These rates were not adjusted for HIV infection, maternal antiretroviral regimen, or maternal CD4 count.

The overall perinatal transmission rate in this cohort was 11.5%; while the overall infant mortality at 12 months of age was 10%. This study reports that 28% of infants infected with HIV demised before the age of 1 year compared to the 5.9% of infants who demised that were uninfected at 6 weeks. There was a significant risk of mortality in those infants that were HIV infected (p=0.002). These results are in keeping with current literature. That HIV infected infants have a higher mortality when compared to HIV exposed and uninfected infant is known.[50,51] In addition, infants that are exposed but uninfected are at higher risk than the HIV unexposed infant of death. [50] The study did not explore this association, because the cohort only consisted of HIV exposed infants and those infants that were unexposed were excluded.

Advanced maternal HIV disease, characterised by low CD4 counts, high antenatal viral loads and co-infections with TB, CMV, hepatitis C, human herpes virus 8, are associated with increased shedding of not only the HI virus but also other viral infections. It has been

suggested that this phenomenon increases the risk of congenitally and vertically acquired neonatal infections. This is further exacerbated by the decreased passive transfer of immunoglobulins from an immunocompromised mother to her newborn, either transplacentally or via breast milk, resulting in an increased risk for future infection like measles.[56] These factors would have very likely affected the outcomes of the infants. It would be important to closely document the types of infections that the infants in this cohort would have been exposed to and had developed and how this may have influenced their mortality. However, the design of this study is not geared to accommodate all these factors.

Newell et al. estimated that the mortality of HIV infected infants at 12 months was 35.2% compared to those infants that were exposed but uninfected (4.9%). They noted that this was reported from a research setting with better health support than other settings.[51] Thus the authors suggested that the mortality rates may be even higher. The mortality rate in this study's cohort is unexpectedly similar to what was reported by Newell et al. Here the mortality in the infected infants was found to be 28% and 5.9% in the uninfected infants. This was lower than expected, for a cohort that was comprised 63.9% LBW compared to the Newell et al. study that comprised 10% LBW.

Moreover, it is likely that in those infants whose mothers had demised postnatally, the mortality rate would be higher. These patients are also more likely to be lost to follow up at the neonatal clinic. Newell et al., reported a higher infant mortality rate in uninfected infants, that lost their mothers.[51]

The neonatal clinic experienced a very high loss to follow up rate and this must be considered when looking at the reported infant mortality rate in this study. The majority of the infants born within the study period and that were booked for follow up at the neonatal clinic, were not brought for follow up by their caregiver. Of the 463 patients that attended the neonatal follow up clinic for their first visit 4-6 weeks postnatally, only 188 patients had records to ascertain their outcome a year later. The percentage of infants that were loss to follow up in this study was 59% (275/463).

The loss to follow up rate impacts on many factors, including undetermined HIV transmission rates and mortality rates. It is a significant problem faced both in practice and in a research setting. Large trials, whether simple or complex, experience substantial rates of loss to follow up, particularly in Africa. Some factors include low maternal and paternal education, geographical location and high neonatal and infant mortality.[89] These factors reflect the environment in which this study was done.

LBW is a known factor associated with increased loss to follow up, as they have a higher NMR and IMR. [90] Moreover, maternal HIV infection is linked to higher NMR and IMR.[37] This cohort is by majority LBW with all mothers being HIV infected with an expected high loss to follow up rate. The transmission and mortality rates should be interpreted with caution particularly when comparisons are being made to other studies, as these factors have the potential to distort these rates.

The study showed that early HIV infection was associated with a significantly higher rate of suspected or proven sepsis during the admission of the neonate. Studies have reported on similar findings, but generally with confirmed bacterial infections.[38]

Of significance was that HIV infected infants required less ventilation than the uninfected infants. In a predominantly LBW cohort, premature infants with respiratory distress syndrome generally require ventilation. It has been established that HIV infected infant are more likely to be born small for gestational age and growth retarded. The results suggest that infants that are infected are probably more mature and thus at a lower risk for diseases of prematurity.

Of note is that perinatal asphyxia did not contribute much to the infant mortality. Only 1 of the infants reported to have demised, was diagnosed with perinatal asphyxia while admitted to the nursery.

Other neonatal problems were not significantly associated with either HIV infection or infant mortality.

## *4.2 Bias and limitations*

Selection biases existed in this sample of patients as they were sick infants and were essentially at higher risk for morbidities and mortalities, thus the finding are not generalizable to healthy newborns. The maternal background illnesses also place them in an inherently higher risk category.

The data on the feeding practices were prone to recall bias. It should be assumed that the maternal report on feeding practices is based on a 24hr recall. Ideally a more rigorous enquiry on the feeding practices at each neonatal follow-up interview should be done. However, since this was a retrospective study we could not validate the feeding choices and it was likely that the mothers had changed their feeding practices.

Those infants that demised missed their scheduled appointments and would have been considered "lost to follow up", had we not been told this information during rescheduling. This is a confounding factor, as those infants who demise are automatically loss to follow up and the result is that we are able to account for a lot more live infants.

Similarly, if the mother was too ill to attend the clinic or if she had demised, the infant would have been more likely to be lost to follow up , and have higher odds of dying.[51] As a consequence, the mortality rate that we have reported is likely to be underestimated.

A major limitation was the study design. This was a retrospective study and data collection was unavoidably problematic. Records were incomplete and this affected the sample size and the power of the study to compare certain variables against each other. Whereas the use of a prospective longitudinal study design would have been ideal for obtaining transmission rates and long-term infant follow up outcomes, it was not possible without the appropriate manpower and funding.

A further limitation to the study was that it did not compare the outcomes between HIV exposed uninfected infants and HIV unexposed infants. Routine data collection at the clinic, for those infants that were HIV unexposed was not as rigorously maintained as that for those that were exposed. The records for these infants were filed separately in a less organized manner. It would have been possible to collect and analyse this data, however the scale of the study would have been increased and would have required more manpower.

Patients are seen by many doctors in the neonatal clinic; hence the data that was filled in the neonatal follow up form was done by a number of doctors. This affected the consistency in the way the data was documented, and this resulted in incomplete data sets. The effect of this was a reduction in the sample size of groups that we compared.

A further limitation was the inability of the study to report the gestational age of the infants. A distinction between small for gestational age and average size for gestation could not be made because of the lack of data on gestational age. This distinction has implications for diagnosis and prognosis.

# 5 CHAPTER VI: CONCLUSIONS AND RECOMMENDATIONS

## *5.1 Conclusions*

The rates of HIV transmission, while on different ARV prophylactic regimens for PMTCT was parallel with reported international studies and with the National Department of Health figures. HIV transmission in the infants from neonatal unit reflected a similar decreasing trend that was seen locally and internationally.

Results from the use of 7 and 28 day AZT regimens suggest, as current literature has shown, that an increase in the duration of maternal antenatal ARV, in this infant population, is associated with a lower vertical transmission rate.

Although the results were not statistically significant, the study was able to reflect the protective effect of antenatal maternal HAART on vertical transmission and infant mortality rates. However, the maternal HAART coverage, although parallel with the national HAART coverage was sub-optimal. Many mothers, who qualified for HAART, were not commenced.

The early vertical transmission rate was significantly increased by breastfeeding. It can be concluded from this study that in a predominantly LBW population, with vulnerable and most probably premature immunities, meticulous attention needs to be paid to the feeding practices, from the time of admission into neonatal units.

The susceptibility of the immature gastrointestinal tract to infection is high and measures to decrease HIV transmission via this route must be instituted while the infant is admitted in the unit. These should include the strict adherence to AFASS criteria, appropriate exclusive breastfeeding practices, and emphasis on the importance of administering colostrum and "own mother's milk" to the newborn. The importance of ARV prophylaxis over the duration of breastfeeding in an HIV positive mother is highlighted in this study.

The study was able to provide an indirect estimate of the infant mortality in this group of patients. Although infant mortality is subject to many other factors that have not been factored into this study, the data reported here can be used as a point of reference to measure the outcomes of the HIV exposed infants at the follow up clinic at a later stage.

## *5.2 Recommendations*

Pregnant women with advanced maternal HIV disease should be commenced on HAART early in the pregnancy as the risks of premature delivery are high and a longer duration of antenatal ARV exposure is beneficial to the infant with respect to HIV transmission. Though this may not be possible for emergency deliveries at KEH VIII$^{th}$, a system of feedback must be instituted so that the referring centres are made aware of vulnerable mother infant pairs.

The current method of monitoring the performance of the PMTCT programme is not ideal in specialized neonatal care setting as does not take into account the nature of the infants' diseases and the exposures that they are subjected to. The evaluation of PMTCT programmes

normally employs the use of indicators. For example, how many babies received ARV prophylaxis or had HIV DNA PCR tests. These are programmatic indicators that help in improving implementation of interventions. The outcomes do not translate well into clinical outcomes (i.e. long term morbidities, transmission of HIV and survival). A modified system of evaluation of HIV exposed infants discharged from the specialised neonatal care setting is required.

Neonatal intensive care units must prioritise the development of human milk banks in accordance with the Tshwane Declaration, in the effort to reduce infant mortalities and morbidities associated with HIV.

Both the reported transmission rates and the mortality rates in this study provide important information needed for monitoring trends in this setting. Repeated auditing of this nature is required to monitor the impact of current interventions on this population of high risk infants.

The study has highlighted some constraints in the neonatal follow-up system. Loss to follow-up rates is high and ways to reduce this must be explored and implemented. This is a valuable step in improving the monitoring of vulnerable infants and should be viewed as part of a process of development in the health system of the country.

## *5.3 Recommendations for further study*

Alteration of immune response and of clinical presentation has been described in the HIV exposed, uninfected population.[55, 91-93] A study comparing the mortality and morbidity of HIV exposed uninfected and HIV unexposed infants, would help to further define the high risk population.

A prospective cohort study, looking at the feeding practices in HIV exposed premature infants in neonatal units is warranted. The associations between transmissions of HIV via breastfeeding and the patterns of early feeding, type of feeds administered, use of colostrum, and factors that result in disruption of the gastrointestinal tract, including subclinical oropharyngeal trauma resulting from vigorous oral suctioning, need investigation.

The study describes a 38% increase in congenital TB over a decade. Further investigation of the reason for the increase in vertical transmission rate of TB is recommended. The methods of diagnosis of TB in the neonates in this cohort have not been explored. A clinical audit in view of this may be warranted.

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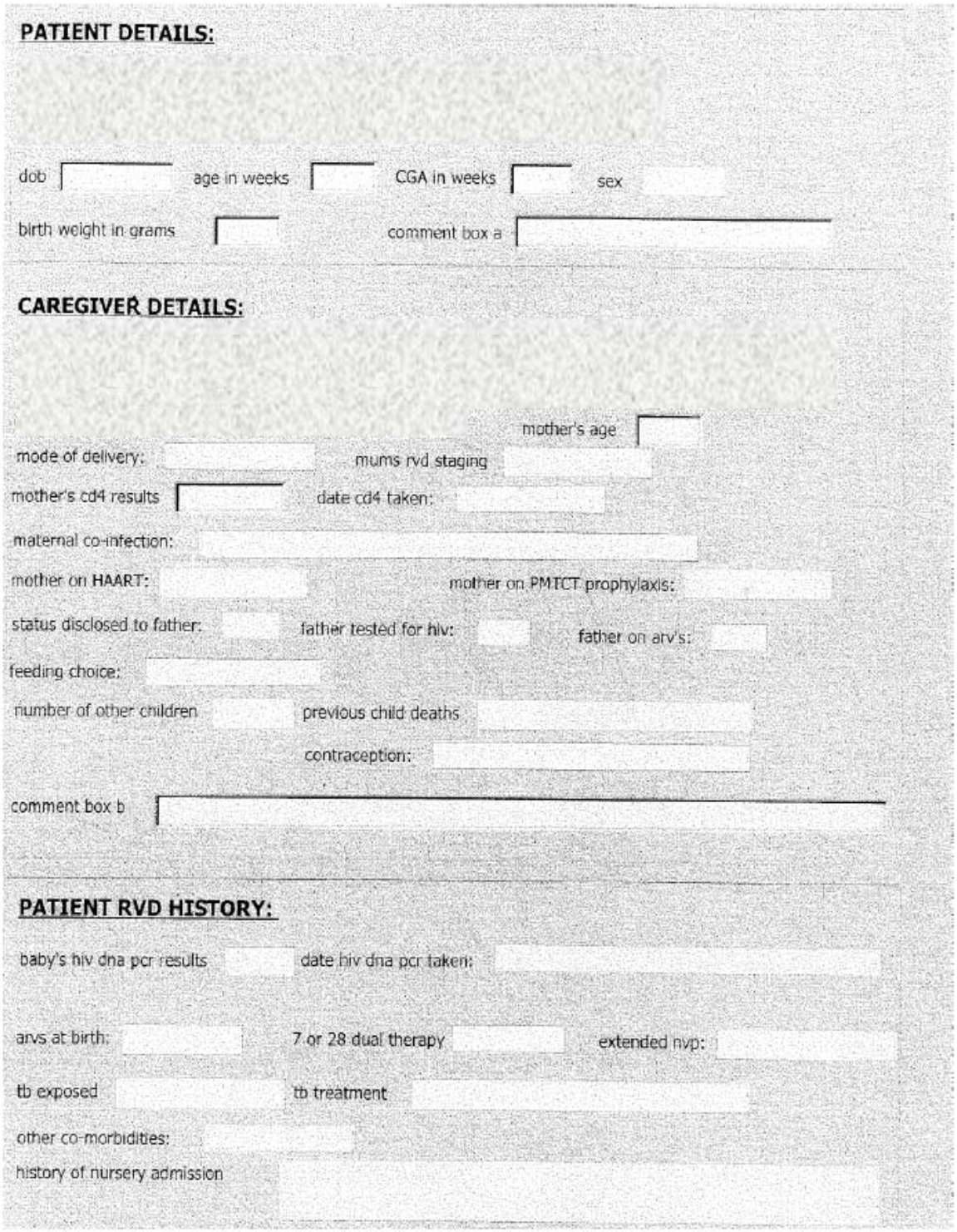
# 7 APPENDIXES

## *7.1 NEONATAL CLINIC FOLLOW UP FORM*



**PATIENT DETAILS:**

dob | age in weeks | CGA in weeks | sex

birth weight in grams | comment box a

**CAREGIVER DETAILS:**

mother's age

mode of delivery: | mums rvd staging

mother's cd4 results | date cd4 taken:

maternal co-infection:

mother on HAART: | mother on PMTCT prophylaxis:

status disclosed to father: | father tested for hiv: | father on arv's:

feeding choice:

number of other children | previous child deaths

contraception:

comment box b

**PATIENT RVD HISTORY:**

baby's hiv dna pcr results | date hiv dna pcr taken:

arvs at birth: | 7 or 28 dual therapy | extended nvp:

tb exposed | tb treatment

other co-morbidities:

history of nursery admission

## *7.2 RESEARCH PROJECT APPROVAL BY POSTGRADUATE EDUCATION COMMITTEE*

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI

11 October 2011

Professor M Adhikari
Dean's Assistant
MMed Programme
NRMSM

Dear Professor Adhikari

**PROTOCOL:" Transmission rates of HIV-1 and mortality rate in high risk infants exposed to HIV, in the PMTCT programme, at the Neotal unit, of King Edward VIII Hospital, Durban, South Africa"N Nair 973119099 – MMSHIV**

The Postgraduate Education Committee ratified the approval of the abovementioned study on 02 August 2011.

Please note:

- The Postgraduate Education Committee must review any changes made to this study.
- The study may not begin without the approval of the Biomedical Research Ethics Committee.

May I take this opportunity to wish the student every success with the study.

Yours sincerely

Professor SJ Botha
**Chair: Postgraduate Education & Research Committee**

CC. Dr N Nair

Biomedical Research Ethics Committee
Westville Campus

## *7.3 RESEARCH PROJECT APPROVAL ROM THE BIOMEDICAL RESEARCH ETHICS COMMITTEE*


**UNIVERSITY OF KWAZULU-NATAL**

**INYUVESI YAKWAZULU-NATALI**

RESEARCH OFFICE
BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 260-4609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx


**18 October 2011**

Dr Nadia Nair
Department of Pediatrics
Enhancing Care Initiative
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

Dear Dr Nair

**PROTOCOL: Transmission rates of HIV-1 and the mortality rate in high risk infants exposed to HIV, in the PMTCT programme, at the Neonatal unit, of King Edward VIII Hospital Durban, South Africa. REF: BE254/010**

## EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 10 December 2010.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 10 October 2011 to queries raised on 25 January 2011 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 18 October 2011.

This approval is valid for one year from **18 October 2011.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/ResearchEthics11415.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **08 November 2011.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

## *7.4 PERMISSION FROM LOCAL HEALTH AUTHORITY*

health
Department:
Health
**PROVINCE OF KWAZULU-NATAL**

**Health Research & Knowledge Management**
10 – 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg, 3200
Tel.: 033 – 395 2895
Fax.: 033 – 394 3782
Email : hrkm@kznhealth.gov.za
www.kznhealth.gov.za

**Reference : HRKM 148/11**
**Enquiries : Mr X. Xaba**
**Telephone** : 033 – 395 2805

Dear Dr N. Nair

**Subject: Approval of a Research Proposal**

1. The research proposal titled **'Transmission rates of HIV-1 and the mortality rate in high risk infants exposed to HIV, in the PMTCT programme, at the Neonatal unit, of the King Edward VIII Hospital (KEH), Durban, South Africa'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby approved for research to be undertaken at King Edward VIII Hospital from this approval to December 2011.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba.

Yours Sincerely

**Dr E. Lutge**
Chairperson: Provincial Health Research Committee
KZN Department of Health
Date: 07/11/2011