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DEVELOPMENTAL STATUS OF HIV EXPOSED PREMATURE INFANTS

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A research report submitted to the Faculty of Health Science, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Masters of Science Physiotherapy.

Johannesburg, 2018

Abstract

South Africa is responsible for a large number of new HIV infections annually. HIV^+ pregnant women can transmit the virus to their unborn children during the in-utero and intrapartum periods if they are not on antiretrovirals (ARVs). In South Africa all HIV^+ pregnant women, regardless of CD4 count, can receive ARVs in order to prevent mother-child-transmission. It is due to this that fewer infants are being born HIV^+.

Studies have shown that premature delivery is likely to occur when a mother is HIV^+. Being born prematurely can have an impact of the development of an infant as some body systems are not yet fully mature.

It has been proven that HIV can have a negative impact on the development and functioning of children but few studies have been done to determine whether HIV and ARV exposure in-utero have an impact on the developing foetus.

Therefore, the aim of this study was to determine if there is a difference between the development of premature infants born at 28-37 weeks gestational age that are HIV exposed uninfected compared to HIV unexposed uninfected at 16 days to six months corrected age. Other objectives included to determine whether clinical and demographic factors are predictive of developmental status.

This non-experimental cross sectional quantitative study was done in a regional state hospital in Gauteng, SA. A once off assessment was done on 30 HIV exposed uninfected (HEU) infants and 30 unexposed uninfected (HUU) infants. They were assessed using the Bayley Scales of Infant and Toddler Development III which assesses cognitive, language and motor development.

The mean developmental scores for all facets of development were within one standard deviation of the norm for both groups. It was found that the HUU infants had lower developmental scores when compared to the HEU infants in the language ($p=0.003$) and motor ($p=0.037$) subscales. Expressive language was more affected than receptive language ($p=0.00$) and both fine ($p=0.00$) and gross motor ($p=0.03$) were affected.

HUU infants with neonatal complications such as meningitis (p=0.02) and NNJ (p=0.01) are more likely to present with language and motor delay when compared to the HEU infants. There was some evidence that HEU infants may present with some motor delay but the neonatal complications had more affect of the neurodevelopment of infants than the HIV and ARV exposure in-utero. Socioeconomic factors such as housing, water, electricity and family structure were well matched between the two groups.

This study suggests that HUU infants with neonatal complications may be more delayed when compared to HEU infected infants. Neonatal complications such as meningitis and NNJ have more impact on infant development than in-utero HIV and ARV exposure. These complications have an effect on expressive language, gross motor and fine motor development. It is of utmost importance for all premature infants to be screened on a regular basis in order to determine delays early on during development in order to ensure early intervention and improved quality of life.

DECLARATION

I Charné Cox declare that this Research Report is my own, unaided work.

It is being submitted for the Degree of Masters in Physiotherapy at the University of the Witwatersrand, Johannesburg.

It has not been submitted before for any degree or examination at any other University.

_____

(Signature of candidate)

_____day of_____20_____in_____

Acknowledgements

I wish to acknowledge the following people for the roles they have played in the completion of this study:

Prof. Joanne Potterton for her incredible guidance throughout the study and always being available to assist and impart her knowledge, even on weekends

Samantha Rosie for your support

Chris Christoforou for assisting me with the statistical analysis and taking time out of your weekends to do this. Also for always having the patience to explain the analysis and help me understand all aspects

Tambo Memorial Hospital Management and staff for allowing me to do my study at the hospital and helping me with translations when English was not the caregiver's first language

TMH physio colleagues for assisting me with my patient loads on days when infants needed to be assessed and for also translating for me when needed. As well as for the encouragement and support

My family and friends for always encouraging, motivating and supporting me throughout the study

Infant Caregivers for participating and allowing me to assess and learn from your babies

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List of abbreviations

ANC	Antenatal care
ARV	Antiretrovirals
BBB	Blood Brain Barrier
BMI	Body Mass Index
BSID III	Bayley Scales of Infant Development III
CI	Confidence interval
CLD	Chronic Lung Disease
CNS	Central nervous system
CP	Cerebral palsy
DoH	Department of Health
GDM	Gestational diabetes mellitus
HAART	Highly active antiretroviral therapy
HEU	HIV exposed uninfected
HIV	Human immunodeficiency virus
HUU	HIV unexposed uninfected
KMC	Kangaroo mother care
LBW	Low birth weight
MTCT	Mother to child transmission
NICU	Neonatal intensive care unit
NNJ	Neonatal jaundice
NNS	Neonatal sepsis
NRTI	Nucleoside reverse transcriptase inhibitor
PCR	Polymerase chain reaction
PI	Protease inhibitor
PMTCT	Prevention of mother to child transmission
PPROM	Preterm premature rupture of membrane
PTB	Premature birth
PVL	Periventricular leukomalacia
RDS/HMD	Respiratory distress syndrome/Hyaline membrane disease
SA	South Africa
SD	Standard deviation
TB	Tuberculosis

TD	Typical development
TMH	Tambo Memorial Hospital
WHO	World Health Organisation

Chapter 1

1. Introduction

1.1 Background

In 2015 there were approximately 36.7 million people living with HIV globally (UNAIDS, 2016). There was also 2.1 million new HIV infections and 1.1 million AIDS deaths in 2015 (UNAIDS, 2016). In 2012 there was a decline in HIV infections among children, which was due to a 62% Antiretroviral (ARV) coverage among pregnant women living with HIV. This reduced the number of children newly infected with HIV by 35% as compared to 2009 (UNAIDS, 2013). South Africa is responsible for 70% of all new HIV infections globally (UNAIDS, 2013). The UNAIDS report of 2016 noted that SA has almost doubled the number of people receiving ARVs and currently has 10.3 million people on treatment.

HIV positive women who are not on ARVs may transmit the infection to their babies during the in-utero and intrapartum periods as well as postpartum via breastfeeding (Hilburn, Potterton, & Stewart, 2010). Ninety five percent of HIV-positive children in South Africa become infected due to transplacental or intrapartum transmission, this is known as vertical transmission. In the absence of ARVs mother to child transmission of HIV is less than 10% during pregnancy, 10-20% during the birthing process and 10-20% during breastfeeding (Hilburn, Potterton, & Stewart, 2010). HIV mother to child transmission has been waning since 2008, when it was 8.5%. By 2012 the transmission rate was 2.6%, in 2013 it was down to 2% and in the 2016 report it was 1.5% which is considerably lower (Department of Health, 2014; Department of Health, 2016).

The Department of Health (DOH) National Report 2013/2014 stated that all women who are HIV^+ can receive ARVs regardless of CD^4 count. The DOH (2014) also noted that 77% of pregnant women that are HIV^+ attending antenatal care (ANC) have received ARVs since the implementation in April 2013 and by 2016 90% of

HIV^+ pregnant women received ARVs in the antenatal period (Department of Health, 2016). According to WHO 73% of all pregnant women living with HIV in 2014 obtained medication to prevent transmission to their babies and 32% of children received HIV treatment .

WHO stated that an estimated 15 million babies are born premature (less than 37 weeks of gestation) every year (WHO, 2018). This is more than 1 in 10 babies. Studies have shown that premature delivery is more frequent in HIV^+ women (Traisathit, et al., 2009). An increasing number of studies suggest that there is a higher risk of preterm birth and low birth weight among babies of women receiving HAART during pregnancy (Darak, et al., 2013). According to Ballot et al (2012) prematurity and low birth weight are both predictors of poor neurodevelopmental outcome.

The increase in preterm births in HIV infected women on HAART has been noted in developed countries in Europe and USA and recently in Africa (Darak, et al., 2013). This could be due to severe immunosuppression from delayed HAART initiation, an increase risk for opportunistic infections in HIV positive individuals as well as poor weight gain (Ezechi, et al., 2013). Extremely premature infants have been shown to have an improved survival rate due to advancing neonatal care but it has also been shown that these infants are more prone to a wide range of health-related complications (Ballot, et al., 2012). Owing to this there is an importance in assessing and monitoring premature infants for developmental delay on a regular basis.

A study done by Powis et al (2011) showed that 16.7% of their HIV infected participants had spontaneous preterm deliveries with 2.6% being very premature. They showed that these premature infants were more likely to experience at least one severe or fatal episode of respiratory tract infection in the first six months of life. They also noted that there was an increase in hospitalisation and mortality in these premature infants. This shows that health care professionals need to monitor these infants and ensure adequate education for the parents and or caregivers on the health of their babies and what they should look out for.

Infants of mothers who have not received HAART and have contracted HIV may show severe neurological and neurodevelopment abnormalities especially in the first

two years of life (Hilburn, Potterton, & Stewart, 2010). With HAART being more available, there are fewer mother to child transmissions with less infants being diagnosed as having HIV. HIV has also shifted from a terminal disease to a chronic illness that can be managed (Hutchings & Potterton, 2013).

Developmental delay of an infant may not only be due to HIV infection or the effect of medication in utero. There is also the effect of the new environment post birth for premature infants that will cause the stress levels of the infant to increase and therefore cause problems with growth and development (Ozdemir & Tufekci, 2013). This happens as extra uterine life exposes the infant to stressors such as disease, noise, light, painful procedures, medication and unnecessary stimulants (Ozdemir & Tufekci, 2013).

There are many other aspects that need to be considered with regards to development. Environmental aspects includes: the physical environment, social environment, family structure and the opportunities for play and exploration (Campbel, Palisano, & Orlin, 2012). Areas of poverty with limited resources and a lack of nutrition also need to be considered (Ali, 2013). One also needs to take into consideration the cultural beliefs and practices of the family as this can mean a difference in childrearing, feeding and child activities (Campbel, Palisano, & Orlin, 2012). Maternal aspects such as maternal mental health, age, nutritional status and medical history can all influence child development (Stevens, 2006; Yanuarti, Rusmil, & Effendi, 2014).

1.2 Problem Statement

With ARVs being available to all HIV^+ pregnant women fewer babies are being born infected with HIV but timely access to care still remains a concern. There are many studies that determine what the effects of HIV/AIDS has on the developmental status of an infant but not many have been done to determine whether exposure to HIV and ARVs in-utero have an effect on the developmental status of the uninfected pre-term infant.

1.3 Research Question

Is there a difference between the development of premature infants born at 28-37 weeks gestational age that are HIV exposed uninfected (HEU) compared to HIV unexposed uninfected infants (HUU), between the corrected ages of 16 days to 6 months?

1.4 Research Aims and Objectives

The aim of this study is to determine if there is a difference between the development of premature infants born at 28-37 weeks gestational age that are HEU compared to HUU infants at 16 days to 6 months corrected age.

1.5 Objectives:

- To determine the developmental status of HUU infants born at 28-37 weeks gestational age, between the corrected ages of 16 days to 6 months using the BSID III.
- To determine the developmental status of HEU infants born at 28-37 weeks gestational age, between the corrected ages of 16 days to 6 months using the BSID III.
- To compare the developmental status of HEU and HUU infants.

1.6 Significance of Study

There have been studies done with regards to HIV exposure in infants but these studies were mainly done in developed and high socio-economic countries such as the UK. They also generally have a small sample size due to drop out in a long term study. There are also not many studies that have been completed in recent years and many are becoming outdated.

Some studies that were conducted include:

- In utero exposure to antiretroviral therapy: feasibility of long term follow-up (Hankin, et al., 2009). This study was conducted in the UK and found that majority of the infants exposed to ARVs had only minor childhood ailments.

- Long-term follow-up of uninfected children born to HIV-infected women and exposed to antiretroviral therapy: survey of parents and health professionals views (Hankin, Newell, & Tookey, 2007). This study was also conducted in the UK and found that both healthcare professionals and parents would like children that are HIV exposed but uninfected to be followed-up, whether via direct contact at a clinic or a telephone call, in order to identify any possible side effects of ARV exposure.

Very little has been done on this topic in South Africa and not for this young (16 days to 6 months).

With the analysis of the statistics it was determined that there is a need for this research at Tambo Memorial Hospital. In 2014 39,1% of all paediatric patients treated by physiotherapy were seen in the neonatal high care and the neonatal follow-up clinic. In 2015 33,4% were seen in the neonatal high care and neonatal follow-up clinic. These statistics reflect the number of premature babies that are being seen at TMH alone. If we can detect any developmental problem at a young age we can begin early intervention at a younger age and potentially reduce the impact of HIV exposure on the child.

Chapter 2

2. Literature Review

2.1 Introduction

This chapter will discuss the causes of prematurity, neurological outcomes of HIV exposure, the effect of ARVs in-utero and outcomes of prematurity. A brief discussion will be done on HIV vertical transmission as well as breastfeeding and MTCT.

The developmental risk factors in developing countries will be discussed under environmental, biological and maternal factors.

Articles discussed in this literature review were sourced from CINAHL, EBSCO host, Science Direct and Google Scholar. Keywords searched included ARVs in-utero, causes of prematurity, outcomes of prematurity, HIV in-utero, ARVs in-utero, PMTCT, HIV exposed uninfected infants.

2.2 Causes of prematurity

Prematurity is defined as an infant born less than 37 weeks of gestational age. This is further split into 3 categories: moderate to late premature (32-37 weeks), very preterm (28-32 weeks) and extremely preterm (<28 weeks) (WHO, 2018). The global rate of prematurity is approximately 30% with over 60% of preterm births occurring in Africa and South Asia (Chiabi, et al., 2013). Globally, about 6.6 million children die before they reach the age of five and five million deaths occur in the first year of life. Developing countries have the highest number of deaths which is more than 98% and in the first month of life Sub-Saharan Africa has the highest risk of death (Debelew, Afework, & Yalew, 2014). Many of these deaths are caused by birth asphyxia, trauma and premature birth (Debelew, Afework, & Yalew, 2014).

The incidence of preterm birth varies from one community to another and depends on a number of factors (Castell, et al., 2013). These factors include low

socioeconomic status, poor maternal nutrition with obesity, maternal age, limited antenatal care, poor healthcare, heavy manual labour, maternal substance abuse, maternal hypertension, maternal diabetes, maternal stress and anxiety, twin pregnancies, trauma and infections (Castell, et al., 2013; De Jongh, et al., 2014; Irshad, et al., 2012; Piscoya, et al., 2012; Xu, et al., 2015).

2.2.1 Maternal age

Maternal age is widely researched with regards to causes of prematurity. Research has shown that teenagers as well as older women are more likely to have infants born prematurely (Castell, et al., 2013). The ages that they found to be high risk were less than 19 and older than 35 years (Xu, et al., 2015).

Teenage mothers are 75% more likely to give birth to premature infants and this could be due to biological immaturity whereby there is a young gynaecological age and they are pregnant before they complete their own growth. The immature internal genitalia may predispose the mothers to increased prostaglandin production and therefore increase the risk of premature births (Castell, et al., 2013). There will also be an increase in stress levels for these young mothers with regards to schooling and stigma of young pregnancies. Research done by Piscoya et al (2012) in Brazil has also shown that there was an increase risk in premature births for young mothers and mothers who have not finished schooling, a low family income and housing conditions that are not adequate (lack of water, no flushing toilets and no garbage collection). The study was done in a maternity ward specific for high risk pregnancies. The mothers were given a questionnaire addressing socioeconomic and demographic variables (Piscoya, et al., 2012).

Mothers older than 35 years are considered to be in advanced maternal age (Suresh, 2015). With demographic and socioeconomic changes over the past few decades older women are falling pregnant and even receiving treatment for infertility (Suresh, 2015). Prematurity is common in this age group as the oocytes and embryos are more vulnerable to harmful environments and there is poorer placental perfusion and impaired transplacental movement of nutrients (Zheng, et al., 2016). Advanced maternal age is also associated with ischaemic placental disease which

may explain a common pathophysiological mechanism for preterm deliveries (Suresh, 2015).

2.2.2 Maternal hypertension

Maternal hypertension complicates approximately 2-10% of all pregnancies (Alam, et al., 2014; Kazemian, et al., 2014). Maternal hypertension has been shown to cause an increase in placenta abruption, preterm labour and low birth weight. Gestational hypertension can be caused by a gestational weight gain of 0.50 kg per week or more (Kazemian, et al., 2014). Obesity is associated with the development of preeclampsia, and these in combination are associated with dyslipidemia, hyperinsulinemia, and glucose intolerance (Madan, et al., 2010).

Preeclampsia is a pregnancy complication that can be associated with an increase in maternal body mass index (BMI) and BMI can be increased due to advanced maternal age (Madan, et al., 2010). Obesity is associated with a number of factors such as poor quality of life and discrimination due to social stigma. These factors may cause adverse pregnancy outcomes and also increases the risk of delivering a premature infant (De Jongh, et al., 2014). According to Madan et al (2010) obesity and pregnancy both contribute independently to a state of chronic inflammation, and it has been suggested that the combined inflammatory response can be harmful for both mother and the foetus.

2.2.3 Gestational diabetes

Diabetes is a worldwide problem affecting 200 million people and approximately 3-5% of all pregnancies are affected by diabetes (Khalid, Fehmida, & Javed, 2015). Diabetes that develops or is noticed for the first time during pregnancy is called gestational diabetes mellitus (GDM) (Khalid, Fehmida, & Javed, 2015; Khan, Ali, & Khan, 2013). There is a global increase in the prevalence of type 2 diabetes in women of child bearing age due to increasing prevalence of obesity and physical inactivity (Khalid, Fehmida, & Javed, 2015; Zawiejska, et al., 2014). GDM may cause an increase risk of pregnancy induced hypertension, pre-eclampsia, antepartum

haemorrhage, premature rapture of membranes and preterm deliveries (Khan, Ali, & Khan, 2013).

2.2.4 Obesity

Obesity as well as pregnancy causes a pro- inflammatory state. Obese pregnant women show significant differences in metabolic and inflammatory parameters as well as vascular abnormalities (Madan, et al., 2010). Obesity also prompts systematic inflammatory responses that are associated with atherosclerosis, which can cause pregnancy induced hypertension (Kazemian, et al., 2014). The increased vulnerability to inflammation and infection in obesity commonly causes chorioamnionitis which may result in premature rupture of membranes and premature births. Studies have shown that the risk of premature deliveries is not only increased by maternal obesity but also by underweight mothers or mothers with very low weight gain during pregnancy (Madan, et al., 2010).

2.2.5 Maternal infections

Another cause of prematurity is maternal infections. Common infections that expecting mothers suffer from are urogenital infections and these are important causes of premature labour (Chiabi, et al., 2013). Infections cause premature deliveries due to bacterial action be it indirect or direct. Early labour occurs due to the release of inflammatory mediators which are stimulated by bacteria (Piscoya, et al., 2012). Another infection that is responsible for up to half of all premature deliveries is periodontal infection (Piscoya, et al., 2012). A study done by Piscoya et al (2012) found that 70 of the 360 premature infants in their study were born to mothers with periodontitis, this is 19.44%. Periodontitis affects the periodontium and is caused by gram-negative bacteria that enter the blood flow, which results in the formation of prostaglandins. These cross the chorioamniotic barrier and infect the amniotic fluid, thereby causing premature membrane rupture and premature labour. Periodontitis has been shown to have a high incidence in African and economically disadvantaged women (Piscoya, et al., 2012).

2.2.6 Obstetric history

A woman's obstetric history is an important aspect to take into consideration when looking at prematurity. Studies have shown a statistically higher prematurity rate in multiparous women as well as women with a higher previous miscarriage rate (Sacona-Ventura, et al., 2009). Sixty percent of twin or triplet pregnancies are born prematurely as compared to 10% of single infant pregnancies. This could be due to the fact that multiple pregnancies are more likely to have abnormal placental function as well as gestational diabetes. On average twins are born at 35 weeks gestation, triplets at 33 weeks gestation, and 30 weeks for quadruplets (Lazarov, Lazarov, & Lazarov, 2016). Preeclampsia is also more common in multiple pregnancies at a rate of 2-5 times more often. Up to 20% of women with twin pregnancies will experience preeclampsia, and the percentage increases in triplet or high-order pregnancies (Lazarov, Lazarov, & Lazarov, 2016). Increased maternal age as well as number of pregnancies can increase the chances of twin births. Twin pregnancies can progress to term but most deliver prematurely.

2.2.7 Premature rupture of membrane

Preterm premature rupture of membrane (PPROM) is when the foetal membrane ruptures before onset of labour, this happens before 37 weeks of gestation. PPROM complicates in the region of 3% of pregnancies and one third of preterm births are caused by PPROM. There are a number of risk factors for PPROM, such as intrauterine infections, lower socioeconomic status, little to no prenatal care, poor nutrition during pregnancy and smoking during pregnancy (Dars, et al., 2014). A study done by Dars et al (2014) found that 20-30 years of age is the age group most affected by PROM.

2.2.8 Maternal smoking and substance abuse

Maternal smoking is well known to affect the intrauterine environment (Zheng, et al., 2016). A history of smoking in pregnant women has been proven to have a 4.5 times greater likelihood of having premature infants (Piscoya, et al., 2012). The highest prevalence of smoking during pregnancy has been found in teenage mothers and the prevalence decreased as the mother's age increased (Zheng, et al., 2016). This

could be due to maturity levels, knowledge of pregnancy from previous births and change in society norms.

Another aspect that is more prevalent in younger pregnant women is substance abuse and this occurs regardless of socioeconomic classes, ages**,** and races. Research has shown that there is a relationship between substance abuse and social problems such as poor nutrition and hygiene, psychological problems and a stressful lifestyle. The prevalence of premature deliveries is higher with maternal substance abuse and is an important aspect to take into consideration along with social situation (Gargari, et al., 2012).

2.2.9 Trauma

Trauma is common in pregnancy, is an important complication in today's times and is one of the key contributors to maternal and foetal morbidity and mortality (Taha, et al., 2013). There is an incidence of 5-7% of trauma during pregnancy, and minor traumas account for the majority (Yerebasmaz, et al., 2015). Common causes of maternal trauma are motor vehicle accidents, falls, assaults and gunshots, home accidents and domestic violence (Taha, et al., 2013; Yerebasmaz, et al., 2015). The most common complication of maternal trauma is preterm labour which occurs in approximately 28% of cases (Taha et al., 2013).

Minor trauma is said to cause unexpected foetal loss and pregnancy may become complicated by preterm birth or placental abruption (Yerebasmaz, et al., 2015). Minor trauma in the first trimester is not threatening to the pregnancy but significant adverse effects on the foetus can be found in the second and third trimesters. Such adverse effects include placental abruption, preterm deliveries, uterine rupture, and direct foetal injury (Taha, et al., 2013). According to Taha et al (2013) premature rupture of membranes can occur within 4 hours of injury and usually ends in a premature delivery. Placental abruption is uncommon and occurs in approximately 6.5/1000 births, but the high foetal death linked with the placental abruption is due mainly to its strong association with preterm delivery (Leone, et al., 2010). Blunt trauma is often caused by home accidents and falls during pregnancy. Falls during pregnancy are common due to orthostatic hypotension, enlarged abdomen, laxity of

the joints of the pelvis, and fatigue, which become more prominent in the third trimester (Yerebasmaz, et al., 2015).

Another aspect of maternal trauma is the one of abuse and violence. Violence towards women is a major personal, social, and global public-health problem (Yerebasmaz, et al., 2015) and it is estimated that pregnant women experience physical or sexual intimate partner violence (IPV) by a male partner at an incidence of 1.2 – 9% (Leone, et al., 2010) but this was a study done in 2010. A more recent study stated that the prevalence of IPV is approximately 1%–11% in high resource countries and 4%–49% in low-resource countries (Yerebasmaz, et al., 2015). An article by Yerebasmaz et al (2015) noted that women were most commonly assaulted by their husbands (57.1%), followed by relatives of the husbands (28.6%) and then the woman's own relatives (14.3%). This physical and sexual violence during pregnancy can increase the risk of psychological and physical health outcomes, including pregnancy complications and birthing complications such as placental rupture and prematurity (Leone, et al., 2010; Yerebasmaz, et al., 2015). Pregnant women that experience violence are more likely to present with preeclampsia, vaginal bleeding, miscarriage, weight gain during pregnancy, hypertension and depression (Yerebasmaz, et al., 2015). Research has also shown that these women are more likely to partake in substance abuse, in order to cope with the stress and fear of the violence and abuse (Leone, et al., 2010).

2.2.10 Manual labour

The work or job of the pregnant women also has an effect on stress levels. This was found amongst women whose work was more physically demanding such as domestic helpers. Pregnant women that work outside of the home are more likely to have premature deliveries (Piscoya, et al., 2012). Maternal education will also affect the type of jobs that these women do and the amount of time they can get off for pregnancy and healthcare visits. This lack of education can also affect the amount of antenatal care that the women attend as they are not aware of the importance of these visits (Irshad, et al., 2012). Women should have at least 4 antenatal visits during pregnancy in order to detect high risk infants (Chiabi, et al., 2013; Piscoya, et al, 2012).

2.2.11 Psychosocial factors

Maternal aspects are not the only risk factors for prematurity. It is also important to look at race and gender of the infant as well as socioeconomic status and environment. Research has proven that male infants are more likely to be born prematurely (Chiabi, et al., 2013; Xu, et al., 2015). According to Xu et al (2015) this is due to a heavier body weight of the male foetus as well as the greater susceptibility to gestational hypertension or infection. The male and female foetuses also have different sex-linked biochemical processes, including oestrogen production (Xu, et al., 2015).

It has been revealed that race has an effect of prematurity as well (De Jongh, et al., 2014). De Jongh et al (2014) explains that "racial disparity may be genetic variations (polymorphisms) that differ in frequency between races. The underlying cellular and molecular pathways that lead to preterm birth may be influenced by race/ethnicity polymorphisms". The study done by De Jongh et al (2014) showed that the highest rate of prematurity was found in the Black population (13.5 %), followed by the White population (8.8 %), the Hispanic population (7.0 %) and the Asian population (6.7 %).

Socioeconomic and environmental factors play an important role in prematurity due to a number of aspects. The developing foetus is susceptible to environmental pollutants such as air pollution, environmental tobacco smoke, pesticides, solvents, metals, radiation, water contaminants and chemicals (Nieuwenhuijsen, et al., 2013). A single mother is also at risk for premature labour due to the lack of financial and psychological support needed to ensure adequate follow-up of their pregnancies (Chiabi, et al., 2013). This could also be due to financial constraints as there may be no breadwinner and therefore will have to work late into the pregnancy.

A recent study noted that 80 % of total neonatal deaths globally are due to prematurity and complications at birth (Weldearegawi, et al., 2015). Preterm infants have a high risk of many complications such as infectious diseases, respiratory complications, intraventricular hemorrhage, and other system involvements (Xu, et al., 2015). Other factors associated with prematurity include pre-eclampsia, foetal distress, small-for-gestational age, and placenta abruption (Madan, et al., 2010). In order to limit the amount of premature births among pregnant women there needs to

be emphasis placed on the importance of antenatal visits as well as educate expecting mothers about sexual and reproductive health and dietary and lifestyle interventions (Castell, et al., 2013; De Jongh, et al., 2014).

2.3 HIV vertical transmission

Without diagnosis and correct treatment the risk of vertical transmission of HIV can be as high as 25%. A high maternal viral load provides the greatest risk for vertical transmission which can occur during intrauterine life, delivery or breastfeeding (Urry & Mardis, 2014).

The HI virus can be passed to the newborn through vertical transmission via breastfeeding. To reduce MTCT a 28 week regimen of ARV prophylaxis should be given to the mother or the child (Kindra, et al., 2012; Melhado, 2012). The risk of HIV transmission, in the absence of intervention, in formula fed infants is 25% and in breastfeeding infants is 35%. Developed countries have been able to reduce vertical transmission to 1% by making use of ARV prophylaxis, caeserian sections and breastfeeding avoidance. This is not possible in the poorer economies due to the burden of malnutrition and HIV (Kindra, et al., 2012). Attitudes and likelihood to breastfeed differs according to cultural beliefs, social beliefs and resources (McGlue, 2014).

In the 1980s all HIV^+ mothers were encouraged not to breastfeed as they felt it was safer for the infant but over time the guidelines have changed as it has become evident that only the nutrients and antibodies in the breastmilk can assist the infants with infections such as pneumonia and diarrhoea. The antibodies strengthen the infant's immune system and therefore together with the ARVs, will decrease the risk of HIV transmission as well as mortality rates (McGlue, 2014).

Breastfeeding in low socioeconomic countries is best due to it being nutritive and sustainable, as well as the ability to enhance the physical, emotional and cognitive development of the infant. It also protects the infants from infectious disease morbidity and mortality (Kindra, et al., 2012; McCrory & Murray, 2013). It has been recommended that HIV^+ mothers should exclusively breastfeed for six months (Kindra, et al., 2012; McGlue, 2014). Those that are breastfed for six months obtain

higher scores on the Bayley scales of Infant Development at 14 months of age and this is due to the exposure of the polyunsaturated fatty acids in the mother's colostrum (Guxens, et al., 2011) .

A study done by Kindra et al (2012) showed that breastfed infants, in the presence of HIV infection, reached all their growth parameters and age appropriate milestones by 14 weeks of age, but by six months of age only BMI was significantly higher than in formula fed infants. The study also found a 69% lower incidence of diarrhoea due to breastfeeding and that formula fed infants were more likely to have hospital admissions and delay in milestones.

Another study done in 1999 by Vestergaard et al looked at the association between breastfeeding and fine motor, gross motor and language skills in eight month old healthy infants. They found that the proportion of infants reaching their milestones increased with the duration of breastfeeding (Vestergaard, et al., 1999). These infants were not HIV exposed or HIV^+ and were also term infants.

Breastfeeding has been proven to improve child growth and brain development, as well as decrease the amount of diarrhoea diseases experienced (Kindra, et al., 2012; McCrory & Murray, 2013). Infants that are breastfed are more likely to achieve their gross and fine motor milestones as well as improve in their problem solving abilities by 9 months of age (McCrory & Murray, 2013). Late preterm infants (34-36 weeks gestation) have a higher risk for complications and therefore need to be breastfed in order to ensure long-term physical and developmental health (Goyal, Attanasio, & Kozhimannil, 2014).

Breastfeeding is not the only method for MTCT of the HI Virus, there are also a number of obstetric aspects that put the infant at risk of HIV infection. These include duration of rupture of membranes, presence of chorioamnionitis and the use of forceps and episiotomy (McCall, Vicol, & Tsang, 2009). Infants born to mothers that are HIV^+ should be given Nevaripine syrup immediately after birth if the mother was not receiving it intravenously during the intrapartum period. If the mother was receiving it then it should be given to the infant 8-12 hours after delivery. The Nevaripine should be continued for 6 weeks. A single dose of Nevaripine should be given to the infant as soon as possible after birth if the mother was not receiving it

during the intrapartum period, if the mother was receiving it then the infant should be given a single dose within 48 hours after delivery (McCall, Vicol, & Tsang, 2009).

2.4 Developmental outcomes of Infants exposed to HIV

Many studies have found a correlation between HIV exposure and prematurity, low birth weights, intrauterine growth retardation, foetal death, neonatal mortality and respiratory complications. The neurological outcomes of HIV exposure on the infant are still poorly researched and understood (Salihu, et al., 2012). A study by Salihu et al (2012) looked at neonatal complications such as foetal distress, cephalohaematoma, intracranial haemorrhage, seizures, feeding difficulties, central nervous system (CNS) complications. The study was conducted in Florida and they extracted the medical conditions directly from the hospital's discharge data. They found that these infants were more likely to have feeding difficulties and seizures. The feeding difficulties seen are poor appetite and being fussy with the type of food they eat. Unexpectedly the study found that HIV exposed infants were less likely to develop foetal distress and cephalohaematoma which was also found in another study done by Ellis et al (2002). This study looked at whether the HI Virus is a risk factor for adverse perinatal outcomes.

The effect of HIV on the system of the infant is not the only aspect to take into consideration. With HIV/AIDS affecting many in SA it is adding to the burden on the country due to maternal and family deaths. Infants are becoming orphans and adding to the economic constraints as well as affecting the development of the infants. The caregiver to child ratios in institutions for orphaned children could have an effect on the development of these infants due to lack of a stimulating environment. Children in foster care may be affected by constantly changing placements, exposure to substance abuse such as alcoholism and drug abuse as well as possible neglect. It can result in physical, emotional and behavioural delay as well as learning difficulties (Jelsma, Davids, & Ferguson, 2011).

A SA study by Jelsma et al (2011) found that there were a larger number of older members in the community, such as grandparents, looking after children and this could be due to single parent households whereby the parent needs to work. This

can cause an environment lacking in stimulation as the elderly caregivers may also have their own health issues. This is said to increase with the rising HIV epidemic in SA (Jelsma, Davids, & Ferguson, 2011).

2.5 Effect of ARVs In-utero

The treatment provided for HIV^+ pregnant women has two objectives and these include improvement of the mother's health and to reduce mother to child transmission (MTCT) (Esker, et al., 2012). With the introduction of antiretrovirals (ARVs) for all HIV^+ pregnant women there have been many beneficial effects for the infant such as the reduction of MTCT. Administration of ARVs to pregnant women provides protection to the infant during pregnancy and with breastfeeding (Chimbwandira, et al., 2013).

MTCT can be reduced to less than 2% with only the initiation of ARVs and no other intervention. The number of mothers receiving ARVs to reduce MTCT has increased from 34% in 2009 to 61% in 2011, worldwide (Darak, et al., 2013). In 2011 a remarkably low 57% of HIV^+ pregnant women in middle and low income countries received the WHO recommended regimen in order to prevent MTCT and approximately 300 000 infants acquired the infection from their mothers in sub-Saharan Africa.

With the administration of ARVs to all HIV^+ pregnant women the infants have a low risk of contracting the HI virus and are born with a negative Polymerase Chain Reaction (PCR) (Mesfin, Kibret, & Taye, 2016). The ARVs should control infection and ensure plasma HIV RNA suppression by the third trimester and at the time of delivery (Esker, et al., 2012). We are still not aware if these ARVs have an effect on the development of the infant in the uterus and there have been concerns with regards to pregnancy adverse effects such as preterm births, LBW, spontaneous abortions and stillbirths (Darak, et al., 2013).

The most common nucleoside reverse transcriptase inhibitors (NRTI) used during pregnancy are zidovudine (AZT) and lamivudine. Lamivudine is the most widely used and this is due to its safety in pregnancy and that it crosses the placental barrier with ease. Protease inhibitor (PI) based antiretroviral therapy (ART) are also widely used

even though there is poor placental transfusion. The reduction in infant viral load is said to be due to the suppression of the maternal viral load (Baroncelli, et al., 2009).

The European AIDS Clinical Society in 2011 recommended atazanavir which is a PI boosted with ritonavir in the treatment of HIV in pregnant women (Esker, et al., 2012) but this is no longer recommended at first line treatment. Research done by Esker et al (2012) stated that infants exposed to atazanavir are at risk for birth defects such as heart defects, chromosome anomalies, musculoskeletal defects, cleft lips or palates, central nervous system defects and renal or urinary system defects.

Research has shown that pregnancy outcomes such as premature births (PTB) and low birth weights (LBW) are associated with PI based ART as well as the timing of the initiation of the ART (Darak, et al., 2013; Mesfin, Kibret, & Taye, 2016; Powis, et al., 2011). A study done by Mesfin et al (2016) showed that there is a 32% increased risk of PTB when a mother is receiving these PI based ART regimes, especially if it is given within the first trimester (<13 weeks) and the third trimester (Darak, et al., 2013; Powis, et al., 2011). Another study done by Darak et al (2013) showed that 45% of women in their study had adverse pregnancy outcomes whereby there were 17% PTB and 27% LBW. This same study also noted that women who were on HAART (highly active antiretroviral therapy) but not on a PI regime were 3.4 times more likely to have a PTB. HAART has been documented in Europe, USA and Africa as being a risk factor for PTB (Darak, et al., 2013).

Barret et al (2003) found that Infants exposed to ARVs during the perinatal period are at risk for poor neurological outcomes such as cognitive delay, behavioural problems, motor abnormalities and convulsions due to the continual mitochondrial dysfunction. This large prospective cohort study looked at 2644 out of 4392 children exposed to antiretrovirals and investigations were carried out using a diagnostic probability scale (Barret, et al., 2003). A large benefit to the ARV treatment is the likelihood of it decreasing the occurrence of neonatal seizures (Landreau-Mascaro, et al., 2002).

Even with these adverse pregnancy outcomes PI based ART is significant for the reduction of MTCT in the developed as well as the developing world and has many verified benefits for the infant as well as the mother (Powis, et al., 2011).

2.6 Outcomes of prematurity

The uterine environment in the third trimester is beneficial for the foetus as it provides sensory stimuli for the vestibular, tactile, kinaesthetic and auditory systems (Guimaraes, et al., 2011). When an infant is born premature they are no longer exposed to these beneficial stimuli and are exposed to a negative environment with high noise levels, no daily dark-light cycle and excessive handling. An infant is hypotonic with CNS immaturity which has a correlation with the large incubator space and gravity which causes extended postures and difficulty with movement in the flexed positions. This situation affects the infant negatively as it is during this time when there is enhanced cerebral organisation and neural plasticity (Guimaraes, et al., 2011).

The last trimester of pregnancy and the first few months post birth are called the perinatal period. Growth during this period has a large effect on the development of most tissues but most importantly it affects the neurocognitive outcome (Simon, et al., 2014). Premature infants are at an increased risk for growth failure, cerebral palsy, developmental delay, and mental retardation (Saigal & Doyle, 2008).

The cortical volume of a late-preterm infant's brain is only 53% of full-term volume and the volume of the white matter increases significantly between 35 and 41 weeks of gestation. The foetal brain only weighs 65% of its full-term potential at 34 weeks of gestation (Nepomnyaschy, et al., 2012). Twenty to 40 weeks of gestation is the critical period of brain development in an infant. At 20 weeks the brain is 10% of its full term capacity and between 20 and 40 weeks the weight increases by 90% (Kinney, 2006).

Whether an infant is born severely or late preterm there are still many consequences. These include longer hospital stays especially in the Neonatal Intensive Care Unit (NICU), high rates of post birth hospital readmissions, higher rates of infant mortality and long term neurological outcomes. Children born between 34 and 36 weeks are at a 70% risk for suffering from a hyperkinetic disorder when compared to their term counterparts. The study found that healthy late-preterm children scored lower than children born term with regards to cognitive ability at the

ages of two and four but there was no significant difference with motor ability, attachment and socioemotional skills. The incomplete development of the cerebral cortex is said to be a possible cause (Kinney, 2006; Nepomnyaschy, et al., 2012).

Periventricular Leukomalacia (PVL) is a common neurological consequence of being born severely preterm but is also said to occur in late-preterm and term infants. PVL affects the immature white matter of the cerebral hemispheres around 24-32 weeks of gestation (Kinney, 2006). Another common complication of prematurity is a cognitive impairment which is said to affect 25-50% of PTB and LBW infants. Cognitive development involves the interaction between biological and environmental factors as with preterm deliveries and therefore preterm infants born to mothers of low socioeconomic status are more likely to have cognitive delay (Wong & Phil, 2013).

Studies have shown that when the age of a premature infant is corrected there is no difference with regards to the start of tooth eruption, walking, talking and bladder control when compared to a term infant (D'Agostino, 2010).

2.7 Developmental risk factors in developing countries

Child development involves cognitive, physical and socio-emotional aspects. These aspects need to function together in the first three years of life (Ali, 2013). An estimation of 200 million children (39%) in developing countries and under the age of five are not reaching their developmental potential. This is due to poverty, malnutrition, high rates of infection, lack of stimulation and education, instability in the home (Ali, 2013). An estimate of 93 million children aged 0-14 years have moderate to severe disabilities and 200 million are cognitively or socio-emotionally delayed (WHO, 2011).

CNS maturity in humans occurs rapidly in utero, in infancy and at puberty (Ali, 2013), which is why we need ensure adequate development throughout a child's life. We often follow-up into infancy but not often do we monitor children into puberty. Intelligence, personality and social behaviour develop during the earliest years of life

and that is why negative aspects of development can affect a child greatly (Ali, 2013). These negative aspects will be discussed further.

2.7.1 Environmental aspects

A child's environment is considered to be the physical and social settings that the child develops and grows in. The physical environment includes the home, daycare centre, school and neighbourhood in which the child lives. The social environment includes interactions and relationships which help to shape development and form behaviour. Social also looks at emotional wellness and support provided for the child by the parents and caregivers (Campbell, Palisano, & Orlin, 2012). It is also important to consider the caregiver environment which is the physical and social environments that the caregivers provide for the child. The environments do not act in isolation but work together to enhance child development (Campbell, Palisano, & Orlin, 2012).

The environment can also be separated into distal and proximal. The distal environment looks at the child's residential area, neighbourhood and community. The schools, churches and hospitals need to be considered in this environment. Children of school going age are influenced more by this environment (Campbell, Palisano, & Orlin, 2012). The proximal environment is the relationship between the child and the caregiver. It includes aspects such as caregiver's knowledge and beliefs, competence of parents, cultural expectations, caregiver physical and mental health, available resources and physical space. Younger children are influenced more by this environment (Campbell, Palisano, & Orlin, 2012).

Family structure shapes family resources and influences the care that the child receives. It affects income, flexibility of employment arrangements and who takes care of the child when the parents are working, as well as time spent with the child. The family functioning looks at parent behaviour and how they bring up the child as it is the parents that need to promote their child's development (Campbell, Palisano, & Orlin, 2012).

Informal support looks at social and professional support. Social support is the child's personal interactions with caregivers, family and the community. Professional

support is provided by doctors, therapists and nurses who need to provide information to caregivers to ensure adequate knowledge of development and health (Campbell, Palisano, & Orlin, 2012).

When looking at the child's environment it is important to look at the home as well as the hospital environment. The home environment needs to encourage participation in family activities, have learning opportunities, play with appropriate toys, have access to special equipment and most importantly have opportunities for play and exploration (Campbell, Palisano, & Orlin, 2012). The hospital environment needs to be considered as some children can spend months in this environment. Factors causing hospital stay includes prematurity, low birth weights, developmental anomalies, pneumonias as well as HIV and TB. The hospital environment is very bright and noisy, the child is subject to many painful procedures, there is less interaction with caregivers which results in less stimulation and the risk of opportunistic infections. All these factors will place stress on the child and impede healing and growth of the child.

Nutrition is also a huge consideration when looking at child development. Malnutrition and micronutrient deficiencies slow physical and cognitive growth as well as increase the susceptibility to infection and disease (Ali, 2013). This will cause the weakening of the immune system and the child will be lethargic thereby decreasing the amount of exploration the child does in their environment. Malnutrition in caregivers affects their productivity at work and home thereby having an effect on income and family support (Ali, 2013). Nutritional anaemia affects 30% of the world's population and about two billion people in developing countries. This will have an effect on attention, intelligence and school achievement (Ali S, 2013). Iron deficiency in pregnant women increases the risk of low-birth weight or premature delivery, perinatal and neonatal mortality, inadequate iron stores in the newborn, decreased activity levels, fatigue and increased risk of maternal morbidity. Iron deficiency can also be responsible for maternal death which in turn will affect households as the infants will grow up without a mother and at times grandparents need to look after these children on their pension money alone. Inadequate iron stores in an infant can impair intellectual development by affecting language, cognitive and motor development (Ali, 2013).

In areas of poverty it is common to see nutritional deficiencies as well as an increase susceptibility to infectious and diarrheal diseases due to poor sanitation and poor quality of drinking water (Ali, 2013). There is an increase risk of infections such as malaria causing neurological and cognitive damage (Ali, 2013). The *Young Lives* project looks at child poverty and they revealed that children with low resources show high rates of cognitive and socio-emotional impairments (Bornstein & Hendricks, 2013).

Social class is measured by income, education and occupation. This affects the resources (financial and material) that the child needs for nutrition and care. It can also have an impact on stress levels and parent self-esteem (Stevens, 2006). Mothers in low socioeconomic conditions usually have other members of the family or community caring for their children (Yanuarti, Rusmil, & Effendi, 2014) as they need to work or look for a job. A large number of children in a family may affect language development (Yanuarti, Rusmil, & Effendi, 2014) as older siblings answer for younger siblings and don't get one on one attention from caregivers. Socioeconomic status will determine how much time and money is available to raise the child, nutrition of the family, stress levels as well as the neighbourhoods in which the child lives (Campbell, Palisano, & Orlin, 2012). These neighbourhoods can be dangerous and the children may interact with inappropriate groups.

A study found that poor maternal education has a "predictive value for poor developmental outcome in children (Ali, 2013). This could be due to poor education about childrearing as well as lack of income. Another study found that "socio-economic status, education, occupation and income of parents are positively associated with child development" (Ali, 2013). A lack of income will affect resources available to the child (Ali, 2013), resources such as food, toys, schooling and access to health care. Culture also influences development as there are different beliefs and practices for different cultures (Campbell, Palisano, & Orlin, 2012). Beliefs could differ on childrearing, feeding, appropriate child activities and the necessity for schooling.

2.7.2 Biological aspects

These factors take into consideration maternal medical history (prior and during pregnancy), problems during labour and neonate condition such as low birth weight, prematurity, jaundice, congenital abnormalities, infection and seizures (Yanuarti, Rusmil, & Effendi, 2014)**.**

The immune system of a neonate responds in a different way to bacteria compared to an adult. Organisms are present in the mother's genitourinary tract and can ascend to infect the amniotic fluid. Microorganisms that the infant is exposed to in the birth canal colonises in the skin and mucosa of the nasopharynx and oropharynx, conjunctivae as well as umbilical cord. The bacteria may pass through the mucosal epithelium into the blood vessels where the bacteria can be transported to the CNS. In the CNS the bacteria are free to replicate as the CSF has minimal immune cells. The cell wall products of bacteria stimulate the production of pro-inflammatory and anti-inflammatory cytokines which causes brain injury, even though it is required to eradicate the bacteria (Heath & Okike, 2010; Ku, Boggess, & Cohen-Wolkowiez, 2015).

Bacterial meningitis is a serious infection in neonates as the incidence is highest during the neonatal period. It infects the central nervous system by causing acute inflammation of the meninges, subarachnoid space as well as brain vasculature. The bacteria infect the amniotic fluid via the mother's genitourinary tract or can infect the infant as they pass through the birth canal. These infants present with fever, lethargy, poor feeding, vomiting, respiratory distress, convuslions and bulging fontanelles (Heath & Okike, 2010; Ku, Boggess, & Cohen-Wolkowiez, 2015).

Meningitis can be detrimental to the infants brain due to cerebral oedema, the presence of inflammatory mediators, free radical scavangers and excitatory amino acids. The long term complications include mental deficiency, seizures, CP, hydrocephalus, behavioural problems, speech and language disorders as well as impaired vision (Heath & Okike, 2010)

When looking at NNJ 70 to 80% of bilirubin is produced during the removal of aged red blood cells by the macrophages and monocytes in the liver and spleen. Macrophages separate haemoglobin molecules into proteins and haeme. Haeme is

then broken down into biliverdin which is processed into unconjugated bilirubin. This bilirubin is insoluble in water and attaches to albumin in order to be transported to the liver for excretion. Once in the liver it becomes conjugated in order to become water soluble and excreted into the bile. The bilirubin that remains in the gut comes across bacteria in the large intestine which converts it to urobilinogen where it is excreted by the kidneys. The neonates gut is very sterile and therefore conversion to urobilinogen is poor and reabsorption of bilirubin is high (Casey, 2013).

Physiological jaundices comes about via a number of factors such as: production of bilirubin due to haemolysis of red blood cells, decreased albumin concentration resulting in decreased delivery of bilirubin to the liver, immature liver pathways causing decreased conjugation of bilirubin and gut bacteria not sufficient enough to convert bilirubin to urobilinogen. Unconjugated bilirubin that is not bound to albumin is able to cross the blood-brain barrier and cause neurological harm. There has been shown to be an increase risk of jaundice in premature infants (Casey, 2013; Pearsall & Morrow, 2016).

Bilirubin entering the BBB affects the DNA, inhibits protein synthesis and affects neurotransmission. The auditory nerve and the extrapyramidal motor system, which controls movement and muscle tone, are sensitive to bilirubin. This can cause disorders involving hearing, co-ordination, posture as well as gait. The most severely affected infants may present with athetoid cerebral palsy (Casey, 2013).

2.7.3 Maternal aspect

Maternal age, equality, nutrition and disease during pregnancy can all affect a child's development (Yanuarti, Rusmil, & Effendi, 2014). Maternal mental health is also important to determine as depressed mothers will provide less nurturing and stimulating environments. Children of mothers with depression often show behaviour problems, attachment issues and cognitive problems later on (Stevens, 2006). Parenting stress is determined by how many roles a caregiver needs to assume, for example a single parent or a grandmother looking after many grandchildren (Campbell, Palisano, & Orlin, 2012).

2.8 Conclusion

In conclusion disability depends on its social and economic contexts and the frequency of developmental disabilities is higher where there is poverty and deprivation (Bornstein & Hendricks, 2013). The understanding of how the physical, social and attitudinal factors in the environment are responsible for children's functional skills and participation is essential for change and adequate quality of life (Campbell, Palisano, & Orlin, 2012). In order for children to enhance their own development they need to be active participants in their environment and explore their surroundings (Campbell, Palisano, & Orlin, 2012). From the research found it has become evident that you cannot look at development as an aspect on its own. It is multifaceted and you need to look at everything in combination in order to ensure adequate child development (Ali, 2013). As Bornstein and Hendricks (2013) stated "A person's environment impacts the experience and extent of disability".

There are many well documented risk factors to child development which include HIV and prematurity.

Chapter 3

3. Methodology

This chapter aims to discuss the methodology used to conduct this study.

3.1 Study Design:

A non-experimental cross sectional quantitative study was used in order to compare the development of HEU and HUU infants.

3.2 Participants:

Participants were recruited from the neonatal follow up clinic at Tambo Memorial Hospital (TMH), Boksburg, Gauteng, South Africa. TMH is a regional state hospital in Boksburg, Gauteng with many specialist services. It is considered a baby friendly hospital and has a six bed neonatal ICU and a large neonatal ward for all premature infants and infants with birthing complications.

The Neonatal follow up clinic is for all infants that are born prematurely at the hospital and need to be monitored post discharge. These infants are monitored for feeding difficulties, weight, developmental delay and general health and well-being. The infants are assessed by the doctor, physiotherapist, occupational therapist, speech therapist, audiologist and dietician. This is in order to detect any problems or abnormalities early in the developmental process. The infants are booked on a monthly basis until they are discharged from the clinic by all medical professionals or referred to the required disciplines when intervention is needed.

All the HIV exposed infants in the study were exposed to ARVs in-utero.

3.2.1 Inclusion Criteria

The inclusion criteria for this study were:

Infants with a gestational age of 28 to 37 weeks,

Infants with a corrected age of 16 days to six months on day of assessment,

HEU and HUU infants. Exposure or non-exposure to HIV was determined by assessing the medical records.

3.2.2 Exclusion Criteria

Exclusion criteria for this study were:

Babies not born in hospital or born at home,

Infants with inadequate medical records whereby not enough information is given,

Unknown maternal HIV status,

Infants with clinically apparent congenital deformities.

3.3 Sample Size

There were a total of 60 participants in the study. Thirty participants in the HUU group and thirty participants in the HEU group. The sample size was calculated as follows:

Using the Bayley Scales of Infant and Toddler Development as the primary outcome: in order to detect a difference in composite scores of 10 and using a standard deviation of 15, 27 infants per group will give a power of 90% and a confidence interval of +- 4.63. No compensation for dropout was necessary as each infant was assessed once.

3.4 Ethical Considerations

Ethical clearance was obtained from the Human Research Ethics Committee (medical) University of the Witwatersrand (clearance number: M160438) (see appendix 1), Gauteng Department of Health (see appendix 3) and Tambo Memorial Hospital management (see appendix 4).

Written informed consent was obtained from the parents/caregivers prior to commencement of assessment of infants that met inclusion criteria. The information obtained from the assessment of the infants was kept anonymous and no names or personal details were revealed. The parents/caregivers had the choice to withdraw from the study at any stage without any prejudice and the infant still received any necessary intervention.

Assessments were done on the same day that the infants attended the Neonatal follow-up clinic in order to minimise any further costs.

If any delays or abnormalities were detected during the assessment of the infant they were referred for the appropriate intervention.

3.5 Variables:

The independent variables include premature infants with a gestational age of 28-37 weeks and a corrected age of 16 days to 6 months.

The dependent variables include the development in HUU and HEU infants. Development includes gross motor, fine motor, cognitive, receptive and expressive language.

The extraneous variables include participants not arriving for their follow-up appointment, the awake state of infant, the health of the infant at the time of assessment and the time of day that the infant is assessed. As these will determine how the infant participates during the assessment.

3.6 Materials and Procedure

3.6.1 Outcome measures:

The Bayley Scales of Infant Development (3rd edition) was used for the assessment of the infants. The BSID-III is a well known diagnostic developmental assessment tool that was derived from the BSID-II and published in 2006.

The Bayley Scales evaluates cognitive, language (receptive and expressive), motor (fine and gross) and social emotional development. Each category has specific items to assess development for specific ages. Each item makes use of specific toys from the provided kit. Each item is either achieved or not achieved by providing a score of 1 or 0. The infants continued through all items as they pass them until they reached their ceiling.

The BSIDD-III has four types of scores which include the scaled scores, composite scores, percentile ranks and growth scores. Scales scores are calculated using the subtest total raw scores. Composite scores are calculated from the subtest scaled scores and can be used to compare a child's performance across all scales.

The BSID is considered to be the gold standard of infant developmental assessment globally. It has sound, well established psychometric properties. The intra-rater reliability coefficients were excellent for the cognitive scale (ICC = 0.92–0.99) and good to excellent for the language (ICC = 0.88–0.98) and motor scale (ICC = 0.85–0.98). The inter-rater reliability coefficients were good to excellent for the cognitive (ICC = 0.87–0.97) and language scale (ICC = 0.76–0.95) and good for the motor scale (ICC = 0.77–0.89) (Yu, et al., 2013). The average reliability coefficients were all greater than 0.94 and across all ages and the average stability coefficients were 0.80 or higher (Bayley, 2006). It has also been noted that "in all infants using the Bayley-III composite scores illustrated acceptable predictability" (Yu, et al., 2013). Convergent validity of the Bayley-III raw scores in comparison to the BSID-II raw scores was good to excellent for the cognitive (r = 0.62–0.78) and motor scale (r = 0.76–0.86) and poor to excellent for the language scale (r = 0.30–0.89) (Yu, et al., 2013).

3.6.2 Procedure:

Participants were sampled from the weekly neonatal follow up clinic at Tambo Memorial Hospital in Boksburg, Gauteng. Consecutive parents and infants attending the Neonatal Follow-up clinic were invited to participate. As the infants met the inclusion criteria they were included into the study and this occurred over several weeks.

An information sheet was drawn up that explained the study to the parent/caregivers. The study was also explained to the parent/caregivers by the assessing therapist. If they did not understand English, the nurses in the unit were asked to translate. The infants whose parent/caregivers consented were seen by all the health care professionals in the usual assessment session first. In this assessment the infants were screened for inclusion and exclusion criteria by the treating therapists in the clinic. The participants that met inclusion criteria were taken into the next room where the parent/caregiver had the study explained to them in more detail. The parent/caregivers had the choice of allowing their infants to be part of the study and a consent form was signed. If they chose not to participate the infant still received normal assessment at the clinic.

Consenting parent/caregivers were asked questions regarding history and demographics and then the infants were assessed using the BSID III. Data was then analysed and conclusions were made.

3.7 Data Analysis

Data was analysed using Microsoft excel and in consultation with a statistician.

The Bayley Scales of Infant and Toddler Development III does not yield one composite outcome. The subscales are separated into motor, cognitive and language facets of development. An abnormal outcome on each subscale is a score of <70 and a score between 70 and 85 determines at risk infants.

Descriptive statistics was done in order to condense the raw data with regards to information on the development of HUU and HEU infants. Tests used were means,

standard deviation (SD) and confidence intervals (CI) in table format. Level of significance was set at 0.05.

Inferential statistics was used to determine the differences between HUU and HEU infants. The data was parametric and the 2 groups were compared using the independent t-test.

Chapter 4

4. Results

In this chapter the results obtained in this study will be presented. Thirty HEU and 30 HUU infants were assessed using the Bayley Scales of Infant and Toddler Development lll.

4.1 Demographic Data

Demographic data was obtained through a questionnaire which was administered prior to commencement of the assessment. The data is presented in table 4.1.

Table 4.1 Demographic information for HEU and HUU groups

Variable		HEU n = 30 Number (%)	HUU n = 30 Number (%)	P value
Gender	Female	15 (50)	9 (30)	0.06
	Male	15 (50)	21 (70)	
Delivery	Caesarian	19 (63)	16 (53)	0.22
	Normal delivery	11 (37)	14 (47)	
Birth Weight	ELBW	2 (7)	3 (3)	0.50
	VLBW	5 (17)	10 (17)	
	LBW	20 (67)	40 (67)	
	AVG	3 (10)	7 (13)	
Gestational age	Mean	33.13 (2.43)	33.20 (2.57)	0.98
	Median	33.50	33.00	

ELBW = Extremely low birth weight; VLBW = Very low birth weight; LBW = low birth weight; AVG = average

There were an equal number of 30 infants in each group. All infants in the study were born premature with the mean gestational age being between 33.13 for the HEU group and 33.20 weeks for the HUU group (p=0.98). There were 43 (71.67%) infants in the late preterm category, 17 (28.33%) infants in the very preterm category

and no infants in the extremely preterm category. The mean corrected age in the HIV exposed group was 2.26 and in unexposed group was 2.9 showing that infants in both groups were of similar ages at assessment. With regards to gender there was no significant difference in proportion between the two groups (p=0.06). The mode of delivery was similar between the groups (p=0.22). The majority of the infants were born with a LBW (67%) and there was no significant difference between the two groups for birth weight categories (p=0.50). The mean maternal age for the HEU groups was 30.10 and for the HUU group was 26.37.

4.2 Socioeconomic information for HEU and HUU groups

Socioeconomic information was obtained through a questionnaire which was administered to the parents prior to commencement of the assessment. The data is presented in table 4.2

Table 4.2 Socioeconomic information for HEU and HUU groups

Variable		HEU n = 30 Number (%)	HUU n = 30 Number (%)	P value
Type of housing	Shack	4 (13)	6 (20)	0.30
	Flat	4 (13)	4 (13)	
	House	18 (60)	20 (67)	
	Not specified	4 (13)	0 (0)	
Running water	No	0 (0)	1 (3)	0.08
	Yes	26 (87)	29 (97)	
	Not specified	4 (13)	0 (0)	
Electricity	N	1 (3)	8 (27)	0.17
	Y	25 (83)	22 (73)	
	Not specified	4 (13)	0 (0)	
Mother present	N	1 (3)	0 (0)	**0.01**
	Y	25 (83)	30 (100)	
	Not specified	4 (13)	0 (0)	
Father present	N	11 (37)	4 (13)	**0.00**
	Y	15 (50)	26 (87)	
	Not specified	4 (13)	0 (0)	
Grandmother present	N	14 (47)	19 (63)	0.40
	Y	12 (40)	11 (37)	
	Not specified	4 (13)	0 (0)	
Siblings	N	5 (17)	12 (40)	0.21
	Y	21 (70)	18 (60)	
	Not specified	4 (13)	0 (0)	
Caregiver during the day	Grandmother	3 (10)	4 (13)	0.26
	Mother	23 (77)	25 (83)	
	Other	0 (0)	1 (3)	
	Not specified	4 (13)	0 (0)	
Receiving grant	N	13 (43)	24 (80)	**0.03**
	Y	13 (43)	6 (20)	
	Not specified	4 (13)	0 (0)	
No. of people per dwelling	mean	5.04(1.71)	4.53(1.28)	0.22

Using the Chi-squared tests no significant difference was seen between groups when looking at the type of housing (p= 0.03), whether there is running water (p= 0.08) and electricity (p= 0.17), if there is a grandmother (p= 0.40) or any siblings (p= 0.21) present and who takes care of the infant in the day (p= 0.26).

A significant difference between groups was seen when comparing whether a mother (p= 0.01) or father (p= 0.00) was present. The HUU group was more likely to have a mother (100%) and father (87%) taking care of them.

A significant difference between groups was also seen when looking at families receiving a grant from the government (p= 0.03). Forty three percent of the HEU infants compared to 20% of the HUU are receiving a grant.

4.3 Neonatal complications for HEU and HUU groups

Neonatal complications were obtained from the infant's discharge summary in the hospital file as well as their Road to Health clinic book. The data is presented in table 4.3.

Table 4.3 Complications for HEU and HUU groups

Variable		HEU n = 30 Number (%)	HUU n = 30 Number (%)	P value
Hydrocephalus	No	29 (97)	29 (97)	0.50
	Yes	1 (3)	1 (3)	
RDS/HMD	No	7 (23)	8 (27)	0.38
	Yes	23 (77)	22 (73)	
Mechanical Ventilation	No	18 (60)	23 (77)	0.08
	Yes	12 (40)	7 (23)	
Supplementary Oxygen	No	6 (20)	6 (20)	0.50
	Yes	24 (80)	24 (80)	
CLD	No	28 (93)	30 (100)	0.08
	Yes	2 (7)	0 (0)	
Pneumonia	No	26 (87)	29 (97)	0.08
	Yes	4 (13)	1 (3)	
NNJ	No	19 (63)	10 (33)	**0.01**
	Yes	11 (37)	20 (67)	
NNS	No	21 (70)	21 (70)	0.50
	Yes	9 (30)	9 (30)	
Meningitis	No	30 (100)	26 (87)	**0.02**
	Yes	0 (0)	4 (13)	
ICU admission	No	17 (57)	22 (73)	0.09
	Yes	13 (43)	8 (27)	
KMC	No	23 (77)	19 (63)	0.13
	Yes	7 (23)	11 (37)	

RDS/HMD = Respiratory distress syndrome/ Hyaline membrane disease; CLD = Chronic lung disease; NNJ = Neonatal jaundice; NNS = Neonatal sepsis; ICU = Intensive care unit; KMC = Kangaroo mother care

Using Chi-squared tests there was no significant difference between the two groups with regards to hydrocephalus (p= 0.50), RDS/HMD (p= 0.38), mechanical ventilation (p= 0.08), supplementary oxygen (p= 0.50), CLD (p= 0.08), pneumonia (p= 0.08), NNS (p= 0.50), ICU admission (p= 0.09) and KMC (p= 0.13).

A significant difference (p= 0.02) was seen in meningitis with more HUU infants affected (13%). NNJ showed to have the biggest significant difference between the

two groups (p= 0.01). Sixty seven percent of infants in the HUU group as compared to 37% in the HEU group were diagnosed with NNJ.

4.4 Developmental scores

The means and standard deviations for cognitive, language and motor development are shown in table 4.4.1. The scaled scores are shown in table 4.4.2.

Table 4.4.1 Developmental scores for HEU and HUU premature infants

Variable Composite scores	HEU n = 30 Mean (SD)	HUU n = 30 Mean (SD)	p value
Cognitive	98.20 (13.68)	98.30 (20.14)	0.97
Language	99.30 (9.70)	91.40 (10.31)	0.00
Motor	104.70 (12.95)	96.70 (15.77)	0.04

T-tests were used to analyse the difference between groups. There was no significant difference in the means of the cognitive composite scores between groups (p= 0.970). Language (p= 0.00) and motor (p= 0.04) composite scores showed a significant difference between groups whereby the HUU had lower developmental scores. All mean composite scores fell within one standard deviation of the norm.

Table 4.4.2 Scaled scores for HEU and HUU premature infants

Variable Scaled scores	HEU n = 30 Mean (SD)	HUU n = 30 Mean (SD)	p value
Language	19.9 (3.40)	17.0 (3.56)	0.00
Expressive	10.8 (1.95)	8.4 (2.19)	0.00
Receptive	9.0 (1.71)	8.6 (2.16)	0.40
Motor	22.3 (2.30)	18.8 (5.21)	0.00
Fine	11.2 (1.61)	9.0 (2.72)	0.00
Gross	11.1 (1.31)	9.8 (2.83)	0.03

When comparing expressive and receptive language scaled scores the expressive language was more affected (p= 0.00) in the HUU premature infants. When comparing motor development, both fine (p= 0.00) and gross motor (p= 0.03) were significantly lower in the HUU premature infants.

4.5 Meningitis

There was a significant difference with regards to more HUU than HEU infants with meningitis (Table 4.3) but the numbers were too small to warrant further investigation.

4.6 Neonatal Jaundice

When looking at neonatal complications, NNJ showed to have the biggest significant difference between the two groups (p= 0.01). Sixty seven percent in the HUU group as compared to 37% in the HEU group were treated for NNJ. Table 4.5 shows the developmental scores for HEU and HUU premature infants treated for NNJ.

Table 4.5 Developmental scores for HEU with NNJ and HUU with NNJ

Variable Composite scores	HEU n = 30 Mean (SD)	HUU n = 30 Mean (SD)	p value
Cognitive	100.45 (10.36)	93.75 (20.32)	0.23
Language	99.73 (6.21)	88.80 (10.40)	**0.00**
Motor	103.64 (13.06)	93.15 (13.79)	**0.05**

The data shows that there is a significant difference in the composite scores for infants that were diagnosed with NNJ, especially in the language (p= 0.00) and motor (p= 0.05) aspects of development.

4.7 Proportion of infants delayed or at risk for delay

Table 4.6 shows the results of the Bayley assessment subscales. A score below 70 is considered to signify developmental delay, between 70 and 85 is at risk of delay and over 85 signifies typical development.

Table 4.6 Results of the Bayley assessment subscales

Subscale		Delayed (score <70) n (%)	At risk (score 70-85) n (%)	TD (score >85) n (%)	p value (test difference in proportions in Delayed between HEU and HUU)
Cognitive	HEU	2 (6.7)	1 (3.3)	27 (90.0)	0.32
	HUU	3 (10.0)	2 (6.7)	25 (83.3)	
Language	HEU	1 (3.3)	0 (0.0)	29 (96.7)	0.50
	HUU	1 (3.3)	6 (20.0)	23 (76.7)	
Motor	HEU	1 (3.3)	2 (6.7)	27 (90.0)	0.50
	HUU	1 (3.3)	6 (20.0)	23 (76.7)	

TD = typical development

The data is comparing the developmental scores in the HEU and HUU groups to determine infants who are delayed, at risk or TD. These scores showed that

although there were no significant differences between the two groups, the HUU group were more delayed in the cognitive subscale (10%) and were at risk for delay in all subscales (6.7% cognitive, 20% language, 20% motor) when compared to the HEU group.

Table 4.7 shows the proportions of infants treated for NNJ that are delayed or at risk for delay.

Table 4.7 Proportion of infants delayed or at risk for delay – NNJ

Subscale		Delayed (score <70) n (%)	At risk (score 70-85) n (%)	TD (score >85) n (%)	p value (test difference in proportions in Delayed between HEU and HUU)
Cognitive	HEU	0 (0.0)	1 (9.1)	10 (90.9)	0.09
	HUU	3 (15.0)	2 (10.0)	15 (75.0)	
Language	HEU	0 (0.0)	0 (0.0)	11 (100.0)	0.23
	HUU	1 (5.0)	5 (25.0)	14 (70.0)	
Motor	HEU	0 (0.0)	2 (18.2)	9 (81.8)	n/a
	HUU	0 (0.0)	5 (25.0)	15 (75.0)	

The data shows that more HUU infants were diagnosed with NNJ. The difference in distribution of infants between the categories was not statistically significant.

Fifteen percent of the HUU NNJ infants showed cognitive delay with 10% being at risk. Five percent of the HUU NNJ infants showed language delay with 25% being at risk. Zero percent of the HUU NNJ infants are showing delay in motor development but 25% are at risk.

Figures 4.1 to 4.3 summaries these results clearly.

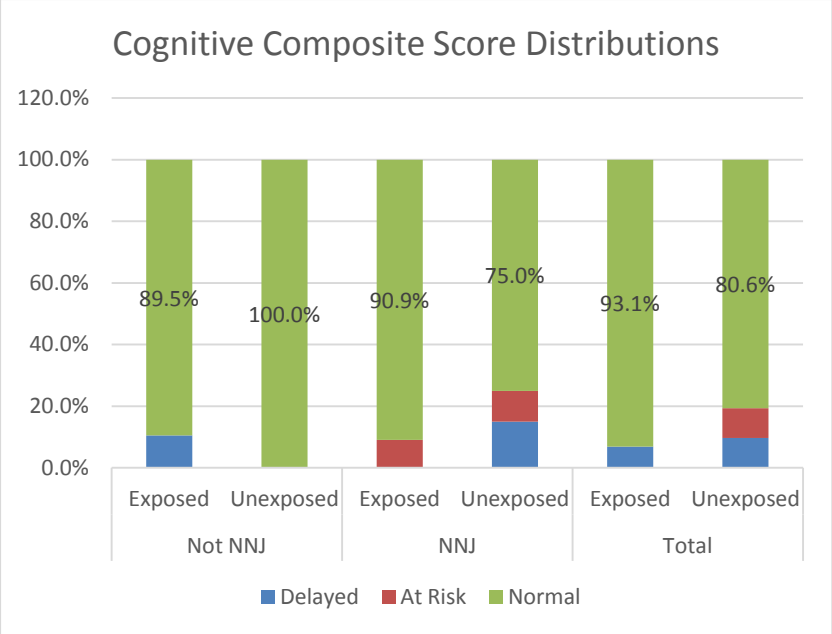


Figure 4. 1 Cognitive composite score distributions – NNJ

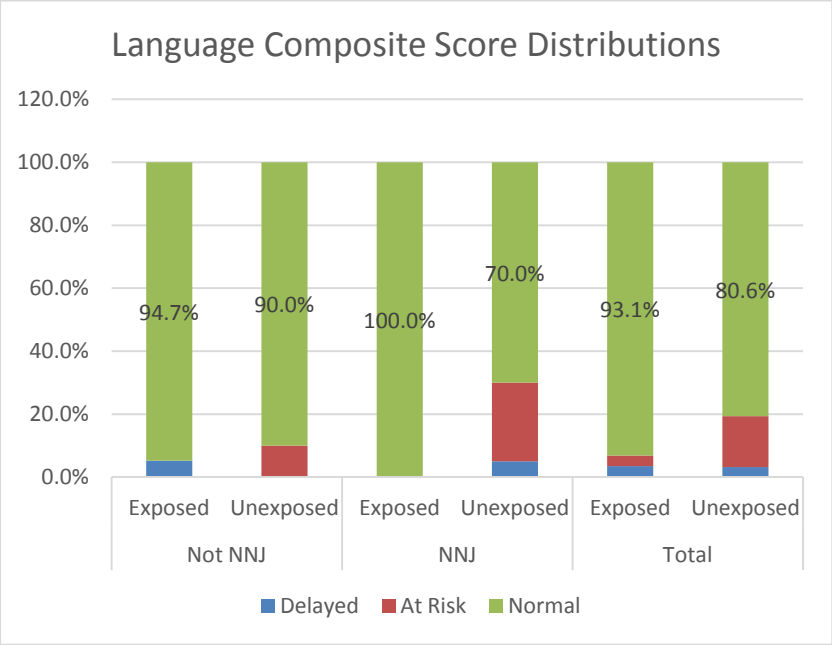


Figure 4.2 Language composite score distributions – NNJ

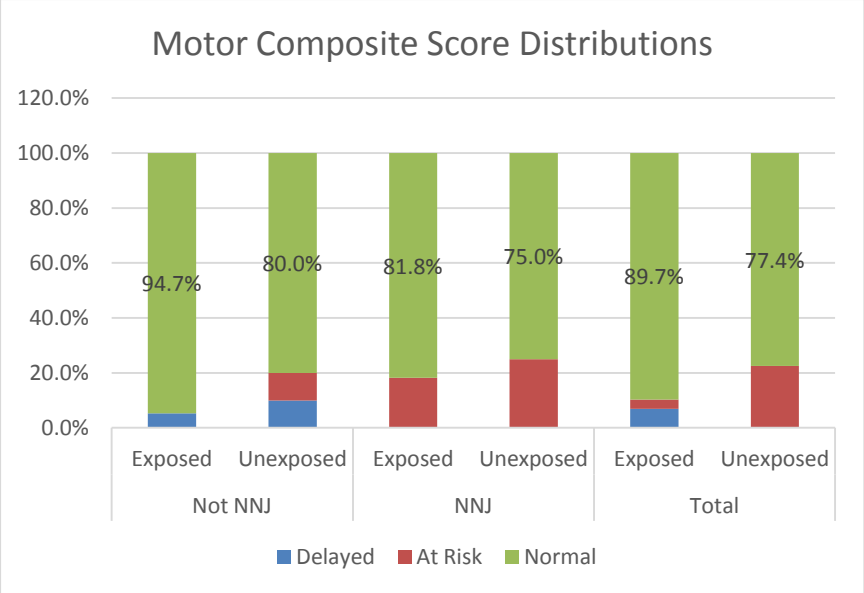


Figure 4.3 Motor composite score distributions – NNJ

4.8 Conclusion

The results of this study showed that HUU infants with neonatal complications such as meningitis and NNJ are more likely to present with language and motor delay when compared to the HEU infants.

There was some evidence that HEU infants may present with some motor delay but the neonatal complications had more affect of the neurodevelopment of infants than the HIV and ARV exposure in-utero.

Despite the fact that most infants were doing well there are still those who would benefit from early intervention and should be referred to the appropriate services

The results presented in this chapter will be discussed in chapter five.

Chapter 5

5. Discussion

In this chapter the results of the study will be discussed, along with limitations and recommendations for clinical practice and future research.

5.1 Demographics

The demographic data collected for the infants in this study showed no significant differences between the HEU and the HUU groups. This indicates that the two groups were well matched for these variables.

5.1.1 Prematurity

There were an equal number of infants (n=30) in each group. The two groups were well matched for prematurity with a mean gestational age of 33 weeks in both groups. The degree of prematurity ranged from 28 weeks to 37 weeks with the majority of the infants being between 31 and 36 weeks premature. Other studies that have assessed the development of HEU uninfected infants have tended to focus on term infants (Springer, et al., 2018; Whitehead, Potterton, & Coovadia, 2013) and have often excluded them. A study by Chaudhury et al, 2017 included infants born prematurely into their study but did not look at mean gestational age and whether the prematurity had an impact on the development of the children.

Prematurity is a known risk factor for developmental delay (Guimaraes, et al., 2011; Nepomnyaschy, et al., 2012) and would have affected both groups in this study equally.

The corrected ages at date of assessment in each group ranged from 16 days to 6 months.

5.1.2 Birth weight

There was no significant difference in the birth weights of the two groups (p=0.50). The infants in both groups were mainly born with a LBW (1500g – 2499g). Birth weight has been shown to have a negative impact on development (Ballot, et al., 2012; Chaudhury, et al., 2017; Oudgenoeg-Paz, et al., 2017). It was found that children born with a LBW are at risk for poor quality of movement and postural control. It is this affected early motor development that may affect cognitive development at a later stage (Oudgenoeg-Paz, et al., 2017). VLBW infants are at a high risk for learning and other difficulties (Ballot, et al., 2012). LBW is a risk factor for both groups in this study with regards to motor and cognitive development.

A SA study done in 2013 noticed a significant difference in the birth weights between HIV infected and HEU infants (Whitehead, Potterton, & Coovadia, 2013). The HIV infected infants were more likely to have a lower birth weight when compared to the HEU group but were within normal ranges. The HEU infants in the 2013 study had an average birth weight but in this study they were more likely to have a LBW. However the study by Whitehead et al excluded infants born prematurely. When comparing the composite scores between the HEU infants in both studies they were similar in all aspects of development. This could show that in this sample birth weight may not have had an impact on their development.

5.1.3 Mode of delivery

With regards to mode of delivery there was also no significant difference between the two groups.

Caesarean section was considered the safer mode of delivery in order to PMTCT but studies have now shown that with adequate control of the mother's viral load the risk of transmission to the infant during delivery can be as low as <0.5%, irrespective of mode of delivery (Raffe, et al., 2017).

5.2 Socioeconomic

When looking at the impact of socioeconomic status on infant development there was no significant difference in proportions between groups with regards to type of housing, whether there is running water, whether there is electricity, if a grandmother is present, if there are any siblings and who takes care of the child most of the time. Other studies have found that the development of HEU children can be affected by socioeconomic and nutritional status (Rajan, et al., 2017).

A Botswanan study by Chaudhury et al, 2017 confirmed that maternal education, age and income are associated with lower developmental scores for cognitive and language development. Their study assessed HEU infants at the age of 24 months and therefore these children had more time for socioeconomic aspects to influence their development.

A difference was seen between groups with regards to whether a mother and father were more likely to be present. Fathers were more likely to be present in the HUU group. A recent study has shown that a two parent household does not necessarily have a positive effect in an infant, which goes against majority of research (Cruise & O'Reilly, 2014). The study was done in Ireland in 2014 and took the primary caregivers of 10 748 infants who were 9 month old and completed the Ages and Stages questionnaire as well as enquired about the social environment and household income. The study found that a two parent household is not necessarily beneficial for the infant and that caregivers that were not the parents didn’t have a negative impact on the infants. The study also found that socioeconomic status did not have a negative impact on infant development (Cruise & O'Reilly, 2014).

Another significant difference noted was that the HEU group was more likely to receive a child care grant from the South African government. This could benefit infant development as the grant should go towards care of the child such as food, sanitation and toys. However, this may also indicate that this group is more vulnerable financially.

5.3 Neonatal complications

Neonatal complications that may impact results but affected both groups equally include hydrocephalus, RDS/HMD, mechanical ventilation, supplementary oxygen, CLD, pneumonia, ICU admission, NNS and KMC stay.

A study by Ballot et al, 2012 looked at the outcomes of premature infants and they found that hypothermia and PVL were significant risk factors for cognitive development, PVL and duration of oxygen were borderline risk factors for motor development and PVL was a risk factor for language development. These factors were not included in this study and are therefore important to take into consideration with regards to infant development.

Recent studies have shown that HEU infants are at risk for opportunistic infections such as pneumonia, tuberculosis and diarrhoea. All of which can have a major impact on the health and development of an infant (Evans, Jones, & Prendergast, 2016; Rajan, et al., 2017).

Meningitis showed to have a significant difference between groups with 13% of HUU infants being diagnosed with it compared to 0% in the HEU group.

The complication that showed to have the biggest difference in proportion was NNJ. Over two thirds (67%) in the HUU group as compared to 37% in the HEU group were treated for NNJ and this will also have an impact on infant development. A study done at Baragwaneth hospital looking at the neurodevelopmental outcome of 40 NICU survivors (mean gestational age 34 weeks) found that NNJ was a risk factor for abnormal language and motor development (Rosie, Potterton, & Pilusa, 2016).

Meningitis and neonatal jaundice are independent well documented causes of neurological impairment in neonates. The impact of these two conditions on the developmental status of the infants in this study will be discussed in greater detail later on in the chapter.

5.4 Neurodevelopment

The BSID III splits the developmental scores in cognitive, language and motor development. Language is further split into expressive and receptive language, motor is further split into gross and fine motor development. These subscales make it easy to determine which aspects of development are mostly affected.

5.4.1 HIV exposed uninfected infants

The mother's of all the HEU infants in this study were on ARVs during their pregnancy thereby ensuring a low viral load. The infants would have received a dose of Nevirapine at birth as well as had a PCR done post birth. Only infants who tested negative were included in the study. If there was any question with regards to the infant's HIV status they were not included in the study.

The developmental scores showed that majority of the HEU infants did well in all aspects of development when compared to the HUU group. The mean developmental scores in the HEU infants were within normal ranges, cognitive was 98.20, language was 99.30 and motor was 104.70. All of which are above 85 and therefore showing typical development. For cognitive development two HEU infants showed some delay and one infant was at risk. For language development one infant showed to have some delay. For motor development one infant showed to have delay and two were at risk for delays.

A similar result was found in a study done in India by Rajan et al in 2017. They assessed 41 HIV exposed infants aged 6 – 18 months and 40 of these children had normal development, as long as their nutritional and medical care was adequate. The same study concluded that the ARV drug exposure in-utero had no affect on the development of the infants. The infants were assessed using the Development Assessment scale for Indian infants (DASII), which is based on the Bayley Scale of Infant Development. They compared HEU infants to HIV infected infants.

A South African study done in Cape Town in 2017 assessed the development of HEU infants at 12 months of age using the BSID III. They found there to be minor difference in neurodevelopmental outcome when compared to HUU infants

(Springer, et al., 2018). The HEU group in this study had a mean cognitive score of 100.46, language score of 91.75 and motor score of 96.5 which are within normal ranges and similar to this study. In contrast Springer et al (2018) found that a higher proportion of HEU infants had a poorer developmental outcome with regards to language development.

When looking at a study with older HEU children (24 months) in Botswana there is still no negative neurodevelopmental outcome when assessed with the BSID III. They assessed 313 HEU infants and concluded that there was no negative neurodevelopmental impact on the child when they are exposed to the HI virus in-utero or the ARV drugs (Chaudhury, et al., 2017) .

A study done in Zimbabwe in 2016 showed that HEU infants had poorer health outcomes when compared to their HUU counterparts. There was 50% more hospitalization within 1 month of birth and higher morbidity and mortality outcomes at the 24 month follow-up. The follow-up results could be related to maternal stability as well as income within the family, all of which will impact the care given to the children. This study looked at morbidity and mortality of these infants but did not determine whether there is an effect on development (Evans, et al., 2016).

Whitehead, Potterton & Coovadia, (2013) compared the development of HIV infected infants to HEU infants and also noted that the mean composite scores (cognitive 93.97, language 100.26, motor 106.48) in the HEU group showed no delay in any aspect of development.

The above mentioned studies tended to exclude premature infants from their sample and those that did make mention of prematurity (Chaudhury, et al., 2017) did not determine whether prematurity in itself will have an impact on development.

5.4.2 HIV unexposed uninfected infants

The mean composite scores in the HUU group (cognitive 98.30, language 91.40, motor 96.70) are within normal ranges but are lower than the HEU group.

The HUU infants had lower developmental scores in the expressive language as well as fine and gross motor subscales of the BSID III. This group showed to have more

neonatal complications such as meningitis and NNJ and this appears to have more of an effect on the infant's CNS than HIV exposure. Both of these complications have been shown to have an impact on the development of an infant and will be discussed in greater detail.

NNJ showed to have the biggest affect on the HUU group. The composite scores were significantly lower in the HUU group with NNJ (cognitive 93.75, language 88.80, motor 93.15) when compared to the HEU group with NNJ (cognitive 100.45, language 99.73, motor 103.64).

HEU infants are likely to be born premature due to the ARVs during pregnancy in order for PMTCT (Nlend, et al., 2016), however HUU infants are born premature when other complications or lifestyles arise (Saltani, et al., 2017; Waetcher, 2014).

There are a number of risk factors for an infant to be born prematurely. Research has shown that poor gestational weight gain is one of these factors and can be seen in areas of poverty where there is not enough money for adequate nutrition. Malnutrition is a risk factor that is commonly seen in poor resource countries. The problem with malnutrition is that the foetus takes the nutrients that it needs from the mother's reserves. Malnourishment can lead to dangerous conditions such as hypertension, preeclampsia and gestational diabetes, all of which will cause premature labour. Not eating correctly will also cause the mother's immune system to be weaker and therefore becoming more susceptible to infections which can cause premature rupture of membrane (Saltani, et al., 2017; Waetcher, 2014).

5.5 Meningitis

In this study 13% (n=4) of HUU infants were being treated for meningitis, compared to 0% in the HEU group.

Meningitis is a bacterial infection of the CNS and has the highest incidence in the neonatal period. It is acute inflammation of the meninges, subarachnoid space and vessels in the brain. If it presents within the first two days to one week of life it reflects vertical transmission, which is the infection coming from the mother. The risk factors include: prematurity, LBW, chorioamnionitis, prolonged rupture of membrane,

premature rupture of membrane, low socioeconomic status, need for resuscitation, prolonged hospitalisation and male infants (Heath & Okike, 2010; Ku, Boggess, & Cohen-Wolkowiez, 2015). The HUU in this study were exposed to the above risk factors for meningitis specifically prematurity, premature rupture of membrane and low socioeconomic status.

The more premature the infant, the worse the prognosis is and the more likely the infant will present with long term complications such as cognitive dysfunction, seizures, CP, hydrocephalus, sensorineural hearing loss, behavioural problems, speech and language disorders and impaired vision (Heath & Okike, 2010; Ku, Boggess, & Cohen-Wolkowiez, 2015; Lin, et al., 2012).

5.6 Neonatal Jaundice

In this study two thirds of the HUU infants were diagnosed with neonatal jaundice. Fifteen percent of the HUU NNJ infants showed cognitive delay with 10% being at risk. Five percent of the HUU NNJ infants showed language delay with 25% being at risk. None of the HUU NNJ infants showed delay in motor development but 25% were at risk with composite scores below 85.

Jaundice occurs when bilirubin is deposited into elastin-rich tissues. Bilirubin is a waste product of red blood cells and is mainly excreted by the liver. The higher levels of circulating bilirubin in neonates is due to the infants having higher concentrations of red blood corpuscles which break down quickly. This can have severe and serious consequences as the bilirubin can cross the blood-brain barrier and attach to the developing brain tissue. The most vulnerable areas of the infant's brain are those that control hearing and motor function (Casey, 2013; Pearsall & Morrow, 2016).

Studies have shown that NNJ does have an effect on development of infants. Rosie, Potterton & Pilusa (2016) found that 37.5% of their 40 neonatal ICU survivors (mean gestational age 34 weeks) were treated for NNJ. These infants were found to be at risk for language and motor developmental delays. This was confirmed in this study as 25% of HUU infants were at risk for language and motor delays, with only 10% being at risk for cognitive delay.

5.7 Challenges of the study

- The study had a small sample size which made it difficult to do meaningful statistical analysis and obtain generalizable results.
- It would have been beneficial to follow up the infants at a later stage to determine whether their development would improve at a later age as the infants were very young. This could also show the impact of socioeconomic aspects on development as the infants would have had time for this to take affect.
- There are many possible confounding factors which may have influenced the results of this study such as infant's awake state, infant's general health, infant's mood and irritability and environmental factors.

5.8 Clinical recommendations based on results

- HIV and ARV exposure in-utero appears to have little effect on the development of an infant. Birth complications such as meningitis and NNJ have a much bigger negative impact on neonatal development. All premature infants, whether HEU or HUU, should be followed up by all healthcare professionals post discharge in order to ensure early intervention if the need arises. If lack of resources and finances doesn't allow for all premature infants to be followed-up the infants treated for meningitis and NNJ should priority and closely monitored for any developmental delays on a monthly basis.
- All premature infants should be closely monitored in the wards post birth for complications such as meningitis and NNJ. Nursing staff should also be reminded of possible signs of meningitis and jaundice as they are more likely to detect it early on while caring for the infant.
- ARVs in pregnancy to control maternal CD4 count are of great importance as they ensure PMTCT and ensuring a healthier infant with less neurodevelopmental complications. The benefits of ARVs in pregnancy greatly outweigh the possible negatives with regards to the infants development and therefore all HIV^+ pregnant women should receive ARVs and all pregnant women should be encouraged to be screened for HIV.

- Doctors and nurses should be educated on cognitive, language, and motor development in infants of different ages or provided with a screening tool that is quick to administer in order to ensure early detection of delay, thereby ensuring early referral to allied health professionals and therefore early intervention.

5.9 Recommendations for future research

- Studies of similar nature with a bigger sample size should be considered
- Studies of similar nature should include a follow-up and reassessment in order to determine whether any delays could be detected at a later stage or whether improvements can be seen.
- A longitudinal study that includes HEU, HUU as well as HIV positive infants is recommended

Chapter 6

6. Conclusion

With ARVs being available for all HIV^+ pregnant women there has been a major impact on the PMTCT. Fewer infants are being born HIV^+ which greatly benefits the infant as the HI virus has a major impact on infant development. It is now important to note whether the ARVs and exposure to the HI Virus have an impact on development in utero.

There have been a few studies that have compared HEU infants to HUU infants but most of these have excluded premature infants. Research has shown that HIV exposure in utero increases the risk for premature delivery which is why premature infants should be included. These studies also assessed infants older than 12 months but if delays can be detected earlier than this then intervention can begin early which can positively impact the infants prognosis.

The main aim of this study was to determine if there is a difference between the development of premature infants born at 28-37 weeks gestational age that are HEU compared to HUU infants. The study also investigated whether clinical and demographic factors may be predictive of developmental status.

Consecutive infants who met the inclusion criteria were assessed at a neonatal follow up clinic using the Bayley Scales of Infant development lll. Clinical data was collected from the infant's file and the caregiver completed a demographic assessment form.

Both groups of infants performed relatively well with all aspects of development falling within the normal range. The HEU infants in the study had higher developmental scores in the expressive language, gross motor and fine motor aspects of development when compared to the HUU group. Through data analysis it was determined that a larger proportion of the HUU infants were treated for neonatal complications such as meningitis and NNJ. It is these complications that had a larger affect on infant neuromotor development than the exposure of HIV and ARVs in-utero.

There is a need for all premature infants to be followed up on a regular basis post discharge from hospital, whether they are HIV exposed or not as there were a few infants in the study that showed delays or were at risk for delay. It is the infants treated for NNJ and meningitis that need a thorough developmental assessment at each visit in order to detect delays in a timely manner and ensure early intervention.

References

Department of Health. *National Annual Report 2013/2014.* [online] Available from: http://www.gov.za/sites/www.gov.za/files/Department_of_Health_Annual_Report_2014.pdf. [Accessed: March 2016]

Department of Health. *National Annual Report 2016/2017.* [online] Available from: http://www.gov.za/sites/www.gov.za/files/Department_of_Health_Annual_Report_2016-17.pdf. [Accessed: March 2018]

UNAIDS AIDS*. Epidemic Update 2013*. [online] Available from: http://www.unaids.org. [Accessed: January 2016].

UNAIDS AIDS. *Global AIDS Update 2016.* [online] Available from: http://www.unaids.org. [Accessed: March 2019]

WHO. *Data and Statistics* [online] Available from: http://www.who.int. [Accessed: January 2016]

WHO. *Preterm birth* [online] Available from: http://www.whi.int/news-room/fact-sheets/detail/preterm-birth. [Accessed: June 2018]

Alam, K., Snover, A., Navid, S., & Tasneem, S. (2014). Gestational hypertension; maternal and fetal outcome in women with role of hyperurecemia. *The Professional Medical Journal*, 969-974.

Ali, S. (2013). A brief review of risk-factors for growth and developmental delay among preschool children in developing countries. *Advanced Biomedical Research*, 1-8.

Ballot, D. E., Potterton, J., Chirwa, T., Hilburn, N., & Cooper, P. A. (2012). Developmental outcome of very low birth weight infants in a developing country. *Biomedcentral Pediatrics*, 1-10.

Ballot, D., Potterton, J., Chirwa, T., Hilburn, N., & Cooper, P. (2012). Developmental outcome of very low birth weight infants in a developing country. *BMC Pediatrics*, 1471-2431.

Baroncelli, S., Tamburrini, E., Ravizza, M., Dalzero, S., Tibaldi, C., Ferrazzi, E., . . . Floridia, M. (2009). Antiretroviral treatment in pregnancy: a six-year perspective on recent trends in prescription patterns, viral load suppression, and pregnancy outcomes. *AIDS Patient care and STDs*, 513-520.

Barret, B., Tardieu, M., Rustin, P., Lacroix, C., Chabrol, B., Desquerre, I., . . . Blanche, S. (2003). Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. *AIDS,* 1769-1785.

Bayley, N. (2006). Bayley Scales of Infant and Toddler Development, Third edition. *Journal of Psychoeducational Assessment,* 180-198.

Bornstein, M., & Hendricks, C. (2013). Screening for developmental disabilities in developing countries. *Social Science & Medicine*, 307-315.

Campbel, S., Palisano, R., & Orlin, M. (2012). *Physical Therapy for Children.* Missouri: Elsevier Saunders.

Campbell, S. K. (2012). The Child's Development of Functional Movement. In S. K. Campbell, R. J. Palisano, & M. N. Orlin, *Physical Therapy for Children* (pp. 37-86). Missouri: Elsevier Saunders.

Casey, G. (2013). Jaundice: an excess of bilirubin. *Kai Tiaki Nursing New Zealand*, 20-24.

Castell, E., Rizo-Baeza, M., Aguilar Cordero, M., Rizo-Baeza, J., & Gil Guillen, V. (2013). Maternal age as risk factor of prematurity in Spain; Mediterranean area. *Nutricion Hospitalaria*, 1536-1540.

Chaudhury, S., Williams, P. L., Mayondi, G. K., Leidner, J., Holding, P., Tepper, V., . . . Lockman, S. (2017). Neurodevelopment of HIV-Exposed Uninfected children at 24 months. *Pediatrics*, 1-10.

Chiabi, A., Mah, E., Mvondo, N., Nguefack, S., Mbuagbaw, L., Kamga, K., . . . Mbonda, E. (2013). Risk factors for premature births: a cross-sectional analysis of hospital records in a Cameroonian health facility. *African Journal of Reproductive Health*, 77-83.

Chimbwandira, F., Mhango, E., Makombe, S., Midiani, D., Mwansambo, C., Njala, J., . . . al, e. (2013). *Impact of an innovative approach to prevent mother-to-child transmission of HIV - Malawi, July 2011-September 2012.* Malawi: Morbidity and Mortality Weekly Report.

Cruise, S., & O'Reilly, D. (2014). The influence of parents, older siblings, and non-parental care on infant development at nine months of age. *Infant behavior and development*, 546-555.

D'Agostino, J. A. (2010). An evidentiary review regarding the use of chronological and adjusted age in the assessment of preterm infants. *Journal for Specialists in Pediatric Nursing*, 26-32.

Darak, S., Darak, T., Kulkarni, S., Kulkarni, V., Parchure, R., Hutter, I., & Janssen, F. (2013). Effect of Highly Active Antiretroviral Treatment (HAART) During Pregnancy on Pregnancy Outcomes: Experiences from a PMTCT Program in Western India. *AIDS Patient Care and STDs*, 163-172.

Dars, S., Malik, S., Samreen, I., & Kazi, R. (2014). Maternal morbidity and perinatal outcome in preterm premature rupture of membranes before 37 weeks gestation. *Pakistan Journal of Medical Science*, 626-629.

De Jongh, B., Paul, D., Hoffman, M., & Locke, R. (2014). Effects of Pre-pregnancy Obesity, Race/Ethnicity and Prematurity. *Maternal and Child Health Journal*, 511-517.

Debelew, G., Afework, M., & Yalew, A. (2014). Determinants and Causes of Neonatal Mortality in Jimma Zone, Southwest Ethiopia: A Multilevel Analysis of Prospective Follow Up Study. *PLOS ONE*, 1-11.

Esker, S., Albano, J., Uy, J., Arikan, D., Jimenez-Exposito, M., Seekins, D., & Tilson, H. (2012). Monitoring the risk of birth defects associated with atazanavir exposure in pregnancy. *AIDS Patient Care and STDs*, 307-311.

Evans, C., Humphrey, J. H., Ntozini, R., & Prendergast, A. J. (2016). HIV-Exposed Uninfected infants in Zimbabwe: Insights into Health Outcomes in the Pre-Antiretroviral Therapy Era. *Frontiers in Immunology*, 1-12.

Evans, C., Jones, C. E., & Prendergast, A. J. (2016). HIV-exposed, uninfected infants: new global challenges in the era of paediatric HIV elimination. *The Lancet*, e92-e107.

Ezechi, O., Gab-Okafor, C., Oladele, D., Kalejaiye, O., Oke, B., Ohwodo, H., . . . Ujah, I. (2013). Pregnancy, obstetric and neonatal outcomes in HIV positive Nigerian women. *African Journal of Reproductive Health*, 160-168.

Gargari, S., Fallahian, M., Haghighi, L., Hosseinnezhad-Yazdi, M., Dashti, E., & Dolan, K. (2012). Maternal and Neonatal Complications of Substance Abuse in Iranian Pregnant Women. *Acta Medica Iranica*, 411-416.

Goyal, N., Attanasio, L., & Kozhimannil, K. (2014). Hospital care and early breastfeeding outcomes among late preterm, early-term and term infants. *Birth Issues in Perinatal Care*, 330-338.

Guimaraes, C. L., Reinaux, C. M., Botelho, A. C., Lima, G. M., & Cabral Filho, J. E. (2011). Motor development evaluated by Test of Infant Motor Performance: comparison between preterm and full-term infants. *Brazilian Journal of Physical Therapy*, 357-362.

Guxens, M., Mendez, M. A., Molto-Puigmarti, C., Julvez, J., Garcia-Esteban, R., Forns, J., & al, e. (2011). Breastfeeding, long chain polyunsaturated fatty acids in colostrum, and infant mental development. *Pediatrics*, e880-e889.

Hankin, C., Lyall, H., Willey, B., Peckham, C., Masters, J., & Tookey, P. (2009). In utero exposure to antiretroviral therapy: feasability of long-term follow-up. *AIDS care*, 809-816.

Hankin, C., Newell, M., & Tookey, P. (2007). Long-term follow-up of uninfected children born to HIV-infected women and exposed to antiretroviral therapy: survey of parents' and health professionals' view. *AIDS care*, 482-486.

Heath, P. T., & Okike, I. O. (2010). Neonatal bacterial meningitis: an update. *Paediatrics and child health*, 526-530.

Hilburn, N., Potterton, J., & Stewart, A. (2010). Paediatric HIV Encephalopathy in sub-Saharan Africa. *Physical Therapy Reviews*, 410-417.

Hutchings, J., & Potterton, J. (2013). Developmental delay in HIV-exposed infants in Harare, Zimbabwe. *Vulnerable Children and Youth studies*, 1-15.

Irshad, M., Ahmad, A., Ahmed, K., Hayat, M., Kareem, R., Hussain, M., . . . Khan, B. (2012). Risk factors for preterm births in a tertiary care hospital, Lady Reading Hospital, Peshawar. *Journal of Postgraduate Medical Institute*, 158-164.

Jelsma, J., Davids, N., & Ferguson, G. (2011). The motor development of orphaned children with and without HIV: Pilot exploration of foster care and residential placement. *BioMed Central Pediatrics*, 1-7.

Kazemian, E., Sotoudeh, G., Dorosty-Motlagh, A., Eshraghian, M., & Bagheri, M. (2014). Maternal Obesity and Energy Intake as Risk Factors of Pregnancy-induced Hypertension among Iranian Women. *Journal of Health Population and Nutrition*, 486-493.

Khalid, T., Fehmida, S., & Javed, N. (2015). Awareness Regarding Gestational Diabetes Mellitus among Pregnant Women at Tertiary Care Hospital, Rawalpindi, Pakistan. *Pakistan Journal of Medical Research*, 87-89.

Khan, R., Ali, K., & Khan, Z. (2013). Maternal and fetal outcome of gestational diabetes mellitus. *Gomal Journal of Medical Sciences*, 88-91.

Kindra, G., Coutsoudis, A., Esposito, F., & Esterhuizen, T. (2012). Breastfeeding in HIV exposed infants significantly improves child health: A prospective study. *Maternal Child Health Journal*, 632-640.

Kinney, H. (2006). The near-term (late preterm) human brain and risk for Periventricular Leukomalacia: A review . *Seminars in Perinatology*, 81-88.

Ku, L. C., Boggess, K. A., & Cohen-Wolkowiez, M. (2015). Bacterial Meningitis in Infants. *Clinical Perinatology*, 29-45.

Landreau-Mascaro, A., Barret, B., Mayaux, M.-J., Tardieu, M., & Blanche, S. (2002). Risk of early febrile seizure with perinatal exposure to nucleoside analogues. *The Lancet,* 583-584.

Lazarov, S., Lazarov, L., & Lazarov, N. (2016). Complications of multiple pregnancies. overwiew. *Trakia Journal of Sciences*, 108-111.

Leone, J., Lane, S., Koumans, E., DeMott, K., Wojtowycz, M., Jensen, J., & Aubry, R. (2010). Effects of Intimate Partner Violence on Pregnancy Trauma and Placental Abruption. *Journal of Womens Health*, 1501-1509.

Lin, M.-C., Chi, H., Chiu, N.-C., Huang, F.-Y., & Ho, C.-S. (2012). Factors for poor prognosis of neonatal bacterial meningitis in a medical center in Northern Taiwan. *Journal of Microbiology, Immunology and Infection*, 442-447.

Madan, J., Chen, M., Goodman, E., Davis, J., Allan, W., & Dammann, O. (2010). Maternal obesity, gestational hypertension, and preterm delivery. *The Jouranl of Maternal-Fetal and Neonatal Medicine*, 82-88.

McCall, J., Vicol, L., & Tsang, G. (2009). Healthy mothers, healthy babies: preventing vertical transmission of HIV/AIDS. *Nursing bc*, 26-30.

McCrory, C., & Murray, A. (2013). The effect of breastfeeding on neuro-development in infancy. *Maternal and Child Health Journal*, 1680-1688.

McGlue, C. (2014). Midwifery services in South Africa and the UK. *British Journal of Midwifery*, 596-599.

Melhado, L. (2012). Antiretroviral therapy given to mother or child reduces risk of HIV transmission from breast-feeding. *International Perspectives on Sexual and Reproductive Health*, 167-168.

Mesfin, Y., Kibret, K., & Taye, A. (2016). Is protease inhibitors based antiretroviral therapy during pregnancy associated with an increased risk of preterm birth? Systematic review and a meta-analysis. *Reproductive Health*, 1-9.

Nepomnyaschy, L., Hegyi, T., Ostfeld, B. M., & Reichman, N. E. (2012). Developmental outcomes of Late-Preterm Infants at 2 and 4 years. *Maternal and Child Health Journal*, 1612-1624.

Nieuwenhuijsen, M., Dadvand, P., Grellier, J., Martinez, D., & Vrijheid, M. (2013). Environmental risk factors of pregnancy outcomes: a summary of recent meta-analyses of epidemiological studies. *Environmental Health*, 6-16.

Nlend, A. E., Motaze, A. N., Tetang, S. M., Zeudja, C., Ngantcha, M., & Tejiokem, M. (2016). Preterm birth and low birth weight after in utero exposure to anitretrovirals initiated during pregnancy in Yaounde, Cameroon. *Plos One*, 1-10.

Oudgenoeg-Paz, O., Mulder, H., Jongmans, M. J., van der Ham, I. J., & van der Stigchel, S. (2017). The link between motor and cognitive development in children born preterm

and/or with low birth weight: A review of current evidence. *Neuroscience and Biobehavioral Reviews 80*, 382-393.

Ozdemir, F. K., & Tufekci, F. G. (2013). The effect of individualised developmental care practices on the growth and hospitalisation duration of premature infants: the effect of mother's scent and flexion position. *Journal of Clinical Nursing*, 3036-3044.

Pearsall, R., & Morrow, G. (2016). Jaundice in Newborns. *World of Irish Nursing*, 51-52.

Piscoya, M., Ximenes, R., Silva, G., Jamelli, S., & Coutinho, S. (2012). Maternal periodontitis as a risk factor for prematurity. *Pediatrics International*, 68-75.

Powis, K., Kitch, D., Ogwu, A., Hughes, M., Lockman, S., Leidner, J., . . . Shapiro, R. (2011). Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor - based HAART during pregnancy. *The Journal of Infectious Diseases*, 506-514.

Raffe, S., Curtis, H., Tookey, P., Peters, H., Freedman, A., & Gilleece, Y. (2017). UK national clinical audit: management of pregnancies in women with HIV. *Biomedcentral Infectious Diseases*, 1-6.

Rajan, R., Seth, A., Mukherjee, S. B., & Chandra, J. (2017). Development assessment of HIV exposed children aged 6-18 months: a cohort study from North India. *AIDS Care*, 1-7.

Rosie, S., Potterton, J., & Pilusa, S. (2016, October 28). *Wits Institutional Repository environment on DSpace.* Retrieved from WIReDSpace: http://hdl.handle.net/10539/21314

Rutta, E., Gongo, R., Mwansasu, A., Mutasingwa, D., Rwegasira, V., Kishumbu, S., . . . Ramadhani, H. (2008). Prevention of mother-to-child transmission of HIV in a refugee camp setting in Tanzania. *Global Public Health*, 62-76.

Sacona-Ventura, C., Buttigieg, G., Felis, N., Gulliamier, R., & Gatt, M. (2009). Risk factors for prematurity in the Maltese Islands: 1999–2006. *International Journal of Risk and Safery in Medicine*, 177-184.

Saigal, S., & Doyle, L. W. (2008). An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet*, 261-269.

Salihu, H., August, E., Aliyu, M., Stanley, K., Weldeselasse, H., & Mbah, A. (2012). Maternal HIV/AIDS status and neurological outcomes in neonates: A population-based study. *Maternal & Child Health Journal*, 641-648.

Saltani, H., Lipoeto, N. I., Fair, F. J., Kilner, K., & Yusrawati, Y. (2017). Pre-pregnancy body mass index and gestational weight gain and their effects on pregnancy and birth

outcomes: a cohort study in West Sumatra, Indonesia. *BMC Women's Health*, 102-114.

Simon, L., Frondas-Chauty, A., Senterre, T., Flamant, C., Darmaun, D., & Roze, J.C. (2014) Determinants of body composition in preterm infants at the time of hospital discharge. *The American Journal of Clinical Nutrition,* 98-104.

Springer, P. E., Slogrove, A. L., Laughton, B., Bettinger, J. A., Saunders, H. H., Molteno, C. D., & Kruger, M. (2018). Neurodevelopmental outcome of HIV -exposed but uninfected infants in the Mother and Infants Health Study, Cape Town, South Africa. *Tropical Medicine & International Health*, 69-78.

Stevens, G. (2006). Gradients in the health status and the developmental risks of young children: the combined infuences of multiple social risk factors. *Maternal and Child Health Journal*, 187-199.

Suresh, V. (2015). Advanced Age Maternal Conception Modern Era Etiology for high risk mother, fetus and newborn. *International Journal of Multidisciplinary Approach and Studies*, 97-104.

Taha, E., Nasralla, K., Khalid, A., & Ali, A. (2013). Blunt abdominal trauma to a pregnant woman resulting in a child with hemiplegic spastic cerebral palsy and permanent eye damage. *BioMedCentral*, 517-525.

Traisathit, P., Mary, J., Le Coeur, S., Thantanarat, S., Jungpichanvanich, S., Pornkitprasarn, W., . . . Lallemant, M. (2009). Risk factors of preterm delivery in HIV-infected pregnant women receiving zidovudine for the prevention of perinatal HIV. *J Obstet Gynaecology*, 225-233.

Urry, K., & Mardis, C. (2014). Current considerations of HIV and HCV testing and the risks of vertical transmission during pregnancy. *Medical Laboratory Observer*, 8-10.

Vestergaard, M., Obel, C., Henrikson, T. B., Sorensen, H. T., Skajaa, E., & Ostergaard, J. (1999). Duration of breastfeeding and developmental milestones during the latter half of infancy. *Acta Paediatrica*, 1327-1332.

Waetcher, M. (2014). Malnutrition, unhealthy lifestyles and scheduled deliveries: the causes of prematurity. *Midwifery Today*, 38-39.

Weldearegawi, B., Melaku, Y., Abera, S., Ashebir, Y., Haile, F., Mulugeta, A., . . . Spigt, M. (2015). Infant mortality and causes of infant deaths in rural Ethiopia: a population based cohort of 3684 births. *BioMedCentral Public Health*, 770-777.

Whitehead, N., Potterton, J., & Coovadia, A. (2013). The neurodevelopment of HIV-infected infants on HAART compared to HIV-exposed but uninfected infants. *AIDS Care*, 497-504.

Wong, H., & Phil, E. (2013). Nature or nurture: A systematic review of the effect of socio-economic status on the developmental and cognitive outcomes of children born preterm. *Maternal and Child Health Journal*, 1689-1700.

Xu, H., Dai, Q., Xu, Y., Gong, Z., Dai, G., Ding, M., . . . Hu, F. (2015). Time trends and risk factor associated with premature birth and infants deaths due to prematurity in Hubei Province, China from 2001 to 2012. *BioMedCentral Pregnancy and Childbirth*, 329-339.

Yanuarti, H. P., Rusmil, K., & Effendi, S. H. (2014). Environment as a risk factor in delayed development in premature, low-birthweight and mild asphyxia children. *Pediatrics International*, 720-725.

Yerebasmaz, N., Cirik, D., Aydin, S., Kocer, M., Kayikcioglu, F., & Mollamahmutoglu, L. (2015). Does the minor trauma during pregnancy have any effect on perinatal outcome? *Dicle Medical Journal*, 410-415.

Yu, Y.-T., Hsieh, W.-S., Hsu, C.-H., Chen, L.-C., Lee, W.-T., Chiu, N.-C., . . . Jeng, S.-F. (2013). A psychometric study of the Bayley Scales of Infant and. *Research in Developmental Disabilities*, 3875-3883.

Zawiejska, A., Wenda-Ozegowska, E., Radzicka, S., & Brazert, J. (2014). Maternal hyperglycemia according to IADPSG criteria as a predictor of perinatal complications in women with gestational diabetes: a retrospective observational study. *Journal of Maternal-Fetal and Neonatal Medicine*, 1526-1530.

Zheng, W., Suzuki, K., Tanaka, T., Kohama, M., & Yamagata, Z. (2016). Association between Maternal Smoking during Pregnancy and Low Birthweight: Effects by Maternal Age. *PLOS ONE*, 1-9.

Appendix 1: Ethics approval

R14/49 Miss Charné Cox

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160438

NAME: (Principal Investigator)	Miss Charné Cox
DEPARTMENT:	Physiotherapy Tambo Memorial Hospital
PROJECT TITLE:	Developmental Status of Premature Infants who are HIV unexposed versus HIV exposed
DATE CONSIDERED:	06/05/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Joanne Potterton
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	17/08/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in April and will therefore be due in the month of April each year.

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 2: Title approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

10 January 2018
Person No: 364904
PAG

Miss C Cox
30 Du Toit Street
Ravenswood
Boksburg
1459
South Africa

Dear Miss Cox

Master of Science in Physiotherapy: Approval of Title

We have pleasure in advising that your proposal entitled *Developmental status of HIV exposed premature infants* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 3: GDoH approval

Ekurhuleni
METROPOLITAN MUNICIPALITY

EKURHULENI RESEARCH CLEARANCE CERTIFICATE

Research Project Title: Developmental status of HIV exposed premature infants.

Research Project Number: 14/07/2016-3

Name of Researcher(s): Ms Charne Cox

Division/Institution/Company: DoH – Tambo Memorial Hospital.

DECISION TAKEN BY THE EKURHULENI HEALTH DISTRICT RESEARCH COMMITTEE (EHDRC)

- *THIS DOCUMENT CERTIFIES THAT THE ABOVE RESEARCH PROJECT HAS BEEN FULLY APPROVED BY THE EHDRC. THE RESEARCHER(S) MAY THEREFORE COMMENCE WITH THE INTENDED RESEARCH PROJECT.*
- *NOTE THAT THE RESEARCHER WILL BE EXPECTED TO PRESENT THE RESEARCH FINDINGS OF THE PROPOSED RESEARCH PROJECT AT THE ANNUAL EKURHULENI RESEARCH CONFERENCE.*
- *THE RESEARCH COMMITTEE WISHES THE RESEARCHER(S) THE BEST OF SUCCESS.*

DR. J. SEPUMA

DEPUTY CHAIRPERSON: EKURHULENI METROPOLITAN MUNICIPALITY
Dated: 27/07/2016

DR. R. Kellerman

CHAIRPERSON: GAUTENG DEPARTMENT OF HEALTH (EKURHULENI REGION)
Dated: 27/07/2016

Appendix 4: TMH approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

OFFICE OF THE CEO
Dr. A. Naidoo
Tambo Memorial Hospital
: (011) 898-8317
: (011) 892-0358
: AvisN@gpg.gov.za

MEMO

To : Ms Charne Cox

From : Dr A Naidoo – Chief Executive Officer

Date : 18 August 2016

Subject : **Request to Carry Out Research at Tambo Memorial Hospital**

This serves to grant permission Ms Charne Cox to carry out a research study: *Development status of HIV exposed premature infants* at Tambo Memorial Hospital. This permission is granted in light of improving the skill capacity of the Gauteng Department of Health.

The permission is granted in line with the code of ethics or research.

The information of the Gauteng Health Department will be used for the purpose of research and it will be utilized discreetly and that confidentiality will be maintained at all times.

The permission is granted in good faith with the notion and understanding that the abovementioned clause is upheld.

Furthermore, there should be no financial implication to the hospital.

The collection of data will be the responsibility of the researcher.

Thank you,

Dr A Naidoo
Chief Executive Officer

TAMBO MEMORIAL HOSPITAL
DR. A. NAIDOO
2016 -08- 18
CEO
GAUTENG PROVINCIAL GOVERNMENT

Appendix 5: Information sheet

Information Sheet

Study title: Developmental status of HIV exposed premature infants

Good day parents

My name is Charne Cox and I am employed as a physiotherapist at Tambo Memorial Hospital (TMH). I am doing my research on the developmental status of HIV exposed premature infants. Research is a process where you try find an answer to a question. In this research I am trying to determine whether antiretrovirals can have an effect on the development of the baby in the uterus.

I am asking your permission to include your child in this research study. Your child will be assessed using a recognised screening tool. It is a once off assessment that will be done at your convenience at TMH. I will ask you as a parent a few questions and I will also collect some information from your babies file. I will then assess your babies cognitive, language, motor and social-emotional development. This assessment will take approximately 30 minutes. I will provide you, as the parent, with feedback of the results once the assessment is complete.

There are no risks involved for this study. There is also no direct benefit for you as the parent or for your infant but by allowing your infant to take part in this study I will be able to assess their development and determine whether your child is on track or not. If I determine that there is a delay your child will be referred on for the appropriate intervention such as physiotherapy, occupational therapy, speech therapy and audiology. Your baby will also be part of a study that can help other babies in the future.

Participation of your infant in this study is voluntary and if you do not provide permission there will be no penalty or loss of benefits. You may discontinue participation at any stage during the study and there will be no penalty or loss of benefits.

Efforts will be made to keep personal information confidential. The results of the assessment will be made known but the infant's identity will not be disclosed. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law.

For more information with regards to this study please contact Charne Cox on 011 898 8224 or in the physiotherapy department at TMH.

If you would like to report any complaints or problems you can contact the Human Research Ethics Committee (HREC) on:

Prof. P Cleaton Jones: Tel 011 717 2301, email peter.cleaton-jones1@wits.ac.za

The administrative officers Ms Z Ndlovu/ Mr Rhulani Mkansi/ Mr Lebo Moeng:

Tel: 011 717 2700/2656/1234/1252

Email: zanele.ndlovu@wits.ac.za / rhulani.mkansi@wits.ac.za / lebo.moeng@wits.ac.za

Appendix 6: Consent form

Consent Form

I have been asked to give consent for my infant to participate in this research study titled: Developmental status of HIV exposed premature infants.

I will be asked questions with regards to my infant and then he/she will be assessed by Charné Cox, the research investigator. The information will be kept confidential and I can withdraw my infant from the study at any time without any loss of benefit to my infant.

I have read the information sheet, or it has been read to me. If I do not understand English this study was explained to me in a language that I understand.

I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my liking. I consent voluntarily for my infant to participate in this study.

I ……, parent of ……, give permission for my infant to take part in this study.

Date: …….. Time: …….. Place: ……..

Parent Witness

Appendix 7: Data collection sheet / Demographic questionnaire

Data Collection Sheet

Infant Code		**Date of birth**	
Gender			

Birth:	Term	Preterm	Weeks preterm:	Corrected age:
Delivery:	NVD	C-section	Reason for C-section:	
RVD status:	Exposed	Unexposed	PCR positive	PCR negative
Birth weight and height:				
Current weight and height:				
Apgars:				

Birth Weight:	ELBW (<999g)	VLBW (1000 - 1499g)	LBW (1500 – 2499g)	Average (>2500g)	
Neuro:	IVH I	IVH II	IVH III	Hydrocephalus	
Respiratory:	RDS/HMD	Mechanical ventilation		O_2	CLD
Infections:	Pneumonia	Seizures	NNJ	NNS	Meningitis
Other:	PDA	HIE I	HIE II	HIE III	ROP
	Down Syndrome	Cleft lip/palate	CP		
ICU:	Y / N	**Days in ICU:**			
KMC:	Y / N	**Days in KMC:**			
Other complications:					

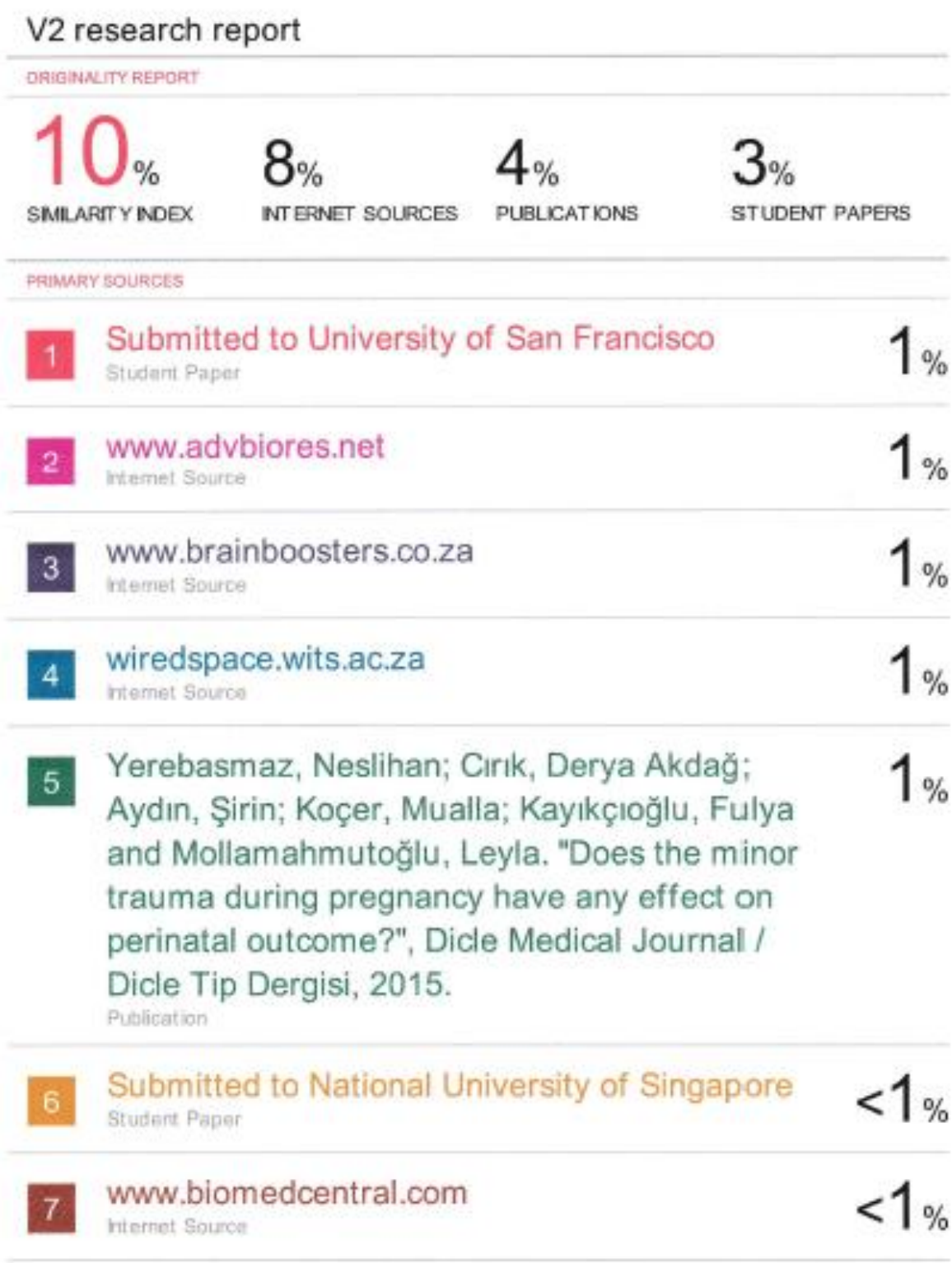
Demographics

Area	Rural	Urban	Other:	
Type of house	Flat	House	Shack	Other:
Running water	Yes	No	Inside	Outside
Electricity	Yes	No		
Toilet	Inside	Outside	Distance from house:	
Number of people per room:				
Other:				

Family

Structure	Mom	Dad	Grandparents	Siblings
Number of siblings:				
Other premature births	Yes	No	Causes:	
Who looks after infant in day:				
Grant	Yes	No	Type:	
Maternal history	HPT	Diabetes	Other:	
Other:				

Appendix 8: Originality report



V2 research report

ORIGINALITY REPORT

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