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The Neurodevelopment of HIV Positive Infants on HAART Compared to HIV Exposed but Uninfected Infants

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ABSTRACT

HIV continues to affect thousands of children in South Africa. HIV not only has a negative impact on growth, morbidity and mortality but also adversely affects neurodevelopment. The virus is able to enter the central nervous system and cause damage which results in encephalopathy. A high percentage of infants infected with HIV are delayed. The roll out of HAART in South Africa was started in 2004 and in 2010 new guidelines to improve access were implemented. Although HAART is effective in improving growth, decreasing morbidity and mortality its effects on neurodevelopment are generally unknown. Very little high quality research has been done on the effects of HAART on neurodevelopment especially in developing countries and on infants.

Therefore, the aim of this study was to compare the neurodevelopment of HIV positive infants on HAART to HIV exposed uninfected infants. Other objectives included monitoring growth parameters, illnesses and hospital admissions in the infants and determining maternal health during pregnancy. The HIV positive group was also stratified according to CD4 percentage at baseline to determine if this has an effect on development and growth.

To meet the objectives a longitudinal study was conducted at the Empilweni Clinic at Rahima Moosa Mother and Child Hospital, Johannesburg. Twenty seven HIV positive and 29 HIV exposed uninfected infants were studied over a six month period. HIV positive infants were assessed prior to initiating HAART and then for six months while on HAART. HIV exposed uninfected infants were studied for six months. The Bayley Scales of Infant and Toddler Development 3rd Ed (Bayley III) was used to assess development in the infants. Weight, height and head circumference were measured at each visit and questions regarding illnesses and hospital admissions were asked. Blood results were recorded at each visit and pregnancy history was determined at baseline.

It was found that HIV positive infants scored significantly lower when compared to HIV exposed uninfected infants for motor and language development at baseline ($p = 0.00$), at three months follow up ($p=0.00$) and at six months follow up ($p = 0.00$). Cognitive development was also significantly lower when compared to the HIV exposed uninfected group at baseline ($p = 0.03$) and visit one ($p = 0.00$). By

six months follow up there were no significant differences between the two groups for cognitive development ($p = 0.30$). No significant improvement in language ($p = 0.46$) and motor function ($p = 0.91$) occurred over time, however developmental scores did not decrease. A significant increase in cognitive scores were seen from visit one to visit two in the HIV positive group ($p = 0.0161$). There was a trend for HIV positive infants with lower CD4 percentages to perform significantly worse on developmental scores compared to HIV positive infants with higher CD4 percentages.

Weight was significantly lower in the HIV positive group at baseline compared to the HIV exposed uninfected group ($p = 0.00$), but improved significantly over the course of the study and by six months follow up there were no significant differences between the groups ($p = 0.45$). Hospital admissions and illnesses also decreased with time.

Maternal health during pregnancy was similar between the two groups with the only difference being that the mothers of the HIV exposed uninfected group used AZT significantly more than the mothers of the HIV positive infants ($p=0.008$).

This study suggests that HIV positive infants are delayed when compared to HIV exposed uninfected infants. HAART may help to prevent further delay however does not reverse damage already present. There is a need for therapists to be involved in HIV clinics in order to provide early developmental screening as well as rehabilitative services to those children in need.

DECLARATION

I, Nicole Whitehead, declare that this is my own unaided work except for the help given by the persons listed under the acknowledgements.

Signed this day in Johannesburg

Signature

Date

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ABBREVIATIONS USED

AIDS	-	Acquired immunodeficiency syndrome
ANC	-	Antenatal Care
ART	-	Antiretroviral Therapy
ARVs	-	Antiretrovirals
Bayley III	-	Bayley Scales of Infant and Toddler Development 3rd Edition
BSID	-	Bayley Scales of Infant Development
CNS	-	Central Nervous System
CSF	-	Cerebrospinal fluid
CT	-	Computed tomography
DOH	-	Department of Health
HAART	-	Highly Active Antiretroviral Therapy
HI	-	Human immunodeficiency
HIV	-	Human Immunodeficiency Virus
MRI	-	Magnetic Resonance Imaging
MTCT	-	Mother to Child Transmission
NNRTI	-	Non Nucleoside Reverse Transcriptase Inhibitor
NRTI	-	Nucleoside Reverse Transcriptase Inhibitor
NVP	-	Nevirapine
PCR	-	Polymerase Chain Reaction
PI	-	Protease Inhibitor
PMTCT	-	Prevention of Mother to Child Transmission
RMH	-	Rahima Moosa Hospital
SD	-	Standard Deviation
VL	-	Viral Load
WHO	-	World Health Organization
ZDV	-	Zidovudine

Chapter 1

INTRODUCTION

1.1. Background

Sub-Saharan Africa has the highest prevalence of Human Immunodeficiency Virus (HIV) in the world. In 2010, 22.9 million people were living with HIV in sub-Saharan Africa, accounting for two thirds of people living with HIV around the world. Worldwide 2.5 million children are infected with HIV and in 2010, 390 000 new infections occurred in children. South Africa has 5.6 million people infected with HIV, the largest population of people living with HIV in the world (UNAIDS, 2011; Department of Health South Africa, 2010). Huge strides have been made globally and especially in sub-Saharan Africa in the last few years in order to decrease new HIV infections and to increase coverage of prevention of mother to child transmission (PMTCT) and access to highly active antiretroviral therapy (HAART). In sub - Saharan Africa new infections in children have been decreased by 32% (UNAIDS, 2011). Even though vertical transmission of HIV has decreased, children still become infected with HIV and this results not only in poor growth increased morbidity and mortality but also affects neuro-development (Van Rie et al, 2007).

HIV is able to enter the central nervous system (CNS) very early on in pregnancy resulting in neuronal injury (Van Rie et al, 2007; Epstein et al, 1999; Lyman et al, 1990). As the child's brain is still developing it is vulnerable to injury (Epstein et al, 1999; Lyman et al, 1990). HIV infects macrophages and monocytes are able to enter the CNS. Once in the CNS, monocytes and macrophages interact with astrocytes and cause the production and release of inflammatory products as well as neurotoxins that result in neuronal damage (Epstein et al, 1999; Wilfert et al 1994; Epstein et al, 1993).

This neuronal injury causes a progressive encephalopathy in children. The clinical signs of the encephalopathy include loss of developmental milestones, symmetrical pyramidal motor abnormalities, impaired brain growth and acquired microcephaly (Epstein et al, 1999). It also causes calcification in the

basal ganglia which may be correlated with progressive encephalopathy (Belman et al, 1986). Cognitive, behavioral and motor problems are also evident (Epstein et al, 1999; Epstein et al, 1987). Various studies have been conducted and clearly show that children infected with HIV experience neurodevelopmental delays (Bailleu and Potterton, 2008; Potterton et al, 2009b; Van Rie et al, 2007). The prevalence of neurodevelopmental delay may be as high as 60% in HIV positive children (Van Rie et al, 2007) and it may occur in infants as young as 4 months (Chase et al, 1995). A study conducted in South Africa by Bailleu and Potterton (2008) found that 97% of children infected with HIV were delayed in gross motor development and 82.5% were delayed with language development.

When comparing HIV positive children to sero-revertors and HIV negative children using the Bayley Scales of Infant Development (BSID) it has been found that motor, language and cognitive development are all delayed significantly in the children who are HIV positive (Van Rie et al, 2008; Drotar et al, 1997; Nozyce et al, 1994; Msellati et al, 1993). More severe delays in development are present in younger children (Van Rie et al, 2008). HIV positive children have a 30% chance of developing a motor delay compared to HIV negative children and also have a 60% chance of developing an abnormal neurological finding (Drotar et al, 1997). Blanchette et al (2001) found that 47% of HIV positive children present with abnormal brain scans.

All these studies were conducted on antiretroviral therapy (ART) naive children or were conducted before HAART became readily available. Various studies have shown a number of positive effects with the initiation of HAART in children.

HAART is able to decrease viral loads to undetectable levels and to increase CD4 percentages in children with HIV infection (Bracher et al, 2007; Janssens et al, 2007; Song et al, 2007; Resino et al, 2006;). HAART has also been shown to decrease viral RNA present in cerebrospinal fluid (McCoig et al, 2002). Growth parameters such as weight and height are positively affected with HAART (Buonoro et al, 2008; Guillen et al, 2007). HAART has been shown to decrease the incidence of opportunistic infections as well as hospital admissions (Violari et al, 2008; Chiappinni et al, 2007; Nesheim et al, 2007). Most importantly HAART is able to decrease mortality. A large study by Violari et al (2008) conducted in South Africa,

found that when antiretrovirals (ARV's) are initiated early on there can be a 76% reduction in mortality and a 75% reduction in disease progression. Resino et al (2006) also found that the earlier ARV's are initiated the better.

Very few high quality studies have looked at the effects of HAART on neurodevelopment. Most of the studies have been conducted in developed countries and on older children. Often in the studies the children have also initiated HAART throughout the study period.

Raskino et al (1999) found that combination therapy of ZDV and DDI significantly improves cognitive and motor function. However, a study on neuropsychological function and HAART found no significant improvements in neuropsychological function (Jeremy et al, 2007). Lindsey et al, (2007) found that HAART therapy containing protease inhibitors have positive effects on neurodevelopment, however, the effects are limited. This study's results need to be analysed carefully as the groups were not similar at baseline and the childrens' mothers had high IV drug usage throughout their pregnancies, this may have affected the results. Ferguson and Jelsma (2009) found no difference in motor performance in children on HAART and those ineligible for HAART. They also found no difference for motor function to not be influenced by length of time on HAART.

A debate persists about when it would be best for ARV's to be initiated. Early initiation may lead to children learning poor adherence habits, the virus becoming more resistant to drugs and the adverse effects of prolonged exposure of the drugs to children (Welch and Gibb, 2008). However, studies have shown decreased mortality as well as slower disease progression with the early initiation of HAART in children who are HIV positive (Violari et al, 2008; Resino et al 2006).

1.2. Problem Statement

Studies looking at the effects of HAART on neurodevelopment are often of poor quality and have taken place in developed countries. These are irrelevant in the South African setting as most of the population

live in poor socioeconomic circumstances. It would be useful to see the effects of HAART on neurodevelopment especially in sub-Saharan Africa as here there is the highest prevalence of HIV in the world. The South African government has now established new guidelines as to when HAART should be initiated in children. As of April 2010 HAART should be initiated in all children less than one year of age regardless of CD4 count or percentage (Department of Health South Africa, 2010). The effects on mortality and reduction of opportunistic infections have been discussed above but no study has been conducted in sub-Saharan Africa looking at the possible neuro protective effects of HAART if initiated at high CD4 counts. If HAART were to have a positive effect on neurodevelopment it would support its early initiation. A study of this nature would also help determine what services still need to be made available to children infected with HIV.

1.3. Aim of Study

The aim of this study was to determine the neurodevelopment of HIV positive infants initiating HAART and to compare them to HIV exposed but uninfected infants.

1.4. Objectives of the Study

- To compare neurodevelopment in HIV exposed uninfected infants and HIV positive infants on HAART.

- To compare the neurodevelopment in the HIV positive group starting HAART at a more advanced stage of disease and an earlier stage (or at higher and lower CD4 percentages).

- To compare weight, height and head circumference between the groups.

- To compare illnesses and hospital admissions between the HIV positive and HIV exposed uninfected infants.

- To compare maternal health between mothers of HIV positive infants and HIV exposed uninfected infants.

Chapter 2

LITERATURE REVIEW

2.1. Introduction

This chapter will briefly discuss the epidemiology of HIV, transmission and prevention of transmission of HIV, how HIV affects the child and the effects of highly active antiretroviral therapy (HAART) on HIV. An in depth discussion will be presented on normal central nervous system (CNS) development and neurodevelopment in the child as well as factors influencing development. The effects of HIV on the developing CNS and on neurodevelopment as well as the effects of HAART on neurodevelopment will be presented. The effects of HIV exposure on the uninfected child will be summarised briefly.

Articles discussed in this literature review were sourced from Pubmed, CINAHL, the Cochrane Collaboration, EBSCO Host and Science Direct. Keywords in the literature search included HIV, neurodevelopment, HAART, CNS development, normal development, HIV encephalopathy, HIV exposed uninfected child.

2.2. Epidemiology of HIV

Worldwide, there are 34 million people living with HIV. In 2010 there were 2.7 million new HIV infections and 1.8 million deaths due to acquired immune deficiency syndrome (AIDS). Two and a half million children live with HIV and in 2010 there were 390 000 new infections in children. New HIV infections and AIDS related deaths have decreased dramatically since the peak of the epidemic in 1997. Infections in children have decreased by 15% since 2001 and AIDS related deaths in children have decreased by 20% (UNAIDS, 2011).

Coverage of prevention of mother to child transmission (PMTCT) has increased dramatically especially in the last two years. Worldwide, 48% of pregnant women are receiving effective treatment to prevent vertical transmission of HIV (UNAIDS, 2011). Access to treatment for HIV has also increased dramatically.

In 2010, 47% of people eligible for antiretrovirals (ARV's) were receiving them, however ten million adults and children are still in need of ARV treatment (UNAIDS, 2011).

Sixty eighty percent of people living with HIV reside in sub-Saharan Africa. Sub-Saharan Africa accounts for 70% of the new infections seen worldwide. There are 22.9 million people living with HIV in sub-Saharan Africa and in 2010 nearly two million new infections occurred in this region. Even though sub-Saharan Africa carries the burden of HIV infections, huge strides and accomplishments have been made in this region in terms of reducing transmission as well as decreasing mortality. The number of new infections has decreased by 26% since 1997. New infections in children have decreased by 32% since 2004 and AIDS related deaths in children have been decreased by 27%. Coverage for PMTCT has increased to more than 80% in most sub-Saharan African countries (UNAIDS, 2011).

South Africa continues to have the largest HIV epidemic worldwide (UNAIDS 2011; South Africa DoH, 2010). There are 5.6 million people living with HIV in South Africa (UNAIDS, 2011). This accounts for 17.9% of the population (South Africa DoH, 2010). There are also 330 000 children living with HIV in South Africa (UNAIDS, 2011). The main mode of transmission of HIV in South Africa is due to heterosexual sex followed by mother to child transmission (South Africa DoH, 2010). Huge strides have been made in the prevention and treatment of HIV in South Africa. The number of pregnant women with HIV has stabilised in the last three years and 30% of children are now receiving ARV's (South Africa DoH, 2010). Access to PMTCT has increased to 93%; however, mother to child transmission (MTCT) rates remain high at 16% (South Africa DoH, 2010)

Even though improvements are being seen in terms of decreases in new infections and decreases in HIV related deaths, a large number of children still live with HIV and have a variety of problems associated with the infection.

2.3. Vertical Transmission of HIV

The primary way in which HIV infection occurs in children is through mother to child transmission, however infection may occur due to exposure to infected blood products, through unsafe incision practices as well as through sexual abuse (Prendergast et al, 2007).

Children may become infected with HIV through transmission from their mothers during gestation or labour and delivery or through breastfeeding. This is termed mother to child transmission (MTCT) of HIV (Paintsil and Andiman, 2009; Volmink et al, 2008; Kourtis et al, 2006). Without any intervention the risk of MTCT of HIV may range from 12 - 40% (Paintsil and Andiman, 2009; Ogundele et al, 2003; Kourtis et al, 2001).

During gestation the risk for transmission is highest in the later stages of pregnancy (Volmink et al, 2008; Kourtis et al, 2006; Ogundele et al, 2003; Kourtis et al, 2001). Kourtis et al (2001) developed a model for the timing and distribution of MTCT of HIV. In 2006 she and her colleagues reviewed the literature again to determine the timing of HIV transmission. They found that a third of MTCT of HIV occurs during gestation and two thirds during labour and delivery. They found that less than five percent of transmission occurs early on in gestation and that 50% occurs between 36 weeks of gestation and labour. Volmink et al (2008) who also conducted a review had similar findings. They found that 80% of MTCT of HIV occurs in late pregnancy and labour.

Certain factors may increase the risk of MTCT of HIV during pregnancy. A high viral load and low CD4 count appear to be the most important risk factors for transmission (Fitzgerald et al, 2010; Garcia et al, 1999; Mofenson et al, 1999). Women with AIDS or an advanced disease stage, a CD4 count of less than 700 and a high viral load have a higher risk of transmitting infection to their infants (Fitzgerald et al, 2010; The European Collaborative Study, 1992;). Other risk factors include chorioamnionitis as well maternal co-infections with malaria and sexually transmitted illnesses (Paintsil and Andiman, 2009; Volmnink et al, 2008; Mofenson et al, 1999; The European Collobrative Study, 1992).

During labour there is a high chance of MTCT of HIV (Volmink et al, 2008). Transmission during delivery may be increased with instrumental deliveries, epsiotomies, perineal laceration, intrapartum haemorhage, foetal electrode monitoring and prolonged rupture of membranes (Paintsil and Andiman, 2009; Kourtis et al, 2001). Transmission may occur due to the high chance of direct contact of the foetus with the mother's blood and secretions (Kourtis et al, 2001).

Breastfeeding is also responsible for a high percentage of MTCT of HIV (Paintsil and Andiman, 2009; Volmink and Marais, 2008; Kourtis et al, 2006; Ogundele et al, 2003; The European Collaborative Study, 1992). Kourtis et al (2006) found that in 40% of HIV infected children, 15% of them may have become

infected due to breastfeeding. Cells, like macrophages, infected with HIV as well as free viral particles are present in breastmilk. When breastfeeding, the virus is able to cross the mucosal surface in an infant's mouth especially if damage is present and thus cause HIV infection in the child (Ogundele et al, 2003). Risk of transmission of HIV from breastfeeding is higher in the earlier stages of breastfeeding due to the high viral load present in colostrum (Kourtis et al, 2006; Ogundele et al, 2003). Factors that may increase the risk of transmission through breastfeeding include: advanced maternal illness, low CD4 counts, high viral loads, recent HIV infection, maternal disease progression, mastitis, breast fissures and breast abscesses as well as infant oral candidiasis (Paintsil and Andiman, 2009; Ogundele et al, 2003). Mixed feeding also increases the risk of transmission due to possible damage to the gut and the HI virus penetrating the gut (Paintsil and Andiman, 2009; Ogundele et al, 2003).

Therefore, in summary MTCT of HIV can occur during pregnancy, labour and delivery as well as through breastfeeding. Most transmission occurs later on in gestation and during labour and delivery. If the mother is breastfeeding there is a high chance of transmission due to the HI virus being present in breastmilk. Factors that may increase the risk of transmission include: high maternal viral load, low maternal CD4 counts, advanced illness, chorioamnionitis as well as associated maternal infections such as malaria and sexually transmitted diseases. Prolonged labour and rupture of membranes as well as the use of epsiotomies and instruments during delivery may also increase the chances of the infant coming into contact with the mother's infected blood and secretions and therefore increases the risk of transmission.

Interventions to prevent mother to child transmission of HIV are therefore essential and need to target decreasing viral load during pregnancy, helping the mother maintain a healthy pregnancy and preventing transmission through breastfeeding. The interventions available as well as their effectiveness will be discussed below.

2.4. Prevention of Mother to Child Transmission of HIV

Huge strides have been made in the last 15 – 20 years in reducing MTCT of HIV. In resource rich countries MTCT rates have been decreased to one to two percent (Volmink and Marais, 2008; Townsend et al, 2008). However, in poorer settings the prevention of mother to child transmission (PMTCT) of HIV remains a huge problem (Paintsil and Andiman, 2009). Various treatment interventions are available for PMTCT of HIV.

In 1994 a double blind, placebo controlled, randomised controlled trial by Connor et al found that a regimen of zidovudine (ZDV) from 14 weeks gestation, during labour and delivery and given to the infant for six weeks post delivery was effective in reducing MTCT rates by 67.5%. This study brought about huge improvements in the care of HIV positive pregnant women in the prevention of MTCT, however it was a complex regimen that was quite costly. The use of this regimen would not be feasible in poorer settings. Shaffer et al (1999) found that short course oral ZDV taken from 36 weeks of gestation onwards and then every three hours from the onset of labour decreases MTCT by 50%. This regimen is far simpler and more cost effective to administer (Shaffer et al, 1999). Several other studies have also shown that ARV's administered during pregnancy are effective in reducing MTCT rates (Fitzgerald et al, 2010; De Cock et al, 2000; Garcia et al, 1999). Large systematic reviews have shown that triple ARV regimens administered during pregnancy and labour and given to the child post birth are more effective in reducing MTCT rates compared to short courses of AZT (Siegfried et al, 2011; Chigwedere et al, 2008; Volmink and Marais, 2008). However, Garcia et al (1999) showed that any regimen of ZDV throughout pregnancy significantly decreases MTCT compared to no ZDV.

ARV's given as PMTCT help decrease maternal viral load and provide prophylaxis to the infant. It helps to decrease the exposure of the infant to the virus during pregnancy and delivery and in the infant provides prophylaxis against infection (Paintsil and Andiman, 2009; Connor et al, 1994; Chigwedere et al, 2008).

Transmission of HIV from breastfeeding still remains a problem and rates of transmission may be as high as 24 – 44% (Lehman et al, 2008). In resource poor settings breastfeeding remains the best option for most mothers as access to clean water and an adequate nutritional substitute is limited. Often there is a cultural stigma associated with formula feeding (Doherty et al, 2011; Palombi et al, 2007). Breastfeeding is effective in decreasing child mortality and morbidity, preventing pneumonia and diarrhoea and is an affordable way to provide adequate nutrition to the infant (Volmink and Marais, 2008; Ogundele and Coulter, 2003; De Cock et al, 2000). Formula feeding is an option but needs to be acceptable, feasible, affordable, sustainable and safe (Paintsil and Andiman, 2009; WHO, 2009; Ogundele and Coulter, 2003; De Cock et al, 2000). Palombi et al (2007) found that provision of formula feeds and water filters is extremely costly and being on HAART while breastfeeding is just as effective in decreasing MTCT rates. Hamsy et al (2010) found that HAART provides protection against transmission of HIV in the pre and postnatal periods but not against infant mortality. Breastfeeding was found to be the most effective means in improving child survival.

If breastfeeding is the best option for the mother, breastfeeding practices should be modified in order to achieve low transmission rates. Studies have suggested that there should be exclusive breastfeeding for four to six months and then early cessation, prolonged breastfeeding should be avoided, there should be no mixed feeding and breastmilk could possibly be treated with heat or microbial agents to inactivate HIV (Doherty et al, 2011; Volmink and Marais, 2008; Ogundele and Coulter, 2003; De Cock et al, 2000). Care of the mother during breastfeeding is also important. Mastitis and sore and cracked nipples need to be prevented (Ogundele and Coulter, 2003). An ARV regimen as prophylaxis may also decrease the risk of MTCT from breastmilk (Doherty et al, 2011; Lehman et al, 2008). Mothers on HAART who breastfeed are at low risk for transmitting HIV to their infant (Hamsy et al, 2010; Palombi et al, 2007).

Other measures that have been studied for PMTCT include vitamin A supplementation, immunotherapy and vaginal cleansing, however, there is little or no evidence to support these interventions (WHO, 2011; Volmink and Marais, 2008; De Cock et al, 2000). Elective caesarian section at 38 weeks gestation may also decrease the risk of MTCT; however the feasibility of its use in lower income settings is questionable. There are high cost implications as well as surgical risks involved with this intervention (Volmink and Marais, 2008).

The World Health Organization (WHO) has developed clinical guidelines for the reduction of MTCT. They recommend that an HIV positive woman who is pregnant and has a CD4 count of less than or equal to 350 cells/mm^3, or has stage three or four HIV disease be started on HAART. Post birth the infant should be placed on AZT or nevirapine (NVP) for the first four to six weeks of life regardless of method of feeding. If the woman is not eligible for HAART two options have been designed for ARV prophylaxis. The woman can be started on either AZT or triple ARV prophylaxis at 14 weeks gestation and this would continue throughout pregnancy. The infant should receive a single dose of NVP post birth and then either NVP or AZT for the first four to six weeks of life. If the mother is breastfeeding, NVP or AZT administered to the infant should continue until one week after cessation of breastfeeding (WHO, 2010).

South Africa has adopted these guidelines in their policy on PMTCT. All HIV positive women with a CD4 count of less than or equal to 350 cell/mm^3 or with stage three or four disease or with TB co-infection will be initiated on lifelong ART. Post delivery the infant will receive NVP prophylaxis for six weeks.

Women not eligible for ART will be provided with ARV prophylaxis. AZT is provided from 14 weeks gestation, a single dose of NVP is administered at onset of labour, and three hourly AZT is provided throughout labour. Postnatally a single dose of Tenofovir and Emtracitabine will be administered to the mother. The infant will receive NVP prophylaxis for six weeks. If the child is breastfeeding and the mother is not on ART the child will continue taking NVP until one week after cessation of breastfeeding (South Africa, Department of Health 2010).

The South African Department of Health recommends that caesarian sections only be performed if indicated for obstetric complications and not to decrease MTCT. The use of safer delivery techniques is advocated. These include: preventing prolonged rupture of membranes, avoiding invasive monitoring procedures and assisted instrumental deliveries as well as episiotomies and also only suctioning the infant if meconium stained liquid is present. Mothers should be counselled on feeding choices and should make a decision based on maximizing child survival. If the mother chooses not to breastfeed commercial formula will be provided free of charge for six months (South Africa, Department of Health 2010).

Through PMTCT levels of MTCT have been reduced. However, access to services still remains a problem and children are still becoming infected with HIV which leads to catastrophic consequences later on in life if untreated (Chopra et al, 2010; Paintsil and Andiman, 2009). The effect of HIV on the child, especially the neurological and developmental consequences of HIV, will be discussed further in this literature review.

2.5. The Effects of HIV on the Child

Even though PMTCT is effective in reducing HIV infections in children, some infants still become infected with HIV. Without adequate treatment, the risk of developing a wide variety of medical complications is high. Risk of mortality is also greatly increased.

Children who are infected with HIV progress far quicker to AIDS compared to adults (Shetty, 2005). It has been shown that up to 20% of children may progress rapidly to AIDS within the first year of life, this ultimately leads to death. Other children may survive for many years before becoming symptomatic

(Prendergast et al, 2007; Newell et al, 2004; The European Collaborative Study, 1994). The median age of onset of HIV symptoms in children is five months (Shetty, 2005)

Due to immune suppression, HIV infected children may present with several conditions including recurrent fever, lymphadenopathy, chronic diarrhoea, vomiting, ear infections, various skin conditions, oral candidiasis as well as coughing (Shetty, 2005; Taha et al, 2000; Emodi and Okofor, 1998). They may also present with more severe conditions such as hepatosplenomegaly, pneumocystis jirovecii pneumonia, cytomegalovirus, tuberculosis, meningitis, lymphoid interstitial pneumonitis and recurrent bacterial infections (Prendergast et al, 2007; Shetty, 2005; Emodi and Okafor, 1998).

HIV positive children often have high rates of hospital admissions. In a South African study conducted before the rollout of ARV's it was found that hospital admissions in paediatric wards increased significantly, there were also increased numbers of readmissions (Zwi et al, 1999). The increase in hospital admissions was due to the HIV epidemic. Reasons for hospital admissions often include oral candidiasis, various respiratory infections, anemia, failure to thrive, diarrhoea, tuberculosis, malaria and meningitis (Kourtis et al, 2007; Zwi et al, 1999; Vetter et al, 1996).

HIV infected infants are at a high risk for growth failure. Poor growth is associated with poorer immune function and increased risk of disease progression (Isanaka et al, 2009). Incidence of failure to thrive has been reported to be as high as 70% in HIV positive children (Isanaka et al, 2009). Weight for age z scores and height for age z scores are often significantly lower when compared to HIV exposed uninfected children and healthy, unexposed children (Isanaka et al, 2009; Miller et al, 2001). Problems in growth can be detected from as early as three to four months of age (Isanaka et al, 2009).

The European Collaborative Study (2003) conducted a prospective comparative study on a large sample of HIV positive children and HIV exposed uninfected children and followed them from birth until ten years of age. The study monitored the participants' growth. They found that HIV exposed uninfected children are significantly taller and heavier when compared to HIV positive children. They also found that viral load as well as disease stage impacts upon growth. A similar study was performed in South Africa on a far smaller sample and for a shorter period of time (Bobat et al, 2001). In the South African study similar findings were reported. Bobat et al (2001) found that attainment of height was a far bigger problem and that stunting continued to persist in HIV positive children. Height may have been

influenced more in this population as socioeconomic circumstances play a role in stunting (WHO, 1986). The population studied in the South African study would have come from poor socioeconomic circumstances. Potterton et al (2009b) also found that a population of HIV positive children from poor socioeconomic circumstances were underweight and stunted when compared to international norms. All the studies discussed above found that weight for age and height for age z scores were significantly lower and that HIV infected children were undernourished and stunted, however wasting was not noted (Potterton et al, 2009b; The European Collaborative Study, 2003; Bobat et al, 2001)

Various reasons may explain why HIV positive children are at risk for problems in gaining weight and height. Children with HIV often have increased metabolic requirements as well as disturbances in metabolism due to a chronic viral infection (Isanaka et al, 2009; Miller et al, 2001). HIV positive children often develop infections such as diarrhoea and oral candidiasis (Isanaka et al, 2009). Oral candidiasis would result in difficulty eating and with the intake of food, resulting in decreased caloric intake and therefore decreased growth (Isanaka et al, 2009). Persistent diarrhoea results in malabsorption of nutrients which would adversely influence growth (Isanaka et al, 2009; The European Collaborative Study, 2003; Bobat et al, 2001; Miller et al, 2001). Neuro endocrine abnormailities as well as growth hormone deficiencies have been reported in HIV positive children, this would in turn influence their growth (Isanaka et al, 2009; Prendergest et al, 2007; Bobat et al, 2001). High viral loads result in an altered immune response which in turn may affect metabolism (The European Collaborative Study, 2003). Often HIV infected children come from very poor socioeconomic backgrounds, this is associated with poor growth (Isanaka et al, 2009; The European Collaborative Study, 2003; WHO, 1986). Caregivers may not have enough money to buy adequate food for the child and social and emotional support for caregivers may be lacking (Isanaka et al, 2009). Growth is important to look at in HIV infected children as it may be indicative of morbidity and mortality and may affect neurodevelopment (Isanaka et al, 2009; Abubakar et al, 2009)

Mortality in HIV infected children is high. In a Sub-Saharan Africa study Taha et al (2000) found that by three years of age 89% of children with HIV die. In a review Prendergast et al (2007) found that in sub-Saharan Africa 45 – 59% of HIV Infants die by two years of age. Lallement et al (2010) found that 21% of paediatric deaths are due to HIV and HIV associated conditions. The peak for mortality is at two to three months of age (Bourne et al, 2009). Taha et al (2000) noted that once AIDS defining symptoms are

present the median length of survival is ten months. Death in HIV positive children is often caused by pneumonia, diarrhoea and wasting

HIV also results in various neurological manifestations in children and these will be discussed in depth later in this review.

2.6. Highly Active Antiretroviral Therapy (HAART)

There is no cure for HIV; however, treatment through ARV's is possible. Treatment is in the form of highly active antiretroviral therapy (HAART) (Pozniak, 2007). With HAART a combination of three or more ARV's are used (Riordan and Bugembe, 2009; Pozniak, 2007). HAART is aimed at reducing viral loads and improving immune function. By doing this disease progression is slowed, opportunistic infections prevented and mortality reduced (Riordan and Bugembe, 2009; Pozniak, 2007).

Several ARV's are available and are divided into three classes according to their mode of action. Nucleoside reverse transcriptase inhibitors (NRTIs) were the first ARV's to be developed (BIPAI, 2010). They prevent the formation of viral DNA by blocking reverse transcriptase (BIPAI, 2010). Non-nucleoside reverse transcriptase inhibitors (NNRTIs) also bind to the enzyme reverse transcriptase and in doing so prevents viral RNA from replicating (BIPAI, 2010; Riordan and Bugembe, 2009). Protease inhibitors (PIs) bind to protease enzymes and cause the formation of defective viral particles that are unable to replicate (BIPAI, 2010; Riordan and Bugembe, 2009). For HAART, it is usual for two NRTIs to be used in combination with either a NNRTI or PI (Riordan and Bugembe, 2009).

Unfortunately, there are several side effects that may occur with the use of ARV's. These include mitochondrial toxicity, lactic acidosis, neuropathies, cardiomyopathy, pancreatitis, hypersensitivity, rashes, gastrointestinal disturbances and lipodystrophy to name a few. Resistance to the drugs may also develop and therefore they may be less successful in decreasing viral replication and improving immune function (Riordan and Bugembe, 2009).

Due to resistance developing to the various classes of drugs and because some children do not tolerate the drugs well, new classes of drugs are being developed (BIPAI, 2010; Riordan and Bugembe, 2009). Second generation protease inhibitors have fewer complications than PIs currently being used and the

risk of dyslipidemia appears to be far less (Riordan and Bugembe, 2009). Entry inhibitors include attachment inhibitors and fusion inhibitors, they prevent HIV from binding to the CD4 cells and entering the cells (BIPAI, 2010; Riordan and Bugembe, 2009; Pozniak, 2007). Integrase inhibitors as well as maturation inhibitors are also being studied (Riordan and Bugembe, 2009).

The use of HAART is able to significantly decrease viral loads in children infected with HIV. In many studies viral loads become undetectable in a large proportion of children (Peacock-Villada, 2012; Musoke et al, 2010; Sutcliffe et al, 2008; Bracher et al, 2007; Janssens et al, 2007; Song et al 2007; McKinney et al, 2007; Reddi et al, 2007; Resino et al, 2006). Mckinney et al (2007) and Bracher et al (2007) showed that after twelve to sixteen weeks of HAART, viral loads in a population with a mean age of six years became undetectable. Jannsens et al (2007) had a similar finding, they found that after 12 months on HAART viral loads in 81% of children became undetectable. Musoke et al (2010) found that viral loads became undetectable in 50% of cases after 48 weeks of treatment in children aged less than a year. CD4 percentages as well as CD4 cell counts increase significantly with the initiation of HAART (Peacock-Villada, 2012; Sutcliffe et al, 2008; Bracher et al, 2007; Janssens et al, 2007; Song et al, 2007; Natu and Daga, 2007, McKinney et al, 2007; Resino et al, 2006), however it appears that after 12 – 18 months these numbers will stabilise and plateau and no further improvements will be seen (Sutcliffe et al, 2008; Resino et al, 2006). In a retrospective study Resino et al (2006) found that if children were initiated on HAART with CD4 percentages of less than 5% they would never gain CD4 percentage of more than 25 %.

Disease progression on HAART is also reduced. The progression to stage three and four and to AIDS is significantly decreased with the initiation of HAART (Sturt et al, 2012; Chiappini et al, 2007; Foster and Lyall, 2005). The incidence of opportunistic infections is reduced (Sutcliffe et al 2008; Nesheim et al, 2007) and there are fewer hospital admissions when a patient is receiving treatment (Violori et al, 2008; Sutcliffe et al, 2008; Foster and Lyall, 2005).

Growth parameters improve with the initiation of HAART. Often, prior to the initiation of HAART weight for age and height for age z scores are well below two standard deviations of the norm (Sutcliffe et al, 2008; Bolton-Moore et al, 2007). These scores seem to increase significantly with the use of HAART (Musoke et al, 2010; Buonora et al, 2008; Sutcliffe et al, 2008; Guillen et al, 2007; Song et al, 2007; Natu

and Daga, 2007; Bolton-Moore, 2007; Reddi et al, 2007). Body mass index however appears to stay relatively stable (Musoke et al, 2010).

More importantly HAART is able to decrease mortality (Sturt et al, 2012; Peacock-Villada et al, 2011; Violori et al, 2008; Chiappini et al, 2007; Janssens et al, 2007; Song et al, 2007; Sutcliffe et al, 2008; Reddi et al, 2007; Foster and Lyall, 2005). With the use of HAART the likelihood of survival improves. In South Africa Violori et al (2008) and Reddi et al (2007) have shown significant reductions in mortality with the use of HAART. Risk factors associated with increased mortality even when on HAART include: low CD4 percentage at initiation, low weight for age z scores, younger age, WHO stage three and four, high viral loads at initiation, severe malnutrition and the presence of other infections such as pneumonia and tuberculosis (Peacock-Villada et al, 2011; Sutcliffe et al, 2008; Bolton-Moore et al, 2007; Reddi et al, 2007). It appears that most deaths occur shortly after treatment is initiated (Sturt et al, 2012; Sutcliffe et al, 2008; Bolton-Moore et al, 2007; Reddi et al, 2007), if children are able to survive for the first 90 days to six months after treatment initiation, outcomes are generally good (Sutclliffe et al, 2008; Bolton-Moore et al, 2007).

Although the benefits of HAART are clear, a debate still persists regarding the best time for its initiation in children. If HAART is started too early there may be poor adherence habits, risk of the virus becoming resistant to the drugs, increased risk of drug toxicities, and generally there is uncertainty about the effects of prolonged exposure to the drugs (Welsch and Gibb, 2008).

Guidelines have been established by the World Health Organization to assist clinicians in decision making. The WHO suggests that HAART be initiated in the following children:

- Children less than two years of age to start HAART immediately regardless of CD4 counts.
- Children between two to five years with a CD4 percentage of less than or equal to 25% or a CD4 count of less than or equal to 750cells/mm^3.
- Children older than five years with a CD4 count of less than 350 cells/mm^3.

(WHO, 2010)

In South Africa rollout of ARV's started in 2004. Since then changes have been made to clinical guidelines. HAART will now be initiated in the following circumstances:

- Children who are under one year of age regardless of their CD4 counts.

- Children aged one to five years who are symptomatic with WHO stage three or four disease or CD4% of less than 25% or CD4 count of less than 750cells/mm^3.
- Children older than five years who present with WHO stage three or four disease or with a CD4 count of less than 350 cells/mm^3.

(South Africa National Department of Health, 2010)

2.7. Normal Child Development

2.7.1. Development of the Central Nervous System

The development of the CNS is an extremely complex, intricate process starting at conception and continuing through adulthood (Hadders-Algra, 2010; Stiles and Jernigan, 2010; de Graaf-Peters & Hadders-Algra, 2006). It is a dynamic process that is both additive and regressive (Anderson et al, 2011). Knowledge of how the CNS develops assists in creating an understanding of how adverse events affect neurological function and of stages of vulnerability in the CNS (de Graaf-Peters & Hadders-Algra, 2006).

This section aims to create an understanding of how the CNS develops in order to identify periods of vulnerability and to develop an understanding of the neurological consequences of HIV.

The CNS starts developing at three weeks gestational age (Anderson et al, 2011, de Graaf-Peters & Hadders-Algra, 2006). Stem cells in the epiblast layer of the embryo give rise to neural progenitor cells through a cascade of molecular and genetic signaling (Stiles and Jernigan, 2010; de Graaf-Peters & Hadders-Algra, 2006). These neural progenitor cells form the neural plate (Stiles and Jernigan, 2010). The neural plate then forms the neural tube (Anderson et al, 2011; Stiles and Jernigan, 2010; Kramer and Allan, 2002).

Neural proliferation will commence at six weeks gestation and continues until midgestation (Anderson et al, 2011; Stiles and Jernigan, 2010; de Graaf-Peters & Hadders-Algra, 2006). As neurons are produced they begin to migrate in a radial fashion to various areas creating a six layered neocortex (Anderson et al, 2011; de Graaf-Peters & Hadders-Algra, 2006; Stiles and Jernigan, 2010). Migration starts early on and will peak at three to five months gestation (de Graaf-Peters & Hadders-Algra, 2006). Migration occurs in an “inside-out” manner whereby new born cells cross through earlier cells to the surface and

are therefore more superficial (de Graaf-Peters & Hadders-Algra, 2006; Stiles and Jernigan, 2010). The migration of the neurons is regulated by interactions between other neuronal and glial cells, glycoproteins, GABA and glutamate (de Graaf-Peters & Hadders-Algra, 2006). HIV is able to disrupt the function of glial cells and also affects the production of GABA in the central nervous system (Wilfert et al, 1994).

Once neurons are in their appropriate location neural networks need to be established (Stiles and Jernigan, 2010). The neurons begin to differentiate and form neuronal processes which are the axons and dendrites of the CNS (Hadders-Algra, 2010; Stiles and Jernigan, 2010; de Graaf-Peters & Hadders-Algra, 2006,). The formation of axons and dendrites allows for communication between neurons (Stiles and Jernigan, 2010). Neurotransmitters and neurotrophic factors as well as glial cells which include oligodendrocytes and astrocytes will also be produced (Stiles and Jernigan, 2010).

Axons and dendrites start to grow. Growth of axons and dendrites starts in the second trimester and accelerates in the third trimester, this process is highly active in the first year of life and will continue until five years of age (de Graaf Peters and Hadders-Algra, 2006). Axons are long and need to travel some distance to their final destinations (Stiles and Jernigan, 2010; Webb et al, 2001). The axons have growth cones at their tips to assist with elongation and finding their target location (Anderson et al, 2011; Stiles and Jernigan, 2010). Axonal path finding is controlled by contact attraction and repulsion as well as chemo attraction and repulsion (Webb et al, 2001). Dendrites start to branch (arborise) - initially this is a slow process but speeds up in the third trimester and remains active until five years of age (de Graaf-Peters & Hadders-Algra, 2006). The branching of dendrites is controlled by genetically determined signaling and incoming axons that induce dendrite formation (Webb et al, 2001). As the growth occurs, sulci and gyri start to form in order to accommodate the increased cortical mass (Anderson et al, 2011).

Along with dendritic growth, there is synaptogenesis (Anderson et al, 2011). Synaptogenesis is the process of the formation of increased synaptic density and starts at eight weeks gestation and continues postnatally up to three years of age. (Anderson et al, 2011; de Graaf-Peters & Hadders-Algra, 2006). A synapse is created when an axon makes contact with a dendrite (Webb et al, 2001). The formation of synapses is controlled by both spontaneous genetic inputs as well as environmental inputs which signal neurotransmitter release (Webb et al, 2001). It is thought that there is such an overproduction of synapses to allow for increased capacity for improved recovery if prenatal or post natal brain injuries

occur, to prepare the brain for environmental inputs and to assist with the onset of cognitive function (Anderson et al, 2011; Webb et al, 2001). Both Smith et al (2000) and McGarth et al (2006) have showed that HIV infection may occur early on and during gestation. HIV would impact the development of the CNS at different stages. HIV may affect the creation of neural networks through synaptogenesis and dendritic and axon growth. If it affects CNS formation at this stage, delays in cognitive, language and motor function will be seen (McGarth et al, 2006)

Myelination also has to occur. It is mainly a post natal process that starts at 12 weeks gestational age and peaks during the first two years of life, it then slowly continues until the age of 40 (Anderson et al, 2011; de Graaf-Peters & Hadders-Algra, 2006). Oligodendrocytes that are formed are responsible for myelin formation (de Graaf-Peters & Hadders-Algra 2006). Myelin is a fatty layer that acts as insulation around the axon and assists with rapid transmission of electrical impulses and ensures efficient impulse conduction (Anderson et al, 2011; de Graaf-Peters & Hadders-Algra, 2006; Webb et al, 2001). If any disruption in myelination occurs there will be decreased conduction velocity, increased refractory periods as well as conduction failures (Webb et al, 2001). Often myelination is decreased in children presenting with developmental delay (Webb et al, 2001). Myelination has been shown to be decreased in children infected with HIV. Decreased myelination may result in cognitive delays but would also cause global developmental delays. If myelination is affected early on in gestation, motor abnormalities will be present (McGarth et al, 2006). If myelination is affected later on in childhood, cognitive function will be more influenced (McGarth et al, 2006)

For brain re-organisation to take place and for effective functional neural networks to be created, structures made during brain development must be eliminated (Stiles and Jernigan, 2010; de Graaf-Peters & Hadders-Algra, 2006). Prenatally, apoptosis of neurons and neuroprogenitor cells occurs (Anderson et al, 2011; Stiles and Jernigan, 2010; de Graaf-Peters & Hadders-Algra, 2006). Apoptosis is an intrinsic form of programmed cell death and helps to control the number of neurons in the CNS (de Graaf-Peters & Hadders-Algra, 2006). Apoptosis will result in the loss of more than 50% of neurons initially produced (Anderson et al, 2011; Hadders-Algra, 2010; Stiles and Jernigan, 2010). The process ensures that cells with poor or unnecessary synaptic connections are eliminated (Anderson et al, 2011). Synaptic pruning also occurs (Anderson et al, 2011; Stiles and Jernigan, 2010; de Graaf-Peters & Hadders-Algra, 2006; Webb et al, 2001). Synaptic pruning is the loss of a synapse in the absence of cell death, the neuron is not lost, however, synaptic density decreases (de Graaf-Peters & Hadders-Algra,

2006; Webb et al, 2001). Approximately 40% of synapses seen during peak synaptogenesis will be eliminated by adulthood (Webb et al, 2001). Synaptic pruning is paired with synaptogenesis (de Graaf-Peters & Hadders-Algra, 2006). Many synapses are lost in the first two years of life and synaptic pruning continues from puberty to adulthood (Anderson et al, 2011; de Graaf-Peters & Hadders-Algra, 2006). Synaptic pruning will assist with neural development and plasticity (de Graaf-Peters & Hadders-Algra, 2006). Pruning is influenced by the competition for neurotrophic factors, by afferent inputs and by the decreased presence of GABA as well as the number of synapses that are active (Stiles and Jernigan, 2010; Webb et al, 2001). It may be regulated by environmental inputs (Webb et al, 2001). Pruning allows for the elimination of inappropriate synapses and allows arborisation of appropriate dendrites resulting in a complex neural network forming which ultimately assists with normal human development (Webb et al, 2001). A central feature of HIV infection in children is cortical atrophy (Belman et al 1986; Decarli et al 1993; Brouwers et al 1995). Neuronal loss in the white matter and subcortical regions has been documented in (Everall et al, 1991; Wiley et al, 1986). Neurotoxins released in the CNS by HIV infected monocytes cause neuronal death (Epstein and Gelbard 1999, Tardieu et al 1992, Epstein and Gendelman 1993). If this occurs early on in CNS development global developmental delays will be present (Van Rie, 2007; McGarth et al, 2006) and abnormal reflexes as well as hypotonia or hypertonia may become evident (Mitchell, 2001; Tardieu et al, 2000; Armstrong, 1993)

The development of well functioning neural circuits is dependent on appropriate genetic and molecular signaling as well as from inputs from the environment and experiences obtained (Hadders- Algra, 2010; Stiles and Jernigan, 2010; Webb et al, 2001). Initially genetic signaling is essential but later on environment and experience are important to ensure appropriate brain development (Hadders-Algra, 2010).

As can be seen brain development is a complicated process involving many steps. It starts in the third week of gestation with the formation of the neural tube. Neural proliferation occurs and migration takes place to develop the gross structures of the CNS. Neurons differentiate into axons and dendrites. Neurotrophic factors and neurotransmitters are also produced. The brain grows in size. Elimination of neural components through apoptosis and synaptic pruning needs to occur in order to establish complex, optimal functioning neural networks. All of these processes are initially dependent on genetic and molecular signalling and then later become dependent on environmental inputs. Development of the CNS will affect infant development later on. Infancy is a critical period in brain development as

structures are growing rapidly (Webb et al, 2001); an insult in a particular area or during a particular stage of development may have dire consequences for the child.

HIV is a neurotrophic virus and is able to enter the CNS early on. Infection of the CNS may even occur prior to birth (McGarth et al, 2006; Smith et al, 2000). The infection may result in catastrophic consequences in the developing brain. An understanding of the normal development of the CNS is essential in gaining an understanding of how HIV influences CNS development. An in depth discussion on the neuro pathophysiology of HIV will be presented later in this review.

2.7.2. Cognitive Development

As the brain develops and matures through neural re-oraganisation cognitive development occurs (Stiles, 2000; Von Hofsten, 2009; Johnson and Munakata, 2005). Cognition is the ability to process information from the environment, to adapt to the information and to make decisions; it involves the mechanisms of learning and memory (Cromwell and Panksepp, 2011). Piaget first described cognitive development as occurring in stages that are influenced by interaction from neural structures and the environment (Law et al, 2011; Campbell et al, 2000). Various other models to explain how cognitive development occurs have been developed and cognitive development is now thought to be more dynamic and occurring through interaction between genetic, neural structures and experiences and environment (Johnson and Munakata, 2005; Campbell et al, 2000; Stiles, 2000). Most recently Bayesian learning and Bayesian networks involved in cognitive development have received a lot of attention in the literature (Gopnik and Tenebaum, 2007).

The development of cognitive function is highly dependent on the plasticity of the nervous system (Stiles, 2000). Plasticity is a dynamic process whereby there are structural and functional changes in the nervous system in order to adapt to the environment (Stiles, 2000). During childhood the brain is still developing and maturing and there is continuous re-organisation of neural networks (Stiles, 2000; Johnson and Munakata, 2005). For cognitive development to occur there is interaction between the environment and the nervous system (Stiles, 2000). Cognitive development is dependent on synaptic activity as well as the maturation of the subcortical system, prefrontal cortex and temporal lobe region (Stiles, 2000). Cognition may arise from either error driven learning or from self organisational learning (Johnson and Munakata, 2005). With error driven learning infants learn a skill by making so called

mistakes, responding to them correctly and changing. They learn to expect certain things from making errors (Johnson and Munakata, 2005). Self organisational learning occurs when an input from the environment alters task performance and creates a neural representation to perform a particular task (Johnson and Munakata, 2005).

Cognition starts early on and will continue in childhood and throughout adolescence (Johnson and Munakata, 2005; Stiles, 2000). A crucial period for its development is between eight to twelve months of age (Law et al, 2011). Early on there is a large amount of synaptic activity in the frontal cortex (Law et al, 2011). The neonate begins to explore and cognitive development starts (Von Hofsten, 2009). The neonate is able to recognise sounds, can differentiate its mother's voice, some colour perception skills are present and the child will respond visually to moving or three dimensional stimuli (Law et al, 2011). As time passes the child develops a visual preference for faces and he or she is able to identify their mother's face (Law et al, 2011). At one month of age there is increased myelination in the nervous system and with this comes improved attention and visual focusing (Law et al, 2011). By two months of age the child is able to discriminate between colours and can follow a moving object (Law et al, 2011; von Hofsten 2009). Object permanence develops, this is the ability to know that an object continues to exist even though it is hidden (Baillaregeon, 2004). Piaget thought that this skill only develops from eight months of age, however, in various studies Baillaregeon and colleagues have shown that object permanence starts developing from as early as two and a half months and continues to become more advanced in the first year of life (Baillaregeon, 2004). From three months of age the cortical and subcortical structures develop, there is the development of depth perception, facial recognition and the development of preference to patterns (Law et al, 2011). The child starts to visually prefer novel objects at this stage (Shinskey and Munakata, 2010). The infant will then start to follow objects. From six months of age they will fixate on objects and will attempt to get hold of them, they will reach and try to grasp both stationary and moving objects and problem solving through exploration and movement begins (von Hofsten, 2009). From eight to nine months of age more novel seeking behaviors start to develop and children start to look for novel hidden objects rather than familiar objects (Shinskey and Munakata, 2010). This behavior is essential for problem solving and for higher cognitive functioning (Shinskey and Munakata, 2010). The development of problem solving skills continues into the second year of life due to increased activity in the cortex and cerebellum. Children start to relate objects to each other (von Hoften, 2009). Memory skills develop from about eight months of age and continue to mature (Catherwood, 1993).

Cognition can be seen in infants from a very early stage, it develops as neural structures mature and through experience and interaction with the environment (Baillargeon, 2004; Stiles, 2000). Environmental and neural structural constraints as well as the child's motivation play a role in the development of cognition (Cromwell and Panksepp, 2011; Johnson and Munukata, 2005; Baillargeon, 2004). In order for cognitive development to occur the child needs to be given the opportunity to explore and to be stimulated (Von Hofsten, 2009).

2.7.3. Motor Development

From infancy through to adulthood children pass through a sequence of events in order to gain specific motor milestones in terms of posture, dexterity as well as locomotion (Vereijken, 2010). Development of motor function is highly variable (Roze et al, 2010; Vereijken, 2010; Hadders-Algra, 2010). In attaining their motor milestones a child may skip a particular stage or take longer to achieve a particular milestone compared to other children (Vereijken, 2010). Therefore, it is important to note that there is a wide range in which children develop motor function (Edwards and Sarwark, 2005).

Various theories on how motor function develops exist. Initially the neural maturationist theory was developed by Gesell (Hadders-Algra, 2000a). In this theory it is believed that motor development comes about as a result of the increased cortical control over primitive reflexes over a certain period of time (Hadders-Algra, 2010; Hadders-Algra, 2000a, Hadders-Algra, 2000b; Forssberg, 1999). This theory does not consider that other factors contribute to motor development. The Dynamic Systems Theory was then developed. This theory states that motor behaviors develop from interactions between various sub systems such as the infant's strength, body weight, mood and environmental experiences (Forssberg, 1999; Hadders-Algra, 2000a; Hadders-Algra, 2000b; Kamm et al, 1990). The theory postulates that motor function arises from self organisation of various subsystems and not simply from the maturation of the CNS (Kamm et al, 1990; Hadders-Algra, 2000a). To address the nature versus nurture debate Edelman developed a new theory to explain the development of motor function (Hadders-Algra, 2010). This is the Neuronal Group Selection Theory. This theory states that motor development occurs in two phases - a phase of primary variability and a phase of secondary or adaptive variability (Hadders-Algra 2010; 2000a; 2000b). The phase of primary variability allows movement to occur through a central pattern generator (Hadders-Algra, 2000a) which is a neuronal network that can elicit movement without

any sensory or environmental input (Calancie et al, 1994). In this phase primary neuronal repertoires are formed from many different neuronal networks (Hadders-Algra 2000a; 2010; 2000b). The phase of secondary variability occurs as afferent information obtained from experience, changes synaptic connections and ultimately refines movement to make it more functional (Hadders-Algra, 2010; 2000a; 2000b; Forssberg, 1999). In this way a secondary repertoire is created (Hadders-Algra, 2000a). The secondary repertoire allows the child to adapt in various environmental conditions (Hadders-Algra, 2010; 2000a; 2000b). This theory emphasises that there is interaction between both the environment as well as the genes (Hadders-Algra, 2010; 2000a; 2000b; Forssberg, 1999), and development cannot occur appropriately if one of these factors is faulty (Hadders-Algra, 2000b; 2010). This theory has become very popular in discussing how development occurs.

Motor development starts in foetal life (Forssberg, 1999; Hadders-Algra, 2010); this can be attributed to the presence of general movements in the foetus from about seven weeks post menstrual age (Hadders-Algra, 2010). The general movements are created by the central pattern generator (Frossberg, 1999; Hadders-Algra, 2010). These movements continue to exist postnatally (Hadders-Algra, 2010; Forssberg, 1999). At two to four months of age the general movements start to disappear and more functional goal directed movements can be observed in the infant (Hadders-Algra, 2000a; 2010). The reasons for changes occurring in movement is that experience has influenced afferent information resulting in increased activity in the basal ganglia, cerebellum as well as the parietal, temporal and occipital regions of the cortex (Hadders-Algra, 2010), synaptic connectivity is also changing at this stage (Hadders-Algra, 2000a). As increasing afferent information occurs there is selection of more specific movement patterns (Hadders-Algra, 2010) which results in more goal directed activity and function (Hadders-Algra, 2000a).

The development of postural control begins. From early on infants are able to activate trunk muscles in response to external perturbations (Hadders-Algra, 2005). Postural control is essential as it assists in the child developing a vertical position for their head and trunk against gravity and to maintain a stable base for when more functional movements need to occur such as reaching and walking (Hadders-Algra, 2005; Forssberg, 1999). At two to four months of age the infant starts stabilising their head on their trunk in order to visually gaze and track objects (Hadders-Algra, 2010). Successful reaching is usually obtained by four months of age (Hadders-Algra, 2010) but is initially highly variable due to inefficiency in the co-ordination of the trunk, shoulder and neck muscles (Forssberg, 1999) as well as the fact that exploration is still occurring (Hadders-Algra, 2000a). By seven to eight months reaching is better sequenced and

more goal directed (Hadders-Algra, 2010). Reaching develops as the motor cortex and corticospinal tracts develop (Hadders-Algra, 2010).

Sitting will start to occur from six months of age and postural control develops even more (Hadders-Algra, 2005; 2010). At this age there is a high level of activity in the frontal cortices (Hadders-Algra, 2005). Locomotion will then start to occur in the third quarter of the first year of life (Hadders-Algra, 2005; Forssberg, 1999). At nine to ten months of age there is increased activity in the parietal and frontal regions of the brain and with this comes fine tuning of postural muscle contraction (Hadders-Algra, 2005). Antagonistic co-activation of muscles begins to occur (Hadders-Algra, 2005; Forssberg, 1999). Crawling will take place and then walking starts. Initially the gait cycle is very immature and no heel strike is present (Hadders-Algra, 2005; 2010; Forssberg, 1999). Gait at this stage is similar to the movement seen with neonatal stepping (Hadders-Algra, 2000a, Forssberg, 1999). It is believed that with initial locomotion the central pattern generator is responsible for the majority of the movement (Forssberg, 1999), as more experience is obtained the supraspinal structures start to influence the central pattern generator and a more mature gait with heel strike is established (Hadders-Algra, 2000a; 2010). After three to four months of walking experience a more mature pattern of walking can be seen (Forssberg, 1999; Hadders-Algra, 2000a).

From 13 to 14 months there is mastery in skills obtained (Hadders-Algra, 2000a; 2005; Heineman et al, 2010). Improvements are seen in agility, adaptability and the ability to make more complex movements (Hadders-Algra, 2000a, 2005). This is a result of interaction with the environment as well as synaptic re-organisation, feed forward neural planning also assists in the development of postural control at this age (Hadders-Algra, 2005; 2010).

For motor development to occur there is an interplay between genetics controlling the CNS as well as experience that is obtained by the infant. Experience allows for motor solutions to specific environments to be developed and the child learns to adapt to various situations. However, without the development of the CNS the experiences will not occur and may result in delayed or abnormal motor development (Hadders-Algra, 2000b).

2.7.4. Language Development

Language is the ability to use words and to understand them (Kuhl, 2010). It is the ability to make your thoughts and wants known (Kuhl, 2010) and allows for communication with others.

For language development to take place neural re-organisation through pruning and growth has to occur (Bishop, 2000). Various areas in the brain are responsible for the acquisition of language (Bishop, 2000; Mills et al, 1997). In infancy and childhood the right hemisphere of the brain is responsible for the initial development of language (Friederici et al, 2011; Bishop, 2000; Mills et al 1997). As the brain circuitry improves and neural reorganisation takes place the left frontal and posterior temporal hemispheres are largely responsible for language (Friederici et al, 2011; Bishop, 2000; Mills et al, 1997). Neural re-organisation takes place in response to various environmental inputs and experiences (Schjølberg et al, 2011; Kuhl 2010; Bishop, 2000). Only essential information for language is retained (Bishop, 2000).

For appropriate language to occur the child is required to learn a variety of phonemes and syntax. Phonemes are the groups of sounds that are the building blocks for words and syntax is the grammar used (Bishop, 2000). It appears that children will start to learn language by imitating words and sentences (Bishop, 2000). Initially they will not break down the words or sentences but as more vocabulary is obtained words need to be stored in a specific way. Words are stored according to their similar sounds (phonemes) to form a lexicon (Bishop, 2000). As this happens phonological awareness improves (Bishop, 2000). The development of syntax appears to occur in a similar way (Bishop, 2000). This process takes many years and is probably only fully developed when the child learns to read (Bishop, 2000). Learning of the phonemes will occur in the first year and syntax learning takes places between 18 and 36 months (Kuhl, 2010).

Speech and language starts developing from an early age. From one to two months of age the child makes comfort sounds (Oller and Eilers, 1988), by three months they are cooing and at four months squealing, trills and yells can be heard, they also start to form vowel sounds (Oller and Eilers, 1988). During the first six months of life the infant communicates through facial expressions, by gazing and gesturing and starting to vocalise and imitate (Wankoff, 2011). From six to 12 months of age the child is able to distinguish phonemes (Kuhl, 2010). This ability will affect the ability to read later on (Kuhl, 2010). From seven months of age the infant starts forming syllables such as mamama and dadada (Oller and

Eilers, 1988). From 8 months of age infants start to understand single words (Kuhl, 2010) and by 12 months they should understand at least 50 words, this triples in the next two to three months (Mills et al, 1997). From nine months of age joint attention develops as well as turn taking, the infant is gesturing more and is also requesting, the child is able to participate in social routines at this age (Wankoff, 2011). From 12 to 18 months the infant starts to understand concepts and is able to follow simple instructions (Wankoff, 2011). In this time vocabulary will increase dramatically and there will be a "speech explosion" (Kuhl, 2010; Mills et al 1997), by 18 months the child should have a vocabulary of at least 50 words that then increases on a daily basis (Mills et al, 1997). Syntactic learning starts to occur from 18 months (Kuhl, 2010). From two to three years the child is able to engage in simple conversation and from three to four years they are able to tell a story (Wankoff, 2011). Reading skills then develop once the child attends school (Wankoff, 2011).

For appropriate speech and language development to occur there needs to be maturation of the brain, inputs from the environment, experience as well as social interaction (Schjølberg et al, 2011; Kuhl, 2010; Bishop, 2000;). Social interaction appears to be vital in the learning of language as exposure to sounds influences how reorganisation in the brain occurs (Kuhl, 2010). Social interaction assists learning of language by possibly increasing arousal levels to create a better learning environment, increasing the amount of information received, improving the sense of a relationship with the caregiver and increasing the activation of networks in the brain (Kuhl, 2010).

It can be seen that the development of speech and language is a dynamic process occurring form early on in life and continuing throughout childhood. Skills obtained in infancy are essential for development of language at a later stage and various factors influence the development of language, it is not simply dependent on maturation of the brain (Kuhl, 2010; Bishop, 2000).

2.7.5. Factors Influencing Normal Development

Child development is a complex process that is dependent on the brain maturing as well as on environmental inputs (Kuhl, 2010; Grantham-McGregor, 2007; Walker et al, 2007; Bishop, 2000; Hadders Algra, 2000b). Early development of the brain and of certain motor, cognitive and language skills is crucial for success in adolescence and adulthood (Grantham-McGregor, 2007). Various factors are able to disrupt a child's normal development which would result in catastrophic consequences later on in life.

Grantham McGregor et al (2007) estimate that over 200 million children below the age of five years are not achieving their developmental potential. If children do not achieve their developmental potential their ability to receive education and enter the schooling system will be adversely affected, this will affect their ability to find a job and may affect their earnings later in life (Engle et al, 2011; Grantham-McGregor, 2007; Engle et al, 2007). Their ability to be productive members of society will be harmed and poverty will continue to remain a problem resulting in an increased financial burden to the country (Grantham-McGregor et al, 2007).

This section will briefly discuss the various risk factors that affect child development.

A systematic review by Walker et al (2007) divides risk factors into two areas, namely biological risk factors and psychosocial risk factors. The effects of these risk factors depend on their timing, the presence of multiple or co-occurring risks and the reactivity of the child to the risk factors (Walker et al, 2011). Biological risk factors include nutrition, infectious diseases, environmental hazards as well as prematurity and genetic factors (Vieira and Linhares, 2011; Walker et al, 2011; Walker et al, 2007; Mikkola et al, 2005).

Intrauterine growth restriction, child under-nutrition, iodine and iron deficiency are nutritional risk factors. (Walker et al, 2007). Intrauterine growth restriction occurs when the foetus is not receiving adequate nutrition due to poor maternal nutrition. This may be detrimental to the child as brain development is occurring in this time and may be adversely affected. The child may also be born with a low birth weight which contributes to developmental delay. In the long term intrauterine growth restriction results in children developing poorly, they are less active and are at increased risk for behavioral problems (Walker et al, 2007). Child under nutrition is a common problem and will result in stunting. This in turn results in poor cognitive outcomes that continue into the school years and result in increased drop out from school (Walker et al, 2007). Iodine deficiency is associated with mental retardation and affects CNS development (Walker et al, 2007). The addition of iodine in early pregnancy may help in increasing developmental scores. Salt iodisation has been effective in decreasing the adverse effects of iodine deficiency (Engle et al, 2011; Engle et al, 2007). Iron deficiency affects myelination and neurotransmission in the developing brain (Walker et al, 2007). Chronic iron deficiency may result in poor cognitive outcome. Improvements may be seen with iron supplementation (Engle et al, 2007)

Infectious diseases such as intestinal parasites, diarrhoea and malaria adversely affect neurodevelopment and attempts should be made to prevent these diseases (Walker et al, 2007). HIV has severe effects on neurodevelopment, but will be discussed later in this literature review. Environmental hazards such as exposure to water contaminated by lead, arsenic and increased levels of manganese may decrease IQ scores (Walker et al, 2007). Exposure to pesticides may affect analytical and memory skills (Walker et al, 2007).

Prematurity adversely affects neurodevelopment. In a systematic review by Vieira and Linhanes (2011) it was found that preterm infants perform worse in all developmental areas compared to full term children. Extremely preterm infants are the most vulnerable (Vieira and Linhanes, 2011). Children born prematurely may also have decreased quality of life as well as behavioral difficulties. Prematurity may lead to problems in the school going years as well as later in life (Vieira and Linhanes, 2011; Mikkola et al, 2005). Genetic abnormalities as well as the presence of disabilities influence normal development (Walker et al, 2007).

Psycho-social risk factors that may influence development include parents providing cognitive stimulation to their children, parental sensitivity and responsivity, maternal depression and exposure to violence (Walker et al, 2007). Institutionalised children are at risk for developmental delay (Walker et al, 2011). In their systematic reviews Walker et al (2007) and (2011) found that the provision of cognitive stimulation to children improves cognitive function. This improvement may last into adolescence. Cognitive stimulation given by parents improves task orientation, behavior and self confidence and is therefore vital in achieving normal development (Walker et al, 2007; Walker et al, 2011). Engle et al (2007) found that providing stimulation programs directed at children and providing caregivers with information and improving their interaction skills as well as giving nutritional and health support is effective in decreasing developmental delay.

Poverty has a huge effect on development, as it is associated with nearly all the risk factors discussed above. Poverty results in inadequate nutrition, poor sanitation, increased infections as well as increased maternal stress, depression, and a poor maternal level of education (Engle et al, 2011; de Paiva et al, 2010; Grantham-McGregor, 2007). This will all lead to decreased stimulation at home (Walker et al, 2011; Walker et al, 2007). This results in poor cognitive development and affects later life as the child will be unable to access appropriate education (Walker et al, 2007). Inequities in society will continue to

exist and the whole cycle is repeated again, resulting in the problems being handed down to the next generation (Grantham-McGregor et al, 2007).

All of the risk factors discussed above affect families affected by HIV and contributes to HIV positive infants being delayed.

By encouraging normal child development and by decreasing the risk factors associated with poor development education levels will improve, adults become more productive members of society, inequalities are reduced and the cycle of poverty is decreased (Walker et al, 2011).

2.8. Neurological and Developmental Consequences of HIV

2.8.1. Neuro-pathogenesis of HIV

HIV is able to enter the central nervous system early on in infection resulting in an encephalopathy in infants and children (Epstein and Gelbard, 1999; Epstein and Gendelman, 1993; Davis et al, 1992). Radiological studies as well as histopathological studies have shown that there are abnormalities in up to 86% of children with HIV presenting with signs of encephalopathy and in up to 76% of children with no encephalopathic signs (Decarli et al, 1993; Boni et al, 1993; Lenhardt and Wiley, 1989). Even when no signs and symptoms of neurological involvement are present, HIV is still detectable in the CNS (Wilfert et al, 1994).

Radiological findings indicate cortical atrophy, ventricular enlargement, white matter pallor and vacuolation of white matter and calcification of the basal ganglia (Brouwers et al, 1995; Decarli et al, 1993; Belman et al, 1986). Calcification of the basal ganglia appears to be unique in paediatric patients (Decarli et al, 1993; Belman et al, 1986).

Since the 1980's studies have been conducted on autopsied brains in both adults and children infected with HIV. It has been determined that endothelial cells and macrophages are the targets for HIV infection (Wiley et al, 1986). Pathological findings include presence of infected macrophages, monocytes, microglia, endothelial cells as well as formation of multinucleated giant cells (Epstein and

Gelbard, 1999; Luzar et al, 1999; Ioannidis et al, 1995; Sei et al, 1995; Tornatore et al, 1994; Wilfert et al, 1994; Boni et al, 1993; Epstein and Gendelman, 1993; Lenhardt and Wiley, 1989; Navia et al, 1986; Sharer et al, 1986; Wiley et al, 1986;). Perivascular inflammation is present and is often associated with the presence of lymphocytes as well as a reactive gliosis in the CNS (Lenhardt and Wiley, 1989; Sharer et al, 1986; Navia et al, 1985). Reactive astrogliosis is present and alterations in the neocortical dendritic processes have been detected (Wilfert et al, 1994; Epstein and Gendelman, 1993; Lenhardt and Wiley, 1989; Navia et al, 1985). There is no evidence to suggest that neurons are infected directly with HIV, however astrocytes have also been found to be infected with HIV (Tornatore et al, 1994).

Neuronal loss is evident in the central nervous systems of patients infected with HIV and is especially prominent in the white matter and subcortical regions (Everall et al, 1991; Wiley et al, 1986). Wiley et al (1991) detected a 30 – 50% loss of neurons in patients with HIV compared to HIV uninfected patients, and Everall et al (1991) detected a 38% loss of neurons in the superior frontal gyrus of patients with HIV. Although this neuronal loss is present there is no evidence to suggest that neurons are directly infected with HIV (Epstein and Gelbard, 1999, Sei et al, 1995; Wilfert et al, 1994). Authors have suggested that a latent infection may be present in neurons or techniques to detect HIV are not yet advanced enough to detect the presence of HIV in neurons (Ensoli et al, 1997; Tardieu et al, 1992; Lenhardt and Wiley, 1989; Wiley et al, 1986). It appears more likely that the neuronal damage is probably due to indirect effects from other cells in the central nervous system (Epstein and Gelbard, 1999; Sei et al, 1995; Wilfert et al, 1994).

HIV is neurotrophic and causes neural damage either through direct infection into the CNS or through opportunistic infections or both (Blumberg et al, 1994; Epstein et al, 1987; Sharer et al, 1986). In the HIV positive paediatric population it appears unlikely that the damage is due to opportunistic infection and invasion of HIV into the CNS is more likely (Tornatore et al, 1994). It also appears that in the paediatric population HIV infection of the CNS occurs much earlier on in infection compared to adults (Tornatore et al, 1994). Lyman et al (1990), Davis et al (1992), Tornatore et al (1994) and Ioannidis et al (1995) have shown that HIV is able to enter the CNS early on and that CNS invasion may even occur at seroconversion.

Although a lot of research has been conducted since 1985, the exact neuropathogenesis of HIV is still not well understood. Various theories have been developed to explain how neuronal damage occurs with HIV infection.

Research indicates that there are several ways in which HIV is able to enter the CNS.

Macrophages and monocytes are central to the entry of HIV into the CNS. Macrophages and monocytes are infected early on in infection and act as reservoirs for the infection in the CNS (Dunfee et al, 2009; Schmidtmayerova et al, 1996; Tornatore et al, 1994; Peudenier et al, 1991). There are specific binding sites on the macrophages and monocytes that the HI virus is attracted to, HIV attaches itself to these binding sites and enters the macrophages and monocytes (Dunfee et al, 2009). Early on in infection there is a large amount of trafficking of infected macrophages, monocytes and T lymphocytes into the CNS (Dunfee et al, 2009; Van Rie et al, 2007; Schmidtmayerova et al, 1996; Blumberg et al, 1994; Tornatore et al, 1994; Wilfert et al, 1994; Epstein and Gendelman, 1993). Once in the brain an inflammation centre is created and there is increased spread of HIV (Schmidtmayerova et al, 1996). HIV is now able to infect microglial cells, these cells then in turn act as reservoirs for HIV infection (Ioannidis et al, 1995).

The blood brain barrier may also play a role in the entry of HIV into the CNS. The blood brain barrier may be damaged from the HIV infection; this would then allow the entry of the virus directly into the brain (Banks et al, 2006; Blumberg et al, 1994; Epstein and Gendelman, 1993). It has however been reported that with HIV infection there is very limited disruption to the blood brain barrier (Banks et al, 2006). Free viral particles and proteins as well as peripheral cytokines are able to cross the blood brain barrier and result in increased infection in the CNS (Banks et al, 2006; Blumberg et al, 1994; Epstein and Gendelman, 1993).

Once HIV is inside the CNS a number of pathological processes begin to occur which ultimately results in neuronal loss and damage. Numerous studies have shown that there are not enough macrophages in the brain to account for the vast amount of damage with HIV infection (Wilfert et al, 1994). Therefore, it is believed that several indirect processes may be responsible for the damage in the CNS (Epstein and Gendelman, 1999; Wilfert et al, 1994; Blumberg et al, 1994; Wiley et al, 1991; Lenhardt and Wiley, 1989)

Once inside the CNS, infected monocytes are able to adhere to neuronal cells, once attached to the neuronal cells a cytopathic process is initiated which results in neuronal damage as well as increased release of viral particles (Tardieu et al, 1992). The HIV envelope glycoprotein gp120 is able to attach to macrophages and microglia, these cells then interact with neuronal cells to stimulate the release neurotoxins which also result in damage (Epstein and Gendelman, 1999; Schmidtmayerova et al, 1996; Tornatore et al, 1994; Wilfert et al, 1994; Blumberg et al, 1994; Epstein and Gendelman, 1993; Tardieu et al, 1992;).

The neurotoxins believed to be responsible for the damage are tumour necrosis factor α (TNFα) and various cytokines such as IL-β (Van Rie et al, 2007; Schmidtmayerova et al, 1996). High levels of nitric oxide and quinolinic acid have also been detected in brains of patients infected with HIV (Van Rie et al, 2007; Sei et al, 1995). The release of these neurotoxins results in neural damage but may also cause increased recruitment of infected monocytes into the brain (Schmidtmayerova et al, 1996). Infected macrophages also show altered antimicrobial activity (Schmidtmayerova et al, 1996)

More recently the role of astrocytes in the neuropathogenesis of HIV has been studied. It has been shown that astrocytes are infected with HIV (Blumberg et al, 1994; Tornatore et al, 1994; Wiley et al, 1986). There are several ways in which the astrocytes may cause neuronal damage. Infected microglia and monocytes may interact with infected astrocytes to produce neurotoxins (Wilfert et al, 1994; Blumberg et al, 1994; Epstein and Gendelman, 1993). Cytokines such as TNFα, ILβ and arachidonic acid are produced (Wilfert et al, 1994; Blumber et al, 1994; Epstein and Gendelman, 1993). These cytokines cause neuronal damage. TNFα may stimulate HIV transcription in macrophages and astrocytes and cause damage to myelin and oligodendrocytes (Wilfert et al, 1994; Blumberg et al, 1994; Epstein and Gendelman, 1993). TNFα that is secreted may result in dysregulation of glutamate uptake in astrocytes (Epstein and Gelbard, 1999). Glutamate is essential for the maturation of the developing CNS. Increased glutamate would enhance oxidative stress in the neurons which would lead to neuronal death (Epstein and Gelbard, 1999). ILβ results in astrocyte proliferation this in turn amplifies the effects of macrophages and causes increased amounts of pro inflammatory cytokines which results in central nervous system damage (Wilfert et al, 1994) The normal functioning of the astrocytes may be affected by the HIV infection (Van Rie et al, 2007; Tornatore et al, 1994; Wilfert et al, 1994; Blumberg et al, 1994). The infected astrocytes may have difficulty with the uptake of glutamate in the central nervous system, therefore the secretion of anti-inflammatory cytokines is limited. Excess glutamate in the CNS would

also result in neural toxicity (Blumberg et al, 1994; Wilfert et al, 1994). This would lead to insufficient and impaired maturation of neuronal and glial cells in the CNS (Epstein and Gelbard, 1999; Tornatore et al, 1994). Astrocytes may also act as a reservoir for HIV infection, this may then result in increased infection of microglia which adds to the viral burden on the CNS and increased production of inflammatory products and neural toxins (Tornatore et al, 1994)

Zhou et al (2011) have recently postulated that in patients with HIV infection there is dysregualtion of autophagy in the CNS and this contributes to the neuropathogenesis. They found that in HIV positive patients there are significantly increased levels of autophagic proteins and autophagosomes in neuronal cells and this has led them to believe that in HIV there is dysregulation of autophagy which may contribute to neuropathogenis of HIV. Limited research has been done in this area.

Therefore in summary, HIV is neurotrophic and causes damage in the CNS. The hallmark signs of HIV infection in the CNS include cerebral or cortical atrophy, ventricular enlargement, white matter pallor, vacuolation of white matter, basal ganglia calcification, presence of infected macrophages, monocytes, microglia and astrocytes, formation of multinucleated giant cells, perivascular inflammation, reactive gliosis and neuronal loss. Early on in infection monocytes and macrophages become infected with the virus and are able to cross the blood brain barrier to enter the CNS and cause infection of microglia and astrocytes. Free viral particles as well as viral proteins may also cross a disrupted blood brain barrier. Once inside the CNS various pathological processes occur. Monocytes, macrophages and microglia create an inflammation centre where neurotoxins such as TNFα and ILβ are released resulting in neuronal damage. Infected astrocytes interact with monocytes and microglia to produce more neurotoxins. Astrocytic function may be altered resulting in decreased uptake of glutamate, the increased glutamate then results in neural toxicity. Astrocytes may also act as a viral reservoir and increase the viral burden on the CNS. Most recently altered autophagy in the CNS had been implicated in the neuropathogenesis.

From this it can be seen that HIV causes severe damage in the CNS and results in an HIV encephalopathy. Therefore, antiretroviral drugs are required to cross the blood brain barrier and stop the various pathological processes occurring to aim to decrease the catastrophic consequences of HIV encephalopathy (Van Rie et al, 2007; Sei et al, 1995)

2.8.2. The Neurological Effects of HIV

Research has clearly shown that HIV adversely affects neurological function in children (Willen et al, 2006; Mitchell, 2001; Tardieu et al, 2000; Gay et al 1995; Armstrong et al, 1993; Msellati et al, 1993). HIV infected infants often have delays in gaining developmental milestones and may continue to experience delays in cognitive, language and motor function (Van Rie et al, 2007). Delays may occur from as early as four months of age and may worsen if no intervention is given (Chase et al, 1995). This is of major concern. HIV is becoming a chronic illness (Armstrong et al, 1993), due to the initiation of HAART children with HIV are living longer and reaching school going age, developmental delays will affect their academic performance as well as participation and independence later in life (Burns et al, 2008). An understanding of neurodevelopment and the effects that HIV has on it is required so that we can see the challenges facing these children as they grow older and so that appropriate interventions can be planned for them.

2.8.2.1. HIV Encephalopathy

HIV is able to enter the CNS and cause damage as discussed in the previous section. This damage will result in an HIV encephalopathy (Van Rie et al, 2007).

HIV encephalopathy is an AIDS defining illness (WHO, 2005) occurring in a large percentage of HIV infected children and may present itself even before the age of six months (Bruck et al, 2001; Belman et al, 1996). It can be defined as the failure to attain or the loss of developmental milestones (Tardieu et al, 2000). It is accompanied by impaired brain growth, a possible acquired microcephaly, loss of cognitive and motor function, abnormal tone and reflexes, decreased muscle strength, pyramidal tract signs, ataxia and seizures (Willen et al, 2006; Mitchell, 2001; Tardieu et al, 2000; Gay et al, 1995; Armstrong et al, 1993; Msellati et al, 1993). It may eventually lead to spastic quadriparesis (Tardieu et al, 2000). There are various types of encephalopathy.

A static encephalopathy is present when the child attains their various developmental milestones, but at a much slower rate than their healthy peers. There is no loss of function in this type of encephalopathy (Willen et al, 2006; Chase et al, 1995). A plateau progressive encephalopathy occurs when the child has attained certain developmental milestones but then stops developing, no new milestones are attained. Eventually the child may regress and lose previous function (Van Rie et al, 2007; Willen et al, 2006; Bruck

et al, 2001; Chase et al, 1995; Gay et al, 1995). A sub-acute progressive encephalopathy occurs when there is sudden loss of previously attained milestones (Willen et al, 2006; Gay et al, 1995). The progressive encephalopathy may be associated with acquired microcephaly as well as pyramidal tract signs (Van Rie et al, 2007).

Various studies have shown varying rates of incidences for HIV encephalopathy. In a large study on a French cohort it was found that the incidence of encephalopathy in the first year of life is 9.9%, in the second year of life 4.2% and from the third year of life less than 1% (Van Rie et al, 2007; Tardieu et al, 2000). DeCarli et al (1993) found that 54/83 patients she and her colleagues were studying were encephalopathic. HIV encephalopathy presents with various neurological abnormalities and the incidences of these abnormalities are quite high. Msellati et al (1993) reported that 60 – 90% of HIV infected children present with neurological abnormalities, in a retrospective study Foster et al (2006) reported a much lower percentage of 22.5% of HIV positive children presenting with neurological abnormalities. Knight et al (2000) however, reported that 50% of the children in their study presented with neurological abnormalities, however, most of the children had been exposed to drugs during gestation. Brouwers et al (1995) on the other hand found that 73 /87 patients she was studying had neurological abnormalities on CTB. Tahan et al (1996) found that when comparing HIV positive children to serorevertors, the HIV positive group had a much greater percentage of neurological abnormalities.

The so called HIV encephalopathy often presents before other opportunistic infections and AIDS defining illnesses and may even present before the child becomes immune-compromised (Van Rie et al, 2007; Mitchell, 2001; Tardieu et al, 2000; Belman et al, 1996; Chase et al, 1995). In many cases it is the first sign of HIV infection in the child (Potterton and Van Aswegen, 2006; Chase et al, 1995). Once encephalopathy is present, the risk of mortality increases (Mitchell 2001; Tardieu et al, 2000) and the child often becomes more immune-compromised (Tardieu et al, 2000).There may also be increased number of hospitalisations (Potterton and Van Aswegen, 2006). Tardieu et al (2000) found that once HIV encephalopathy is present mean length of survival is 14 months. In this study the majority of children were on AZT and over 30% were on a combination of ARV's.

Several studies have shown risks predisposing the child to developing an encephalopathy.

Belman et al (1996) found that children who present with other AIDS opportunistic infections, greater immuno-suppression, lower CD4 count, poorer growth and have smaller head circumferences have worse neurological outcome. They deduced that disease severity will influence neurological outcome. Tardieu et al (2000) found that the risk of developing an encephalopathy is associated with the mother's CD4 count at birth as well as the child's CD4 count, in the child it may be related to the presence of an enlarged spleen or liver, adenopathy as well as decreased weight. Pollack et al (1996) showed that poor growth and higher viral loads contributed to worse neurological outcome. Van Rie et al (2007) in a review reported that the risk of developing an encephalopathy is related to the child's immune status, viral load, timing of infection, route of transmission as well as maternal health. It can be seen from these studies that the child's health as well as their growth contributes to the risk of developing encephalopathy

Interestingly, McGarth et al (2006) found that the timing of HIV infection plays a role in neurological outcome and functioning. The authors found that if a child was diagnosed in the first 21 days post birth they were 14.9 times more likely to have a delay compared to children without infection. If diagnosed after 21 days of life they were 3.2 times more likely to have a developmental delay when compared to uninfected peers. Neurodevelopment during the first 18 months of life among those who tested positive later on was less affected. Tardieu et al (2000) found that children with early encephalopathy were already different at birth when compared to peers without encephalopathy – they tended to have a smaller head circumference which could be attributed to decreased brain growth during gestation. This could indicate that they were infected earlier on and supports McGarth and colleagues' notion that timing of HIV infection plays a role in neurodevelopment.

The reason that timing of infection plays a role in the risk of developing an encephalopathy is that the brain develops in various stages (Anderson et al, 2011). HIV may attack the brain in a crucial stage of development. Early infection could result in interference with myelination and projection of fibers to various cortical regions, this would cause a global developmental delay. Infection that occurs later on i.e.: intrapartum or postnatally may cause interference in the development of neural networks in the prefrontal cortex, this region is responsible for mental capabilities therefore cognitive function would be affected more (McGarth et al, 2006).

Developmental delay is associated with HIV encephalopathy. Research has been conducted to determine the extent of delay experienced by children with HIV. Many studies have been conducted in first world countries and results may not pertain to the developing world where the majority of HIV infected children live. The various facets of development affected by HIV will be discussed below:

2.8.2.2. The Effects of HIV on Cognitive Development

Rates of cognitive delay may be as high as 90% in children infected with HIV (Armstrong et al, 1993). Newell et al (1995) found that 54% of HIV positive children of school going age had cognitive difficulties. Children who are infected with HIV experience cognitive delays and function below age expected norms (Potterton et al, 2009a; Potterton et al, 2009b; Van Rie et al, 2007; McGarth et al, 2006; Foster et al, 2006; Pearson et al, 2000; Armstrong et al, 1993).

Two systematic reviews have been conducted looking at the effects of HIV on development. Both studies found that HIV infection has a detrimental effect on cognitive development. Sherr et al (2009) found that 81% of studies examining cognitive development in HIV positive children showed that HIV adversely affects cognitive function. Sherr et al (2009) argued that although such a high percentage of studies showed that HIV adversely affects cognitive development the literature is inadequate. In their systematic review a large number of studies were reviewed, however most came from North America and very few of the studies analysed had control groups. There were very broad age ranges of children analysed in the various studies, making comparisons difficult. Abubaker et al (2008) reviewed literature pertaining to sub-Saharan Africa. They were only able to review seven articles and the age range of children studied was also broad in many of the studies. In both systematic reviews, various standardised assessment tools were used between different studies and both of the reviews failed to mention the type of care that the HIV positive groups received. It would have been useful to note if the children were receiving ARV's or not. In both systematic reviews it was difficult to compare studies, as often there was variation in the methodology and quality of the studies, various standardised tools were used and different age groups of children were studied. Very little literature is available pertaining to children in developing countries; this is of concern as the majority of children with HIV reside in sub-Saharan Africa.
A number of studies assessing the effects of HIV on cognitive development have been conducted in developed countries. Pearson et al (2000) studied children aged three months to 16 years who were on ARV's and found that cognitive development is delayed in HIV positive children. In their study there was a large loss to follow up and a very wide age range of study participants. Due to the wide age range

various standardised tests including the Bayley Scales of Infant Development, McCarthy Scales of Children's Abilities and Wechsler Intelligence Scale for Children, Revised had to be used. Different lengths of follow up also took place and children were not followed for the same amount of time. Smith et al (2000) in a USA study also found that HIV positive infants are delayed in cognitive function. The BSID was used to assess infants from birth until the age of 30 months. Not all the infants in this study were receiving ARV therapy.

In the above studies comparisons with healthy or uninfected children were not made and therefore the researchers could not control for other factors that may have influenced cognitive development. In studies comparing HIV positive children to HIV exposed uninfected and healthy uninfected, unexposed controls, the HIV positive children tend to score significantly lower for measures of cognitive function (Bruck et al, 2001; Blanchette et a, 2001; Knight et al, 2000; Pollack et al, 1996; Chase et al, 1995; Gay et al, 1995).

Studies have been conducted in North America on HIV positive infants less than two years of age, who were followed for an extended period of time and compared to HIV exposed uninfected infants. These studies found that HIV positive infants score significantly lower cognitive scores compared to HIV exposed uninfected infants (Blanchette et al, 2001; Knight et al, 2000; Pollack et al, 1996; Chase et al, 1995). Even though all the studies looked at infants and used the BSID, variations between the studies exist. Blanchette et al (2001) studied a group of healthy HIV positive Canadian children and compared them to HIV exposed uninfected children, in their study no mention was made of ARV usage among the study population. They also studied a slightly older population compared to the other studies which studied children from birth until 24 or 30 months of age. Knight et al (2000) also had no mention of ARV usage in their study and their study was retrospective in nature. Pollack et al (1996) reported the use of ZDV in some of the infected children and in Chase et al (1995) all children were aggressively treated with ARV's. In Knight et al (2000) and Chase et al (1995) there was a high percentage of maternal drug use which may have impacted upon results, however the authors do report that the groups studied were similar at baseline. Pollack et al (1996) did not control for maternal substance abuse in their study and mentioned that this could have had an impact on their results. Gay et al (1995) controlled for substance abuse in a sample of HIV positive Haitian women. The infants studied did not receive ARV therapy and it was found that their cognitive development was significantly lower when compared to HIV exposed uninfected children, however a language barrier may have resulted in poorer cognitive test scores and

these participants would have come from worse socioeconomic backgrounds compared to the participants in the other studies. Bruck et al (2001) studied HIV positive children and HIV exposed uninfected children in Brazil using the Child Adaptive Test and Denver Developmental Screen Test and also found that the HIV positive group scored significantly lower when compared to the HIV exposed uninfected group and healthy controls. However, a large percentage of the children in the HIV positive group became institutionalised over the course of the study and this may have impacted the results.

Even though methodology of the studies improved and comparisons were being made between groups of HIV infected and HIV uninfected children and the age range of children studied was narrower, differences still remained between different studies and factors other than HIV may have influenced the results. Many of the children studied had been exposed to drugs during gestation, some children were on ARV's and others were not and once again a variety of outcome measures were used. To draw conclusions from these studies is thus difficult.

More recently a number of studies have emerged from sub-Saharan Africa that indicate that children infected with HIV have severe cognitive delays (Kandawasvika et al 2011; Abubaker et al, 2009; Potterton et al, 2009b; Van Rie et al, 2009; Baillieu and Potterton, 2008; Van Rie, 2008)

Baillieu and Potterton (2008) and Potterton et al (2009b) both conducted studies in an urban South African setting. They both studied HAART naïve, HIV infected children aged less than 30 months using the BSID II. Baillieu and Potterton (2008) found that children infected with HIV functioned 7.63 months below chronological age for cognitive development. Potterton et al (2009b) found that 78% of the sample studied had a cognitive delay. Although power calculations were used to determine sample size in both studies and infants of a very similar age were studied, unfortunately the studies made no comparison with healthy or uninfected children. Abubaker et al (2009) studied ARV naïve HIV infected children and compared them to HIV exposed uninfected and healthy children in Kenya. The children were aged between six months and 35 months. The authors found the HIV positive children scored lower for cognitive development compared to the other groups. Unfortunately in this study the authors used the local Kilifi Developmental Inventory to assess development. Even though the validity and reliability of this tool was determined, the quality of the study would have been better had they used a more internationally recognised standardised tool such as the BSID. Van Rie et al (2009) used the BSID in HIV positive, HIV negative and HIV exposed uninfected children aged 18 to 71 months and followed

them for 12 months. Some of the children received HAART, others only medical care and nutritional support. The majority of children were quite ill suffering WHO stage III or IV disease and had very low CD4 percentages. Unfortunately once again a broad age range of children were studied and children had started HAART throughout the study period which may have impacted upon results. Kandawasvika et al (2011) studied 65 HIV infected Zimbabwean children and compared them to HIV exposed uninfected children using the Bayley Infant Neurodevelopmental Screener and found that HIV positive infants are at high risk for neurodevelopmental delay. Unfortunately very little detail was given on the exact facets of development as only a screening test was used and no mention was made of the use of ARV's in the study population.

It has been found that cognitive function in HIV positive children tends to decline with time (Pollack et al, 1996; Chase et al, 1995; Gay et al, 1995; Nozyce et al, 1994). Both Chase et al (1995) and Pollack et al (1996) found that initially when comparing HIV positive infants to uninfected infants cognitive scores between groups are similar. Pollack et al (1996) then found that at 12 months the HIV positive group had significantly lower scores and these scores remained low at 18 and 24 months of age. It is important to note that in Pollack et al (1996) there was a large percentage of drug exposure during gestation which could impact upon cognitive development. The decline seen in cognitive function may be due to a language barrier influencing test results as the child becomes older (Gay et al, 1995) or because the virus is now affecting areas of the brain responsible for cognitive function. Myelination of the frontal cortex and parietal areas occurs rapidly from this stage and may be affected by the neuro-pathological process of HIV (Fishkin et al, 2000; Gay et al, 1995). In a study conducted in the Democratic Republic of the Congo, baseline cognitive scores of the HIV positive group were significantly lower than those of the HIV exposed uninfected group and healthy controls. However, by 12 months of follow up the HIV positive group had similar cognitive scores when compared to the HIV exposed uninfected children but they were still functioning lower than the healthy controls (Van Rie et al, 2009). In this study they examined children of a very wide age range (18 to 71 months) and children had initiated HAART throughout the course of the study. Care between children also differed, as some received HAART, others only medical care and nutritional support and some received tips on how to stimulate the child. Various standardised tests were also used throughout the study period due to the wide age range of children and this makes comparisons over time difficult.

Some studies have found no differences in cognitive function between groups. Bagenda et al (2006) studied HIV positive Ugandan children aged six to 12 years who were HAART naïve and compared them to HIV exposed uninfected and HIV negative children using the Kaufman Assessment Battery for Children. They found no significant difference in standardised test scores for intelligence, reading and writing between the groups. Fishkin et al (2000) in a USA study compared cognitive functioning in asymptomatic HIV positive and HIV negative controls aged three to five years. They used the Wechsler Preschool and Primary Scale of Intelligence - Revised. In their study they also found no differences for frontal functioning skills when comparing HIV positive children to healthy controls. The age range in their study population was narrower than in Bagenda's study and a different standardised test was also used; therefore it is difficult to draw conclusions from these studies.

HIV positive children often experience learning difficulties and specific areas of cognitive development contribute to these difficulties (Burns et al, 2008; Armstrong et al 1993). Children infected with HIV often have visuo-spatial deficits and difficulties with perceptual tasks (Van Rie et al, 2007; Foster et al, 2006; Smith et al 2006; Fishkin et al 2000; Boivin et al, 1995; Newell et al 1995; Armstrong et al, 1993). There are problems with information processing (Foster et al, 2006; Fishkin et al, 2000; Boivin et al, 1995) as well as with memory skills (Burns et al, 2008; Smith et al 2006 Pearson et al, 2000; Boivin et al, 1995). The ability to sustain attention on a task is also affected (Foster et al, 2006; Fishkin et al, 2000; Pearson et al, 2000; Armstrong et al,1993) Boivin et al (1995) found that visual recognition was also a problem. It appears that areas of cognitive development most affected are those areas reliant on adequate executive function (Van Rie et al, 2007) which depends on frontal cortex development (Fishkin et al, 2000)

Poor cognitive outcome in HIV infected children is associated with severity of the disease (Potterton et al 2009b; Bertou et al 2008; Burns et al, 2008; Foster et al, 2006, Smith et al, 2006; Pearson et al, 2000; Nozyce et al, 1994). The presence of an HIV associated condition predisposes the child to cognitive delay (Foster et al, 2006; Smith et al, 2006; Nozyce et al, 1994). CD4 counts and viral loads are predictive of neuro-cognitive outcome (Pearson et al 2000, Chase et al 1995 and Newell et al 1995). Growth failure also contributes to cognitive development (Potterton et al 2009b; Pollack et al 1996).

The presence of a neurological abnormality or an abnormality on brain scans contributes to worse cognitive function (Thomaidis et al, 2010; Blanchette et al, 2001; Knight et al, 2000; Brouwers et al, 1995). Thomaidis et al (2010) conducted a study in Greece on children aged three to 18 years who were

all on HAART and found that if a neurological abnormality is present, 40% of children have moderate mental retardation and 40% have severe mental retardation. Brouwers et al (1995) found that children with calcifications scored significantly lower on IQ tests. They hypothesize that cognitive dysfunction in HIV is due to structural brain changes caused by HIV rather than environmental influences. Other factors such as poverty, the poor socio-economic circumstances that the children live in and parental death may adversely affect cognitive outcome (Burns et al, 2008; Armstrong et al, 1993).

Studies on the effects of HIV on cognitive development have often looked at a wide age range of children, different standardised tests have been used and often children receive different types of care – some children are on ARV's and others are not. However, when all factors have been considered cognitive development appears to be adversely affected by HIV.

2.8.2.3. The effects of HIV on motor development

Motor development is often affected in children infected with HIV (Baillieu and Potterton, 2008; Foster et al, 2006; McGarth et al, 2006; Pearson et al, 2000; Armstrong et al, 1993). Motor development appears to be affected before cognitive and language function and also seems to be more severely affected than other facets of development (Baillieu and Potterton, 2008; Foster et al, 2006; Drotar et al, 1997). Motor developmental delay in HIV positive children may be present form early on (Abubakar et al, 2008). Chase et al (1995) detected motor developmental delay from as early as four months of age.

In various studies conducted in South Africa high levels of motor delay have been detected. Potterton and Eales (2001) found that 40% of an HIV infected sample of infants presented with motor delays. Unfortunately in this study only a screening assessment was performed. A few years later the standard of assessment tools used in South African HIV studies improved. Baillieu and Potterton (2008) used the BSID II and found that 97% of their sample had a motor delay and were functioning 9.65 months below their chronological age. In this study the infants were HAART naïve and came from very poor socioeconomic backgrounds. Unfortunately, a comparison group was not used in this study. Potterton et al (2009b) found that in a large sample of HIV infected children aged less than two and a half years, 87% presented with a motor delay with three quarters of the sample presenting with a severe delay. In this study the BSID II was also used and most of the children were HAART naïve. The study population also came from poor socioeconomic backgrounds and CD4 percentages at baseline were low. Once again there was no comparison group of uninfected children in the study. In two studies conducted in Cape

Town, South Africa, motor development was also found to be worse in HIV positive children compared to HIV negative children. Ferguson and Jelsma (2009) studied children aged one to 33 months and used the BSID II as their assessment tools. Sixty one percent of their sample was on HAART. Jelsma et al (2011) studied an older population of institutionalised HIV positive children. The children were aged three to six years and were assessed using the Peabody Developmental Motor Scale II. They found that HIV positive children perform worse compared to HIV negative children. In this study all children had been on HAART for five months or more. Unfortunately the children in this study were institutionalised and this may have impacted on the results. Bruck et al (2001) also studied institutionalised children and questioned whether this affected their results. In Jelsma et al (2011) all children resided in institutions and a significant delay was still detected in the HIV positive population. Shead et al (2010) also studied South African institutonalised HIV infected children and compared them to HIV uninfected children . They used the BSID II for their assessment and had similar findings to that of Jelsma et al (2011). Shead et al (2010) also saw no improvement for motor function over time, however the majority of children in this study were not receiving HAART.

Other studies from developing countries have also detected a high incidence of motor delay in HIV infected children (Abubaker et al 2009, Abubaker et al, 2008; Van Rie et al, 2008). Msellati et al (1993) used an independently designed assessment tool to determine motor function in HIV positive Rwandan infants from birth to 24 months. She compared them to HIV exposed uninfected infants as well as healthy controls. The children were not receiving ARV's. Unfortunately no validity or reliability was determined for the assessment tool that was developed therefore results may be questionable. A study in Zaire then used screening tools to determine motor function in ARV naïve HIV positive infants. Although a more standardised assessment tool was used, there was no power calculation and the sample size was small, results were also not analysed by intention to treat (Boivin et al, 1995). Drotar et al (1997) assessed motor function in HIV positive infants from birth to 24 months using the BSID. The study was conducted in Uganda and children did not receive ARV therapy. No power calculation was reported in the study and there were very few HIV positive infants compared to HIV exposed uninfected infants and healthy controls. A large loss to follow up was also seen in this study. Abubaker et al (2009) used the Kiliffi Developmental Inventory to assess 49 HIV positive, HAART naïve children and compare them to HIV exposed uninfected and HIV unexposed uninfected children. They found that the HIV positive group was more delayed for motor development when compared to the other groups. In this study, the use of a more internationally recognised standardised tool would have allowed for better

comparisons with other studies. Van Rie et al (2008) used the BSID II and Peabody Developmental Motor Scales 2nd Edition in HIV positive children from the Democratic Republic of Congo with an age range of 18 – 71 months. They found motor development to be more affected than in the other groups. Unfortunately a wide age range was studied and children had started HAART throughout the course of the study period which may have influenced the results. Children from this study also came from poor socioeconomic backgrounds.

The variety of assessment tools used in studies from developing countries as well as the wide age ranges studied makes comparison between studies difficult. Also, in most studies, children initiate HAART throughout the study period and not all infants are always receiving HAART making it difficult to draw conclusions from the results.

In studies conducted in developed countries motor development has also been found to be adversely affected by HIV. The BSID has been used consistently in most of the studies and a narrower age range of children have been assessed making comparisons between studies easier. Chase et al (1995) compared motor function in HIV positive, HIV exposed uninfected and HIV unexposed uninfected infants aged three to 30 months. The HIV positive infants received aggressive ARV therapy throughout the course of the study and motor delay was detected early on and continued to persist. In this study a large percentage of children were exposed to drugs during pregnancy and this may have influenced the results. No power calculation was done in this study. Knight et al (2000) had similar findings in their retrospective study and also reported a high percentage of infants being exposed to drugs during pregnancy. No data was available on ARV use in this study. Blanchette et al (2001) compared motor development in clinically healthy Canadian HIV positive and HIV exposed uninfected infants and also made no mention of ARV use.

As with cognitive function, motor development seems to decline over time (Burns et al, 2008; Pollack et al, 1996; Nozyce et al, 1994). Gay et al (1995) did not find that motor function declined with time. They studied a group of HIV positive Haitian infants from three months of age and followed them until they turned two years old. The BSID was used in this study and comparisons with an HIV exposed group was made. Unfortunately there was no mention of ARV therapy or disease severity in this study.

Motor abnormalities found in HIV positive children may include increased tone or hypotonia, abnormal reflexes, ataxia and decreased strength (Willen et al, 2006; Tardieu et al, 2000; Mitchell, 2001; Gay et al, 1995; Armstrong et al, 1993; Msellati et al, 1993). It has been found that gross motor function is more delayed than fine motor function in children with HIV infection (Jelsma et al, 2011; Baillieu and Potterton, 2008; Van Rie et al 2007; Msellati et al 1993). Gross motor function may be more delayed due to the fact that often HIV positive children are stunted and lack of nutrition will affect motor outcome, strength is a problem in these children and tone abnormalities may contribute to the problem (Abubakar et al, 2009; Potterton et al, 2009b; Baillieu and Potterton, 2008). Function is often poor in activities requiring postural stability, motor co-ordination as well as a large amount of eccentric strength (Baillieu and Potterton, 2008; Potterton and Eales, 2001). The activities commonly affected include skipping, jumping, stair climbing and sit to stand (Baillieu and Potterton, 2008)

Motor developmental delay is also associated with severity of disease stage (Abubakar et al, 2009; Foster et al, 2006; Nozyce et al, 1994) as well as with CD4 counts and viral loads (Pearson et al 2000; Chase et al, 1995). Physical growth appears to play an important role in motor development (Abubakar et al, 2009; Potterton et al 2009b;; Boivin et al, 1995). Abubakar et al (2009) found that if the child has an advanced disease stage and is underweight, lower scores for motor development can be expected. Those children with abnormalities present on brain scans may perform worse with motor activities (Blanchette et al, 2001; Knight et al 2000; Drotar et al, 1997). There is also increased prevalence of motor delay with increasing age (Potterton et al 2009b; Van Rie et al, 2007).

A vast amount of research is available and shows that HIV affects motor development, however, it is often difficult to make comparisons between studies. Many studies have been conducted in the developed world where prenatal drug exposure is a problem, however care of HIV infected children is often better and participants often come from better socioeconomic backgrounds compared to participants in studies conducted in developing countries. Different studies often use a variety of different assessment tools making comparison difficult. Usually a wide age range of participants are also studied. Results and comparison are also influenced by the fact that ARV's are initiated at various intervals during the course of a study or children don't receive ARV's at all. Although this impacts upon analysis of the results, the evidence still strongly suggests that motor development is influenced by HIV.

2.8.2.4. The effects of HIV on language development

The understanding of how language is affected by HIV is important as language is an essential component of academic success. Appropriate speech and language skills are required for literacy, understanding, and reading capabilities as well as for independence later in life (Brackis-Cott et al, 2009). Considering that language plays such an important role in our lives, very limited research is available on how HIV affects language.

Speech and language is adversely affected by HIV (Baillieu and Potterton, 2008; Van Rie et al, 2007; Pearson et al, 2000; Newell et al, 1995). A number of studies have been done on HIV infected children without comparing them to uninfected children from similar socioeconomic backgrounds.

Baillieu and Potterton (2008) in a South African study found that 82.5% of HAART naïve HIV infected children aged 18 to 30 months had a language delay. Potterton et al (2009b) also used the BSID II in mainly HAART naïve children aged less than two and a half years and found that language was delayed. In both studies the BSID II was used and HAART naive children were assessed. The BSID as well as other standardised tests was also administered on HIV positive, ARV exposed children in the USA aged three months to 16 years and it was found that they were delayed (Pearson et al 2000). Newell et al (1995) also looked at language function in school aged children in the USA, receiving ARV therapy and found that most had speech and language difficulties. In their study they did not use the BSID to assess language. Wolters et al (1997) in the USA used the Reynell, Clinical evaluation of Language and FSIQ to assess language in HIV positive children aged one to 13 years who were HAART naïve at baseline and found that the group was delayed for language function. Only one assessor assessed all the children which would enhance the reliability of the study, however a very large age group of HIV symptomatic children were assessed and this may have adversely influenced the results. It is difficult to make comparisons between the two South African studies and the studies conducted in the USA. The age groups studied were completely different and in the USA studies children were receiving ARV therapy. Different assessment tools were also used in all the different studies, making comparisons difficult.

Language function appears to be significantly decreased in HIV positive children when they are compared to their uninfected peers (Boivin et al, 1995; Brackis-Cott et al, 2009; Coplan et al 1998; Van Rie et al, 2008). Van Rie et al (2008) and Coplan et al (1998) both used the BSID to compare language function in HIV positive infants and HIV exposed uninfected infants and found language scores to be

significantly lower in the HIV positive group. Comparisons between these two studies are difficult as in Van Rie et al (2008) children were not on ARV's and they came from very poor socioeconomic circumstance. Their study was conducted in the Democratic Republic of the Congo whereas Coplan et al (1998) conducted their study in the USA, therefore the socioeconomic situation between the participants in the two studies would have been very different. The age range of infants studied in Van Rie et al (2008) was also much wider than in Coplan et al (1998). Van Rie et al (2008) used the Rosetti Infant Language Scale compared to the ELM 2 used in Coplan et al (1998). This makes comparison between the two studies difficult. Brackis-Cott et al (2009) looked at language function in a HIV positive population that were on ARV's aged nine to sixteen years and compared them to HIV exposed uninfected children and found language to be delayed in the HIV positive group. Once again a far older age group was assessed.

The onset of speech and language delay occurs much later on than with cognitive and motor function. The delay often only becomes apparent once children start having difficulty with their academic performance and reading ability (Brackis-Cott et al, 2009). It appears that language function declines over time (Coplan et al, 1998; Wolters et al, 1997). Coplan et al (1998) in a small sampled, long term follow up study found that out of the nine participants they were studying, seven deteriorated in terms of language function. Wolters et al (1997) studied far more children and also found that language function declines over time, unfortunately no comparison was made with uninfected children in this study.

There appears to be a trend for expressive language to be more delayed than receptive language (Baillieu and Potterton 2008; Foster et al, 2006; Wolters et al, 1997). The discrepancy between expressive and receptive communication seems to persist. Wolters et al (1997) found that even at 24 months expressive language scores were significantly lower when compared to receptive language scores in HIV positive children. The reason for expressive language being more delayed than receptive language may be due to the influence of motor development. Expressive language is dependent on motor development (Coplan et al, 1998) and motor development is often delayed in HIV positive children (Baillieu and Potter ton, 2008; Foster et al, 2006; McGarth et al, 2006; Pearson et al, 2000; Armstrong et al, 1993). Verbal deficits as well as articulation problems are often present in HIV positive children (Boivin et al, 1995; Newell et al, 1995). Brackis-Cott et al 2009 also found that HIV positive

children have poor verbal ability, a limited vocabulary and lack prerequisite skills required for reading, word recognition was also of major concern.

Language development, as with cognitive and motor development in HIV, is related to severity of disease stage, CD4 counts and viral loads (Pearson et al, 2000; Newell et al, 1995). Wolters et al (1997) found that the presence of encephalopathy in the child also predisposes them to language delay especially in expressive language.

Limited research is available on language development in HIV positive children. Comparisons between studies are also difficult to make due studies being conducted in developed and developing countries, the use of HAART in the different studies, the wide age ranges studied as well as the different standardised tests used in the studies. Even though these barriers exist in the research, language development still appears to be adversely affected in HIV positive children.

2.8.3. The Effects of HAART on Neurodevelopment

HAART is clearly effective in reducing mortality and improving general health (Violori et al, 2008). However, its effects on neurodevelopment remain questionable. Very little good quality research has been done to assess the effects of HAART on neurodevelopment. Studies that have been done show contradictory results. Children on HAART are now living longer and if neurodevelopment is still affected in these children it will affect their quality of life later on (Burns et al, 2008).

Several studies have shown some benefit of HAART on neurological outcomes and HIV encephalopathy. Chiriboga et al (2005), Patel et al (2009) and Sanchez-Ramon et al (2005) all found that HAART decreased the incidence of HIV encephalopathy. Chiriboga et al (2005) had no long follow up of the children in their study and simply looked at the incidence of encephalopathy as well as school placement in children infected with HIV. They found that if viral load was undetectable and well controlled there was a decreased likelihood of developing progressive HIV encephalopathy. Patel et al (2009) studied a group of HIV positive children with existing neurological abnormalities who resided in the USA. They followed the children for a number of years and evaluated the incidence of HIV encephalopathy. It was found that with the use of HAART the incidence of encephalopathy is reduced by 50%. Unfortunately in this study they observed patient records which resulted in various clinicians assessing neurological abnormalities and manifestations of encephalopathy. This may have affected the reliability of the study.

All the children in the study had to have an existing neurological abnormality and this may have influenced the results as not all HIV positive children present with neurological abnormalities that are easily detectable. Sanchez-Ramon et al (2005) conducted a retrospective study and had similar findings to Patel et al (2009) and Chiriboga et al (2005). They found that those children not receiving HAART progressed quicker to progressive encephalopathy compared to those receiving HAART. They found that 72% of the children they were studying showed neurological improvement with the initiation of HAART. McCoig et al (2002) performed a double blind randomised control trial on HIV positive children aged seven months to ten years and found that there was a significant decrease in neurological abnormalities after 48 weeks with the initiation of ARV's. Children receiving a triple regimen of ABC/3TC/ZDV performed even better compared to those receiving 3TC/ZDV. They deduced that ARV's should contain a drug that is able to cross the blood brain barrier. Tardieu et al (2000) found contradictory results. They found that even with the treatment of AZT, incidence of encephalopathy was similar in children receiving AZT to those not receiving AZT.

The above studies were conducted in developed countries; therefore the results may differ to that of children in developing countries. In the above studies, only neurological abnormalities were assessed and no tests measuring neurodevelopment were used. When looking at the effects of HAART on neurodevelopmental outcomes various results have been reported.

A number of studies conducted in developed countries have found improvements in neurodevelopment with HAART (Raskino et al, 1999; Wolters et al, 1997; Silva et al, 2009; Tepper et al, 1995). Raskino et al (1999) in a USA study found that a combination of ZDV and DDI was effective in significantly improving cognitive and motor function within 24 weeks of initiation. They studied a large sample of children aged three to 18 years. Due to the broad age range of children studied, a variety of assessment tools were used to determine cognitive and motor function. The assessment tools included the BSID, McCarthy Scales and Weschler tests. To be included in this study all the children had to be symptomatic with HIV and this may have influenced the improvements seen. The improvement seen in health may have resulted in improved neurodevelopmental outcomes instead of HAART influencing neurodevelopment directly. Wolters et al (1997) did not find that cognitive and language function improved with HAART, however they found that cognitive function remained stable over time in the two year follow up study that they conducted. Unfortunately in this study there was no comparison group. Two case studies, one on an adult and one on a child have reported that HAART is beneficial in decreasing neurological

symptoms, reversing abnormalities detected on brain scans and improving cognitive and motor impairments associated with HIV (Silva et al, 2009; Tepper et al, 1998). The fact that the studies reported on two individual cases makes it difficult for results to be applied to the general population.

HAART may not be effective in improving neurodevelopmental functioning but may result in no significant deterioration in function. Foster et al (2006) in a retrospective study found that scores in the BSID, Griffiths and McCarthy Scales stayed the same and did not improve even though participants studied had suppressed viral loads. They reported that motor abnormalities continued to persist. This was a retrospective study and no comparisons were made with a control group, thus making the interpretation of the results difficult. Foster et al (2006) findings are similar to Jeremy et al (2005) who conducted a prospective study where children were followed for 48 weeks after initiating ARV's. They found that even though 44% of the sample studied had undetectable viral loads no significant changes were seen in neuropsychological functioning. In Jeremy et al (2005), no comparison group was assessed to control for environmental factors and a wide age range of children were assessed. Lindsey et al (2007) studied a far narrower age range of children. They compared HIV positive infants to HIV exposed uninfected infants using the BSID II over a 24 month period. They found that cognitive and motor scores remained low in the HIV positive group even though they were receiving HAART. In this study the two groups were not similar at baseline – a far higher percentage of children in the HIV positive group had been exposed to drugs during gestation compared to the HIV exposed uninfected group and this may have adversely affected the results.

All the studies discussed above were conducted in developed countries and most, except for Lindsey et al (2007) studied a very wide age range of children. There is a lack of research available from developing countries and the results from the studies discussed may not pertain to the effects of HAART on neurodevelopment in the developing world.

Two South African studies have also had similar findings. Jelsma et al (2011) and Ferguson et al (2009) both found that children on HAART continued to have motor delays and that being on ARV's did not improve motor development. Jelsma et al (2011) used the Peabody Developmental Motor Scale II to assess motor development in three to six year olds who were institutionalised or in foster care over a six month period. All the children were on HAART prior to the commencement of the study. The researchers found that being on HAART did not predict a better outcome in motor scores and that ARV's

did not result in normal motor development. Unfortunately only motor development was assessed. All the children in this study were on HAART prior to its commencement – improvements that may have occurred earlier on or shortly after the initiation of HAART could not be observed. In this study all the children were institutionalized or residing in foster care, therefore results may not pertain to children living with their biological caregivers. Fergson and Jelsma (2009) found that when studying motor development using the BSID II on HIV positive children there was no significant difference in motor function between children receiving HAART and those not receiving HAART. There were also no significant differences for children on HAART for more than six months or less than six months. Longitudinal follow up was not done in this study, therefore the long term effects of HAART are unknown. In this study the HIV positive group had a high number of hospital admissions and this would have adversely affected neurodevelopment. Comparisons between these two South African studies are difficult as two very different populations were studied and different assessment tools were used.

It appears that ARV's are effective in decreasing the incidence of encephalopathy and in reducing neurological abnormalities in children infected with HIV. However, HAART does not appear to improve development. This may be due to the fact that once damage has occurred in the CNS it is irreversible (Wolters et al, 1997). Due to the weakness in the studies discussed above results should be viewed with care. There is clearly a lack of research in developing countries regarding the effects of HAART on neurodevelopment. Thereofore, there is an urgent need for good quality research to be conducted in this area so as to determine what services are still required by HIV positive children.

2.9. The HIV Exposed Uninfected Child

Due to PMTCT, rates of transmission of HIV infection to children have decreased. This, however, has resulted in a large number of children being exposed to HIV as well as to ARV's in utero. This may place the children's health at risk.

It has been found that the HIV exposed uninfected child may be at risk for increased morbidity. In a case series of eight HIV exposed uninfected children Slogrove et al (2010) found that these children may experience an increased incidence of nosocomial sepsis, PCP as well as bacterial infections. These children also had a high rate of hospital admissions. Mussi-Pinhata et al (2007) also found that HIV exposed uninfected children experience a high number of skin infections, respiratory tract infections and hospitalisations. In a review Filteau (2009) found that HIV exposed uninfected children have an

increased incidence of diarrhoea and if they develop pneumonia they may be at higher risk for treatment failure compared to unexposed children. Koyanagi et al (2011) found that HIV exposed uninfected children have increased sick visits compared to unexposed children. Kuhn et al (2005) found hospital admissions to be due to pneumonia, sepsis and diarrhoea.

Morbidity in the HIV exposed uninfected infant appears to be associated with maternal health. A low maternal CD4 count seems to be predictive of increased morbidity in the HIV exposed uninfected infant (Koyanagi et al, 2011; Slogrove et al, 2010; Mussi-Pinhata et al, 2007; Kuhn et al, 2005,). The HIV exposed uninfected child may also be exposed to a greater number of infections in their household compared to an unexposed child, therefore morbidity may be increased (Filteau, 2009). Due to avoidance of breastfeeding to prevent MTCT of HIV, an increased number of infections may be seen in this population of children (Slogrove et al, 2010; Filteau, 2009; Kuhn et al, 2005).

HIV exposed uninfected children are also at risk of being born prematurely and this is due to the use of ARV's in pregnancy (Martin and Taylor, 2009; The European Collaborative Study, 2003). Some studies have suggested that with the use of ARV's in pregnancy there is increased risk of the child developing mitochondrial damage and toxicity (Poirier et al, 2003), however several large studies have not found similar results (The European Collaborative Study, 2003). Therefore, the use of ARV's in pregnancy at this stage appears to be safe.

Growth in the HIV exposed uninfected infant may be affected. It has been found that early growth especially length for age z scores are significantly lower than in unexposed children (Filteau, 2009; Arpadi et al, 2009). These scores tend to be lower even when corrected for gestational age (Filteau et al, 2009). HEU infants appear to be shorter than unexposed infants in the first six months of life, however they do catch up and anthropometric measurements for these children are within normal ranges. Due to the socio-economic circumstances that these children live in, malnutrition is also a common occurrence (Arpadi et al, 2009; Filteau, 2009).

Mortality in HEU infants is higher than in unexposed infants (Filteau, 2009; Kuhn et al, 2005). Kuhn et al (2005) found a mortality rate of 4.6 % in the first four months of life which then decreased to 1.8% after the neonatal period. Death seems to be due to pneumonia, failure to thrive and sepsis (Kuhn et al,

2005). Mortality is associated with maternal disease stage, maternal CD4 counts, maternal death as well as low birth weight (Filteau, 2009; Kuhn et al, 2005).

Neurodevelopment does not appear to be affected in HIV exposed uninfected children. Alimenti et al (2006) compared the neurodevelopment in HIV exposed uninfected children to HIV unexposed children from similar backgrounds and found that the HIV exposed uninfected children had lower mean scores. However, when they controlled for maternal substance abuse in the study, they found no difference between the groups. Williams et al (2010) found that HIV exposed uninfected children exposed to ARV's during pregnancy does not affect neurodevelopmental functioning. Several other studies have also shown that HIV exposed uninfected children have similar neurodevelopment to uninfected children and they also perform better than HIV positive children on measures of neurodevelopment (Van Rie et al, 2008; Blanchette et al, 2001; Bruck et al, 2001; Drotar et al, 1997; Gay et al, 1995; Boivin et al, 1995; Msellati et al, 1993). It appears that developmental delay in HIV exposed uninfected children is probably due to environmental input, rather than biological factors (Filteau, 2009).

Even though the HIV exposed uninfected child appears to be at higher risk for morbidity and mortality, this is far lower than in HIV positive children. It is therefore imperative that MTCT of HIV be prevented. However, follow up of this population of children would be beneficial to assist in decreasing mortality and morbidity and also to monitor the long term effects of exposure to ARV's (Hankin et al, 2009).

2.10. Developmental Assessment

Developmental assessment tools have been designed in order to detect developmental delays, to determine if children will have future developmental problems, to plan intervention strategies and to allow monitoring of progress over a period of time (Spittle et al, 2008; Heineman and Hadders-Algra, 2008; Tieman et al, 2005). A variety of standardised developmental tools have been designed.

Screening tools have been designed in order to provide a quick, inexpensive way of detecting infants at risk of developmental delays. Screening tools allow for early detection of delays and for appropriate and early referral to appropriate rehabilitative services (Tieman et al, 2005). An example of a screening tool is the Denver Developmental Screening Test. The information provided by a screening tool is limited. At times more in depth developmental assessment is required.

Choosing an appropriate standardised developmental assessment tool depends on a variety of factors.

When selecting an appropriate assessment tool, one needs to decide what the purpose of the assessment is for. Discriminative assessment tools are norm referenced tools that are able to identify children with atypical development and compare them to a normative sample (Spittle et al, 2008; Tieman et al, 2005). These tools are not ideal to use on children with disabilities such as cerebral palsy (Tieman et al, 2005). Examples of discriminative assessment tools include the Peabody Developmental Motor Scales, Bayley Scales of Infant Development, Toddler and Infant Motor Evaluation and Alberta Infant Motor Scale. All these tools have been normed on children from the USA and Canada (Spittle et al, 2008). Evaluative assessment tools measure individual progress over a period of time and are not norm referenced. An example of this type of tool is the Gross Motor Function Measure (Tieman et al, 2005).

A standardised assessment tool should be valid, reliable and responsive (Heineman and Hadders-Algra, 2008; Spittle et al, 2008; Tieman et al, 2005). Reliability refers to the ability of findings on the assessment to be repeated. Validity is the ability of the tool to measure what it reports to be measuring. Responsiveness is the ability of the tool to detect changes over time (Spittle et al, 2008; Tieman et al, 2005). Most standardised tools have been validated and reliability of these tools has been determined.

The clinical utility of the tool should also be considered (Tieman et al, 2005). Many of the standardised tools may be quite costly and may not be feasible to use in a government setting (Spittle et al, 2008). Some tools require the assessor to be trained and training may also be costly (Spittle et al, 2008; Tieman et al, 2005). However, most tools can be used by a variety of health professionals. It is recommended that the assessor be familiar with normal child development, should have experience in handling children and should be able to interpret the results of the test (Spittle et al, 2008; Tieman et al, 2005).

The BSID is considered to be the gold standard in developmental testing (Harris et al, 2005). The use of this tool, its reliability and validity as well as use in South Africa and on HIV positive infants will be discussed further.

2.10.1. The Bayley Scales of Infant and Toddler Development

The BSID is used all over the world to assess developmental functioning in children aged one to 42 months (Milne et al 2011). It is an individually administered, standardized, norm referenced tool that is both valid and reliable (Bayley, 2006). It is also sensitive to detecting developmental delay in children (Harcourt Assessment, 2007).

The Bayley-III was developed in 2006 and is a revision of the BSID II. The Bayley-III was developed so as to improve the quality of the instrument, to update normative data, to simplify administration and to allow for subsets to stand alone (Harcourt Assessment, 2007). Some differences in scores have been detected between the BSID II and Bayley-III, however this may be due to changes seen in the population used to obtain the normative data as well as the test becoming far more specific and precise (Harcourt Assessment, 2007). To obtain normative data 1 700 American children were assessed from different races, genders and geographical locations (Milne et al, 2011; Bayley 2006).

The Bayley-III is used to assess the three main areas of development: cognitive function, language function and motor function (Bayley, 2006). The language component assesses both receptive and expressive language. The motor component assesses both fine motor and gross motor function (Bayley, 2006). The assessment takes approximately 50 minutes to administer. It needs to be administered in a quiet room and one requires a small table and chair to administer certain items of the scale. The child receives a score of one if they are able to do the item administered or a score of zero if they are unable to perform the item. The item must be observed by the assessor. Total scores are added to give a raw score. The raw score is then used to determine scaled scores, composite scores and percentile ranks. The scale has a mean of 100 with a standard deviation of 15 (Bayley, 2006).

The BSID II has been normed on African and South African children (Aina and Morakinyo 2005; Richter et al, 1992). It has also been found to be effective in assessing medically fragile children (Harris et al, 2005; Nicolls and Latchman, 2002). The BSID II has also been used extensively in research to detect developmental delays in various populations including premature infants, infants exposed to alcohol and drugs during pregnancy (van Zwol et al, 2008; Wang et al, 2008; Wielenga et al, 2009) as well as in HIV positive infants (Bailleu and Potterton, 2008; Drotar et al, 1997; Msellati et al, 1993; Nozyce et al, 1994; Potterton et al, 2009; Van Rie et al, 2008).

From this it can be seen that the Bayley-III is a comprehensive assessment tool that assesses cognitive, language and motor function. It is sensitive in detecting developmental delay and is also valid and reliable. It is a widely used research tool and has been used in the HIV positive population.

2.11. Conclusion

Mother to child transmission rates of HIV in South Africa have decreased due to effective PMTCT programs. HIV positive children are now initiating HAART earlier than ever before, resulting in decreased morbidity and improved survival. Children infected with HIV are living much longer. Even though huge strides have been made to decrease new HIV infections, HIV continues to affect many thousands of children in South Africa. HIV adversely affects neurodevelopment and results in deficits in cognitive, language and motor function, it also causes a variety of neurological abnormalities. This in turn leads to poor academic performance and will ultimately affect quality of life later on which will affect the ability of the child to become a productive member of society and will place increased strain on the country.

Even though mortality and morbidity has decreased due to the effect of HAART, little is known about neurodevelopment in these children. Limited research is available on the effects of HAART on neurodevelopment. It would be useful to see the effects of HAART on neurodevelopment especially in sub-Saharan Africa as it has the highest prevalence of HIV in the world. No study has been conducted in sub-Saharan Africa looking at the possible neuro-protective effects of HAART if initiated at a high CD4 count. If HAART were to have a positive effect on neurodevelopment it would support its early initiation. It will also help determine what services still need to be made available to children infected with HIV. Therefore, the aim of this study is to determine the neurodevelopment of HIV positive infants initiating HAART and to compare them to HIV exposed but uninfected infants.

Chapter 3

METHODOLOGY

This chapter aims to discuss the methodology employed in this research project.

3.1. Research Design

This was a longitudinal comparative study.

3.2. Location of Study

The study was conducted at the HIV (Empilweni) Clinic at Rahima Moosa Mother and Child Hospital, Johannesburg. The clinic is serviced by doctors, nurses, counselors, a social worker and a dietician. The majority of children come from the surrounding area which includes Coronationville, Newclare and Westbury as well as from further lying areas including Soweto and Diepsloot. The social circumstances in these areas are poor.

3.3. Participants

To detect a difference of 15 on the Bayley Scales of Infant and Toddler Development III (Bayley III) when using a standard deviation of 15 and power of 90% it was found that the sample for each group was 27 participants. This allowed for a 20% drop out rate and had a confidence interval of ± 4.63.

3.3.1. Inclusion Criteria

- Children aged less than 12 months
- Exposed to HIV but uninfected or
- HIV positive and starting HAART (i.e. not yet on HAART)

3.3.2. Exclusion Criteria

- Institutionalised children
- Premature infants (born before 37 weeks gestation)

- Infants receiving physiotherapy
- Clinically apparent congenital abnormalities

3.4 Outcome Measures

3.4.1 Bayley Scales of Infant and Toddler Development (3rd edition)

The Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III) was used to assess neurodevelopment in the children.

The Bayley-III is a revision of the Bayley Scales of Infant Development 2nd Edition (BSID II). It is a standardized, norm referenced tool that is both valid and reliable (Bayley, 2006). The BSID II has been used in research to detect developmental delays in various populations including premature infants, infants exposed to alcohol and drugs during pregnancy (van Zwol et al, 2008; Wang et al, 2008; Wielenga et al, 2009) as well as in HIV positive infants (Bailleu and Potterton, 2008; Drotar et al, 1997; Msellati et al, 1993; Nozyce et al, 1994; Potterton et al, 2009; Van Rie et al, 2008).

The scale is used to assess development in children aged one month to 42 months. It tests three components of development, namely: cognitive development, language development and motor development. The language component assesses both receptive and expressive language. The motor component assesses both fine motor and gross motor function (Bayley, 2006).

The assessment takes approximately 50 minutes to administer. It needs to be administered in a quiet room and one requires a small table and chair to administer certain items of the scale. The child receives a score of one if they are able to do the item administered or a score of zero if they are unable to perform the item. The item must be observed by the assessor. Total scores are added to give a raw score. The raw score is then used to determine scaled scores, composite scores and percentile ranks. Normative data is available for the Bayley-III. The scale has a mean of 100 with a standard deviation of 15 (Bayley, 2006).

The scale was administered on all children who participated in the study in a small room in the clinic. The scale was administered at baseline, 3 months follow up and 6 months follow up.

Feedback regarding the scores was given to the parents at the final visit.

3.4.2 Anthropometric Measurements

Weight, height and head circumference were recorded at baseline, 3 months follow up and 6 months follow up.

Weight and height were measured by the nurses at the clinic. Head circumference was measured by the researcher using the tape measure provided in the Bayley III kit.

All anthropometric measurements were converted to z-scores using the WHO Anthro computer program.

3.4.3 Pregnancy History

At baseline information regarding the mother's pregnancy was collected. The researcher asked the mother several questions to determine her health during pregnancy, to determine if she received ARV's or AZT during pregnancy and to determine her CD4 count just prior to or just after birth. The researcher also screened the patient files for any relevant information. Data was recorded. The questionnaire can be viewed in Addendum 1.

3.4.4 Child Health

The researcher questioned the mothers and viewed the children's files to determine if they had any illnesses or hospital admissions in the last three months, if immunisations were up to date and if the child was receiving any medication. This data was collected at each visit and recorded. The questionnaire can be viewed in Addendum 2.

3.4.5 CD4 Counts, CD4 Percentages, Viral Loads and ARV's

The most recent CD4 counts, CD4 percentages and viral loads of all the children in the HIV positive group were recorded. This information was obtained from the participants' files.

Once the child had started HAART the names of the medications were recorded. Any changes in the medication were also recorded.

3.5. Procedure

3.5.1. Baseline

3.5.1.1. HIV Exposed Uninfected Infants

The Empilweni Clinic at Rahima Moosa Mother and Child Hospital runs a clinic on a Monday morning for HIV exposed infants. At this clinic PCR tests are done to determine if the child is HIV positive. This test is done at 6 weeks of age. The patients then return 2 weeks later to obtain the results of the test. If the child is HIV negative they are then followed up every 6 months until they are 18 months old.

The researcher attended this clinic on a Monday morning. After a support group was conducted the researcher spoke to the mothers in the waiting room and explained that she was conducting a study to determine if being exposed to HIV results in development problems and to compare this to children who are HIV positive. The researcher then invited anyone who was interested in taking part in the study to come and see her in the room that was made available for the assessments.

The mothers would come see the researcher. The study was explained to them again. The mothers then signed consent.

The mothers were then questioned on their pregnancy history as well as their child's health. Height and weight were recorded from the file and head circumference was measured by the researcher. The researcher then administered the Bayley III.

A follow up date was then given to the mothers.

3.5.1.2. HIV Positive Group

To recruit HIV positive infants the researcher would attend the Empilweni Clinic on a Tuesday and Thursday and screen the files for any new patients.

The researcher would approach the parents, explain the study to them and invite them to participate in the study.

If the parents agreed to take part in the study the informed consent form was signed. The mothers were questioned regarding their pregnancy history and their child's health (see Addendum 1 and 2). Weight and height were recorded and head circumference was measured. Blood results were obtained from the child's file. The Bayley III was then administered.

A follow up date for three months time was arranged with the parents to be on the same day as their next clinic visit.

3.5.2. Three Month Follow Up

At three months follow up both groups were assessed again. Weight, height and head circumference were taken. History regarding the child's health was recorded. The Bayley III was then administered. A follow up appointment was then arranged for 3 months time.

For the HIV positive group CD4 counts, percentages and viral loads were recorded. The HAART regimen that the child was on was also recorded.

3.5.3. Six Month Follow Up

Weight, height and head circumference were taken. History regarding the child's health was recorded. The Bayley III was then administered.

For the HIV positive group CD4 counts, CD4 percentages and viral loads were recorded from the file. The HAART regimen that the child was on was also recorded.

At the final assessment the parents were given feedback on their child's performance in the Bayley III. If the child was found to be delayed according to the Bayley III they were referred to appropriate therapists (i.e.: physiotherapist, occupational therapists or speech therapists). If it was deemed necessary the patient was also referred to a dietician or social worker.

3.5.4. Measures to ensure adequate follow up

Due to the poor socioeconomic circumstances that the participants live in, compliance with appointments is poor. To ensure that participants attended their appointments the researcher would

phone the participant one week prior to their appointment. A text message (SMS) was sent to the participant the day before their appointment to remind them to come.

If the participant did not attend their appointment they were phoned on the same day to rearrange for a new appointment.

3.6 Ethical Considerations

Approval for this study was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical). Clearance certificate M10535 (See Addendum 3).

Permission was also obtained from the CEO at Rahima Moosa Mother and Child Hospital to conduct the study at the clinic (Addendum 4).

Written informed consent was obtained from the caregivers of the infants (Addendum 5 and 6). Infants were assigned a study number and their names did not appear on any documentation in order to assure anonymity.

The caregivers were reimbursed for transport when they attended the visit at 3 months follow up and 6 months follow up.

Feedback on the results found from the assessment was given to all the mothers at the final assessment. If it was found that the child would benefit from rehabilitation, an appointment was arranged for them with a physiotherapist, occupational therapist or speech therapist. If the caregiver expressed other concerns they were referred to either a social worker or dietician.

3.7 Data Analysis

Data was analysed using Stata 10.0/IC for Windows in consultation with a statitistician from Health Research Unit at the University of the Witwatersrand. Twenty seven participants were required in each group in order to detect a difference of 15 on the Bayley Scales of Infant and Toddler Development III

(Bayley III) when using a standard deviation of 15 and power of 90%. This allowed for a 20% drop out rate and had a confidence interval of ± 4.63.

Descriptive statistics were used to condense the raw data. Means and standard deviations were used to describe the data. Comparisons between the HIV positive and HIV exposed uninfected groups were compared using two sampled t tests with equal variance. Level of significance was set at 0.05. Change over time was determined by using a student's t-test and significance was set at 0.05.

The HIV positive group was then stratified according to there CD4 percentages at baseline. They were stratified into a group with CD4 percentages less than 25% and CD4 percentages of greater than 25%. A CD4 percentage of less than 25% is considered to indicate severe immune suppression (WHO, 2010). Comparisons between these two groups were then made using descriptive statistics.

An intention to treat analysis was done and all available data was analysed at every time point. Intention to treat analysis is considered to be the analysis of choice for studies of a pragmatic nature such as this one (Herbert et al, 2005).

The results of this study will be presented in chapter four.

Chapter 4

RESULTS

This chapter aims to present the results of the study. An intention to treat analysis was used to analyse the data. All available data was analysed at every time point.

4.1. Loss to follow up

In this study 56 HIV exposed infants under the age of 12 months were recruited. Of these 27 were HIV positive and 29 were HIV exposed uninfected (HEU) infants. The positive group was then stratified according to their CD4 percentage at baseline. Twelve had a CD4% of less than 25% and 15 had a CD4% of more than 25% at baseline.

Due to the nature of HIV as well as the poor socio-economic circumstances that many of the families face, a high loss to follow up was expected. The figure below represents the loss to follow up seen during the study period.

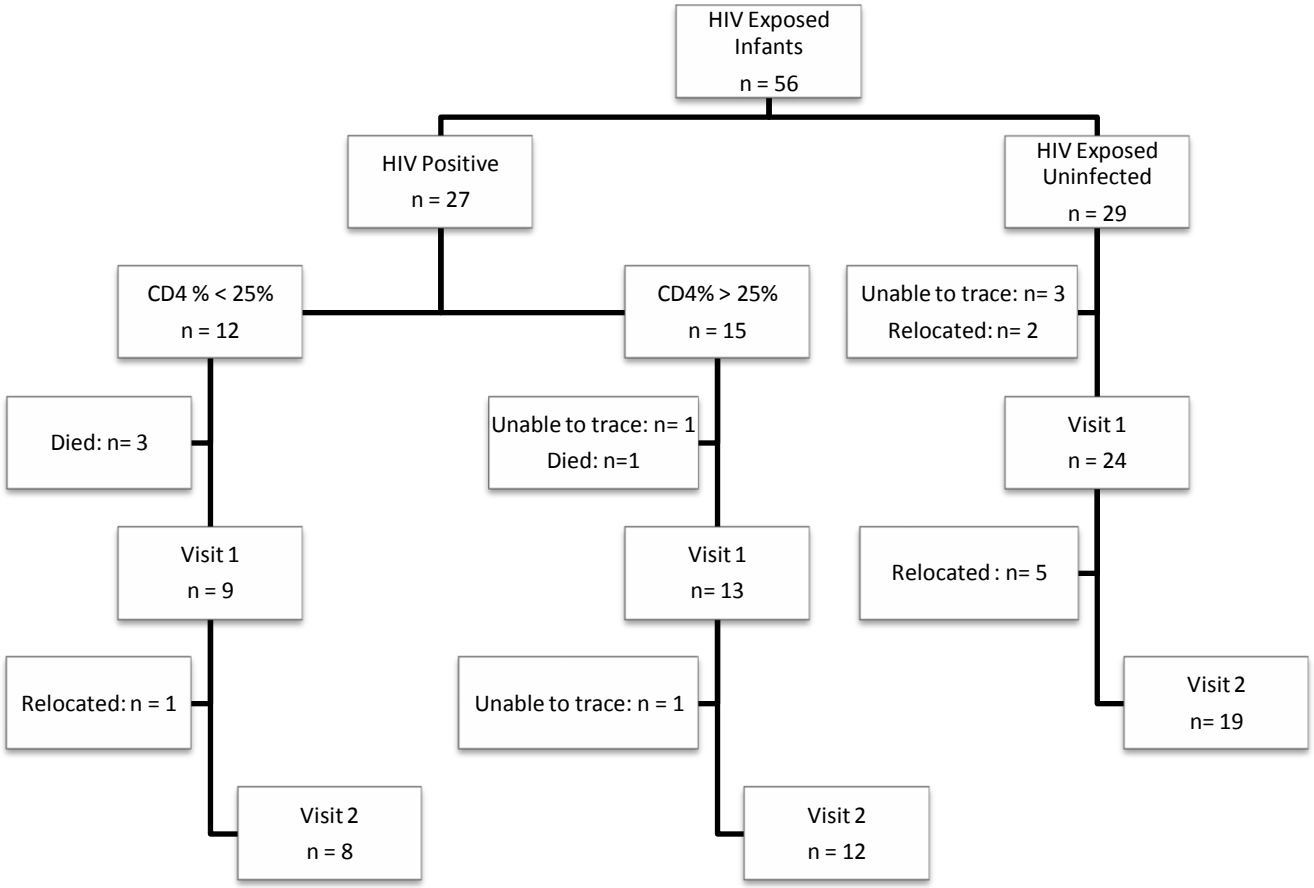


Figure 4.1 Loss to follow up

In this study 17 participants were lost to follow up. Loss to follow up occurred due to a variety of reasons.

The researcher was unable to trace five participants. Contact numbers for these participants no longer worked and the participants did not return to the Empilweni clinic and had defaulted on their treatment.

Eight participants relocated to different provinces during the course of the study. A far higher percentage of participants in the uninfected group relocated compared to the HIV positive group.

Four participants died during the course of the study. All four deaths occurred in the HIV positive group and prior to the 3 month follow up. This means that the infants died shortly after they had initiated HAART.

The total loss to follow up for this study was 30.36%.

4.2. Demographic Data

Demographic data was obtained from the demographic questionnaire that was administered as well as the questionnaire regarding pregnancy history. The data is presented in Table 4.1. The data is presented as means and standard deviations or numbers and percentages. Data between the HIV positive and HEU groups is compared using two sampled t-tests.

Table 4.1 Demographic information for the HIV positive and HIV exposed uninfected groups.

Variable	HIV Positive n = 27	HIV Exposed Uninfected n = 29	p value
	Mean (SD)	**Mean (SD)**	
Age (months)	4.87 (2.8)	3.35 (2.87)	0.05
Gestational Age (weeks)	39.93 (0.38)	40 (0)	0.30
Birth Weight (kg)	2.69 (0.57)	3.27 (0.53)	**0.00***
Variable	**Number (%)**	**Number (%)**	**P value**
Gender	Male: 11 (39.29%) Female: 16 (57.14%)	Male: 17 (60.71%) Female: 12 (42.86%)	0.18
NVP received	Yes: 17 (62.96%) No: 10 (37.04%)	Yes: 29 (100%) No: 0 (0%)	**0.00***
Feeding	Breastmilk: 11 (40.74%) Formula: 16 (59.26%)	Breastmilk: 2 (6.90%) Formula: 27 (93.10%)	**0.00***
Hospital Born at	RMH: 20 (74.07%) Other: 7 (25.93%)	RMH: 28 (96.55%) Other: 1 (3.45%)	**0.02***

The study population was young. Infants in the HIV positive group had a mean age of 4.87 (±2.8) and infants in the HIV exposed uninfected group had a mean age of 3.35 months (± 2.87). There was a significant difference for birth weight between the two groups (p = 0.00). The HIV positive group had a significantly lower birth weight when compared to the HIV exposed uninfected group. There was no significant difference in terms of males and females in the two groups (p = 0.18). A significant difference was seen in terms of infants who received NVP between the two groups. A hundred percent of the participants in the HIV exposed uninfected group received NVP compared to 62.96% of the participants in the HIV positive group (p = 0.00). Significantly more infants were breastfed in the HIV positive group compared to the HEU group (p=0.00). More of the HEU infants were born at Rahima Moosa Hospital compared to the HIV positive group (p = 0.02).

4.3. Maternal Characteristics

The maternal characteristics of the participants are presented in table 4.2. Data is presented as numbers and percentages.

Table 4.2 Maternal characteristics of mothers of HIV positive infants and HIV Exposed Uninfected infants

Variable		HIV Positive n = 27		HIV Exposed Uninfected n = 29		p value
		Number	Percentage	Number	Percentage	
ANC	Booked	20	74.07	28	96.55	**0.02***
	Unbooked	7	25.93	1	3.45	
AZT during pregnancy	Yes	9	33.33	20	68.97	**0.01***
	No	18	66.67	9	31.03	
HAART during pregnancy	Yes	6	22.22	7	24.14	0.87
	No	21	77.78	22	75.86	
NVP at onset of labour	Yes	16	59.26	23	79.31	0.10
	No	11	40.74	6	20.69	
Illnesses during pregnancy	Yes	7	25.93	4	13.79	0.25
	No	20	74.07	25	86.21	
Hospital Admissions during pregnancy	Yes	4	14.81	4	13.79	0.91
	No	23	85.19	25	86.21	
Variable		**Mean**	**SD**	**Mean**	**SD**	**p value**
CD4 Count Prior to delivery		461.58	187.66	412.71	232.83	0.44

Significantly more mothers who had uninfected infants received antenatal care compared to the mothers of infected infants (p = 0.02). Significantly more mothers of uninfected infants received AZT during pregnancy compared to mothers of infected infants (p=0.01). In both groups mothers had a similar number of hospital admissions and illnesses during pregnancy. There was similar use of HAART and NVP at onset of labour in both groups. CD4 counts of the mothers prior to delivery were similar in both groups.

4.4. Blood Results – HIV Positive Group

4.4.1. CD4 counts and CD4 Percentages at each visit

CD4 counts and CD4 percentages over the course of the study are presented in table 4.3. Data is presented as means and standard deviations. It is important to note that blood results were not always available for all the children at each visit. The researcher was reliant on information in the medical records of the children.

Table 4.3 CD4 counts and CD4 percentages at each visit

Variable	Baseline n = 26	Visit 1 n = 9	Visit 2 n = 17
	Mean (SD)	Mean (SD)	Mean (SD)
CD4 count	1322.96 (946.94)	1669.44 (906.91)	2328.53 (770.63)
CD4 %	27.51 (11.23)	26.48 (9.7)	33.01 (7.14)

The mean CD4 percentage at baseline was more than 25% and increased by the 6 month follow up to over 30%. Mean CD4 counts also increased over the study period

Table 4.4 depicts the change seen over time in CD4 counts and percentages in terms of p-values.

Table 4.4 Change in CD4 count and CD4 percentages over time presented by p-values.

Time Frame	CD4 Count	CD4 %
Baseline to Visit 1	0.35	0.81
Visit 1 to Visit 2	0.06	0.06
Baseline to Visit 2	**0.00***	0.08

There was a significant increase in CD4 count from baseline to Visit 2 (p = 0.00). No significant change over time was seen for CD4 percentage (p = 0.08).

4.4.2. Viral Loads

Table 4.5 shows the percentage of undetectable viral loads over time. Due to there being such a high variability in viral loads and due to the viral load numbers being so high, data is more understandable if presented in this format.

Table 4.5 Undetectable viral loads in HIV positive group over time

Time Frame	n	Undetectable Viral Load VL < 50 copies/mL	
		Number	Percentage
Baseline	26	0	0
Visit 1	21	1	4.76
Visit 2	17	4	23.53

Only one child had an undetectable viral load at visit 1. At visit 2 four infants (23.53%) had an undetectable viral load.

4.5. Medical Information

Data in terms of illnesses, hospital admissions, medications and if immunisations were up to date were extracted from the questionnaire administered at each visit. This data is presented in table 4.6. Data is presented in terms of numbers and percentages. T-tests were used to compare the two groups.

Table 4.6 Medical information at each visit for HIV positive and HIV exposed uninfected groups

Variable	Yes/No	HIV Positive		HIV Exposed Uninfected		P value
		Number	Percentage	Number	Percentage	
Baseline		**n = 27**		**n = 29**		
Illnesses	**Yes**	20	74.07	5	17.24	**0.00***
	No	7	25.93	24	82.76	
Hospital Admissions	**Yes**	12	44.44	2	6.9	**0.00***
	No	15	55.56	27	93.1	
Medication	**Yes**	8	29.63	8	27.59	0.87
	No	19	70.37	21	72.41	
Immunisations	**Yes**	27	100	27	93.10	0.17
	No	0	0	2	6.90	
Visit 1		**n = 22**		**n = 24**		
Illnesses	**Yes**	9	33.33	9	31.03	0.97
	No	13	48.15	15	51.72	
	Loss to f/u	5	18.52	5	17.24	
Hospital Admissions	**Yes**	2	7.41	0	0	0.32
	No	20	74.07	24	82.76	
	Loss to f/u	5	18.52	5	17.24	
Medication	**Yes**	6	22.22	5	17.24	0.87
	No	16	59.26	19	65.52	
	Loss to f/u	5	18.52	5	17.24	
Immunisations	**Yes**	20	74.07	24	82.76	0.32
	No	2	7.41	0	0	
	Loss to f/u	5	18.52	5	17.24	
Visit 2		**n = 20**		**n = 19**		
Illnesses	**Yes**	3	11.11	10	34.48	**0.04***
	No	17	62.96	9	31.03	
	Loss to f/u	7	25.93	10	34.48	
Hospital Admissions	**Yes**	1	3.70	1	3.45	0.78
	No	19	70.37	18	62.07	
	Loss to f/u	7	25.93	10	34.48	
Medication	**Yes**	1	3.70	1	3.45	0.78
	No	19	70.37	18	62.07	
	Loss to f/u	7	25.93	10	34.48	
Immunisations	**Yes**	20	74.07	19	65.52	0.49
	No	0	0	0	0	
	Loss to f/u	7	25.93	10	34.48	

At baseline the HIV positive group had significantly more illnesses (p = 0.00) and hospital admissions (p = 0.00) compared to the HIV exposed uninfected group. The illnesses included meningitis, bronchopneumonia, tuberculosis and gastroenteritis. At visit 2 the HIV exposed uninfected group had significantly more illnesses compared to the HIV positive group (p = 0.04). However, these were more common illnesses like a rhinitis or cough and were not as serious as the illnesses experienced by the HIV positive group.

4.6. HAART

All the children were initiated on the same regimen of HAART which included a combination of 3TC/ABC/Kaletra. All the children remained on this regimen except for one child who was started on 3TC/ABC/D4T at visit 2.

4.7. Anthropometric Data

Weights, heights and head circumference are presented in terms of z scores. Table 4.7 shows the mean z scores for both groups at baseline, visit 1 and visit 2. Comparisons between the groups were made using two sampled t-tests.

Table 4.7 Anthropometric Measurements at each visit for HIV Positive and HIV Exposed Uninfected Infants

Variable	HIV POSITIVE	HIV Exposed Uninfected	p value
	Mean (SD)	Mean (SD)	
Baseline			
	n = 27	n = 29	
Weight for age z score	-2.47 (1.93)	-0.002 (0.73)	**0.00***
Height for age z score	-3.19 (2.8)	-2.94 (1.60)	0.67
Weight for Height z score	-0.16 (2.75)	3.5 (2.44)	**0.00***
Head Circumference for age z score	-1.05 (1.32)	-0.86 (1.59)	0.62
Visit 1			
	n = 22	n = 24	
Weight for age z score	-1.15 (1.42)	0.18 (1.5)	**0.00***
Height for age z score	-2.07 (1.81)	-2.21 (1.72)	0.79
Weight for Height z score	0.27 (2.02)	2.22 (1.62)	**0.00***
Head Circumference for age z score	-0.36 (1.56)	0.21 (1.12)	0.16
Visit 2			
	n = 20	n = 19	
Weight for age z score	-0.35 (1.42)	0 (1.42)	0.45
Height for age z score	-0.82 (1.21)	-0.52 (1.58)	0.51
Weight for Height z score	0.12 (1.67)	0.14 (2.06)	0.98
HC for age z score	0.45 (1.46)	0.21 (1.07)	0.57

At baseline the HIV positive group had very low z scores for weight and height. The HIV positive group had significantly lower weight for age z scores when compared to the HIV exposed uninfected group (p=0.00). Weight for height z scores at baseline were also significantly different between the two groups (p = 0.00).

Height for both groups at baseline was similar (p = 0.67), however it was below 2SD of the norm.

At visit 1 weight for age and weight for height z scores were still significantly lower in the HIV positive group when compared to the HEU group. Height for age z scores were still 2SD below the norm for both groups.

By visit 2 anthropometric measurements had improved in both and the HIV positive and HEU groups had normal anthropometric measurements, with no significant differences between the two groups.

Table 4.8 presents the changes that occurred over time for mean weight for age z scores, mean height for age z-scores, mean weight for height z scores and mean head circumference for age z scores for the HIV positive group.

Table 4.8 Changes over time in anthropometric measurements for the HIV positive group (p-values)

	Baseline to Visit 1	Visit 1 to Visit 2	Baseline to Visit 2
Weight for Age	**0.01***	0.08	**0.00***
Height for Age	0.11	**0.01***	**0.01***
Weight for Height	0.55	0.79	0.70
Head Circumference for Age	0.10	0.09	**0.00***

In the HIV positive group a significant increase in weight for age and height for age z scores was seen over the course of the study.

Weight for age from baseline to visit 1 and baseline to visit 2 increased significantly (p= 0.01 and p = 0.00 respectively). Height for age started increasing significantly from visit 1 to visit 2 and from baseline to visit 2 (p = 0.01 and p = 0.01 respectively). Head circumference for age z scores increased significantly from baseline to visit 2 (p = 0.00).

Table 4.9 presents the changes that occurred over time for mean weight for age z scores, mean height for age z scores, mean weight for height z scores and mean head circumference for age z scores for the HEU group.

Table 4.9 Changes over time in anthropometric measurements for the HIV Exposed Uninfected group (p-values)

	Baseline to Visit 1	Visit 1 to Visit 2	Baseline to Visit 2
Weight for Age	0.56	0.69	0.99
Height for Age	0.12	**0.00***	**0.00***
Weight for Height	**0.03***	**0.00***	**0.00***
Head Circumference for Age	**0.01***	0.99	**0.01***

A significant increase in height for age and weight for height z scores were seen over time in the HEU group. Head circumference for age z scores in the HIV exposed uninfected group increased significantly from baseline to visit 1 ($p = 0.01$) and from baseline to visit 2 ($p = 0.01$).

4.8. Developmental Scores

The developmental scores for cognitive development, language development and motor development over time are presented in table 4.10. The data is presented as means and standard deviations. A score of less than 89 places the child in the below average category on the Bayley III and depicts a delay in the particular area of development.

Table 4.10 Developmental Scores for HIV Positive and HIV Exposed Uninfected Groups over time

Variable	HIV POSITIVE	HIV Exposed Uninfected	p - value
	Mean (SD)	Mean (SD)	
Baseline			
	n = 27	n = 29	
Cognitive Composite	86.11 (16.37)	93.97 (9.29)	**0.03***
Language Composite	87.85 (12.81)	100.26 (7.80)	**0.00***
Motor Composite	93.15 (19.32)	106.48 (11.63)	**0.00***
Visit 1			
	n=22	n = 24	
Cognitive Composite	82.5 (17.17)	97.08 (12.42)	**0.00***
Language Composite	85.45 (10.97)	97.25 (10.02)	**0.00***
Motor Composite	91.27 (15.91)	108.08 (13.13)	**0.00***
Visit 2			
	n = 20	n = 19	
Cognitive Composite	94.75 (14.09)	98.95 (10.61)	0.30
Language Composite	90.3 (1.93)	100.21 (10.06)	**0.00***
Motor Composite	93.7 (10.89)	105.58 (10.88)	**0.00***

At baseline the cognitive, language and motor composite scores in the HIV positive group were all significantly lower when compared to the HEU group. Similar results were found at visit 1. At visit 2 the HEU group had significantly higher scores for language and motor composite scores. There was no significant difference in cognitive composite scores between the groups at the second visit.

In the HIV exposed uninfected groups no mean composite scores indicated a delay. The HIV positive group had scores depicting a delay at baseline and visit 1 for cognitive and language development. At visit 2 no delay was detected in mean composite scores for cognitive, language and motor development, however language and motor composite scores were significantly lower in the HIV positive group when compared to the HEU group ($p = 0.00$ and $p = 0.00$ respectively).

Table 4.11 presents the receptive and expressive language scaled scores for the HIV positive and HEU. Data is presented as means and standard deviations.

Table 4.11 Receptive and Expressive Language Scaled Scores for the HIV Positive and HIV exposed uninfected groups over time

Variable	HIV POSITIVE	HIV Exposed Uninfected	p - value
	Mean (SD)	Mean (SD)	
Baseline			
	n = 27	n = 29	
Receptive Language	8.11 (2.62)	10.03 (1.5)	**0.00***
Expressive Language	7.67 (2.24)	10.03 (1.72)	**0.00***
Visit 1			
	n = 22	n = 24	
Receptive Language	8.09 (2.22)	10 (2.48)	0.09
Expressive Language	7.36 (1.53)	9.04 (1.81)	**0.00***
Visit 2			
	n = 20	n = 19	
Receptive Language	9.15 (2.73)	10.37(2.19)	0.13
Expressive Language	7.5(1.64)	9.68 (1.89)	**0.00***

Infants in the HIV positive group had lower scaled scores for expressive language when compared to receptive language at baseline, visit 1 and visit 2.

The HIV exposed uninfected group continuously had significantly higher scores for both receptive and expressive language at all visits.

Table 4.12 presents the fine and gross motor scaled scores for the HIV positive and HEU groups. Data is presented as means and standard deviations.

Table 4.12 Fine and Gross Motor Scaled Scores for the HIV Positive and HIV exposed uninfected groups over time

Variable	HIV POSITIVE		HIV Exposed Uninfected		p - value
	Mean	SD	Mean	SD	
Baseline					
	n = 27		n = 29		
Fine Motor	8.89	3.41	11.24	1.98	**0.00***
Gross Motor	8.56	3.88	10.86	2.25	**0.01***
Visit 1					
	n = 22		n= 24		
Fine Motor	9.18	3.2	11.42	2.83	**0.02***
Gross Motor	8.36	4.14	11.58	2.12	**0.00***
Visit 2					
	n = 20		n = 19		
Fine Motor	9.75	1.62	11.21	1.81	**0.01***
Gross Motor	8.1	2.45	10.58	2.32	**0.00***

Infants in the HIV positive group had lower scaled scores for gross motor function when compared to fine motor function at baseline, visit 1 and visit 2. The HEU group had significantly higher scaled scores for gross motor and fine motor function at all visits when compared to the HIV positive group.

Table 4.13 presents the changes in composite score for each facet of development over the course of the study in the HIV positive group. P-values are used to indicate the change.

Table 4.13 Developmental Changes over time for HIV positive group represented by p-values

	Baseline to Visit 1	Visit 1 to Visit 2	Baseline to Visit 2
Cognitive Composite Score	0.46	**0.02***	0.06
Language Composite Score	0.49	0.11	0.46
Motor Composite Score	0.72	0.57	0.91

No significant changes were seen over time for mean language composite scores and mean motor composite scores in the HIV positive group. A significant improvement was seen for the cognitive composite scores from visit 1 to visit 2 (p = 0.02) and the improvement approached significance from baseline to visit 2 (p = 0.06).

Table 4.13 presents the changes in composite score for each facet of development over the course of the study in the HIV exposed uninfected group. P-values are used to indicate the change.

Table 4.14 Developmental Changes over time for HIV exposed uninfected group represented by p-values

	Baseline to Visit 1	Visit 1 to Visit 2	Baseline to Visit 2
Cognitive Composite Score	0.30	0.61	0.09
Language Composite Score	0.22	0.34	0.98
Motor Composite Score	0.64	0.51	0.79

No significant changes were seen over the course of the study for mean cognitive, language and motor composite scores in the HIV exposed uninfected group.

Table 4.15 presents the percentage of infants with a delay at each time period for the HIV positive and HIV exposed uninfected groups. The infants were considered to be delayed if they fell in the low average, borderline and extremely low categories on the Bayley III.

Table 4.15 Percentage of infants delayed at each visit for developmental outcomes

Outcome Measure	Baseline		Visit 1		Visit 2	
	HIV Positive n = 27	HIV Exposed Uninfected n = 29	HIV Positive n = 22	HIV Exposed Uninfected n = 24	HIV Positive n = 20	HIV Exposed Uninfected n = 19
Cognitive Function	48.15	31.03	59.09	16.67	30	10.53
Language Function	51.85	10.34	63.34	12.50	45	5.26
Motor Function	29.63	10.34	40.91	8.33	40	0

At all time periods, there were a greater percentage of infants with delay for cognitive, language and motor function in the HIV positive group.

The percentage of children delayed for cognitive, language and motor function increased from baseline to visit 1. At visit 2 the percentage of children delayed for cognitive and language development had decreased in the HIV positive group, however motor delay still remained high when compared to baseline.

At visit 2 no HIV exposed uninfected infants had a motor delay, whereas 40% of the infants in the HIV positive group had a motor delay.

4.9. Results for infants in HIV Positive group after stratifying according to CD4 percentage at baseline

In order to analyse the results more closely in the HIV positive group, the infants in this group were stratified according to their CD4 percentages at baseline. They were either in a group who had a CD4% of less than 25% or a CD4% greater than 25%. These results should be viewed with care as the sample sizes are small and only general observations can be made.

4.9.1. Blood Results

Table 4.16 presents the blood results for the stratified sample of HIV positive infants.

Table 4.16 CD4 counts and CD4 percentages at each visit for stratified groups

	CD4% < 25%	CD4% > 25%	p value
	Mean (SD)	Mean (SD)	
Baseline			
	n = 12	n = 14	
CD4 Count	696.42 (709.52)	1860 (797.76)	**0.00***
CD4%	18.15 (5.2)	35.53 (8.34)	**0.00***
Visit 1			
	n = 6	n = 3	
CD4 Count	1704.33 (495.43)	1599.67 (1632.59)	0.44
CD4 %	31.10 (6.84)	17.25 (8.23)	**0.02***
Visit 2			
	n = 7	n = 10	
CD4 Count	2418.43 (774.71)	2265.6 (803.1)	0.35
CD4 %	31.17 (4.65)	34.3 (8.46)	0.20

At baseline the CD4% < 25% group had significantly lower CD4 counts and CD4 percentages when compared to the CD4% > 25% group. At Visit 1 the CD4% > 25% group had a significantly lower CD4% compared to the CD4% < 25% group. At Visit 2 there were no significant differences between the groups for CD4 counts and CD4 percentages. Over the course of the study CD4 counts in the CD4% < 25% group increased.

These results should be viewed with care as blood results at each visit were not available for all the children especially at visit 1. The sample with available blood results was small.

Table 4.17 presents the change over time in CD4 counts and CD4 percentages for the HIV positive group with CD4% < 25% at baseline.

Table 4.17 Change in CD4 count and CD4 percentages over time presented by p-values for HIV positive infants with CD4% of < 25% (p-values)

Time Frame	CD4 Count	CD4 %
Baseline to Visit 1	**0.03***	**0.01***
Visit 1 to Visit 2	0.07	0.44
Baseline to Visit 2	**0.00***	**0.00***

There was a significant increase in CD4 count and CD4 percentage over time for the CD4% < 25% group. No significant change was seen from visit 1 to visit 2 for CD4 percentage (p = 0.44) and CD4 Count (p = 0.07).

Table 4.17 presents the change over time in CD4 counts and CD4 percentages for the HIV positive group with CD4% > 25% at baseline.

Table 4.18 Change in CD4 count and CD4 percentages over time presented by p-values for HIV positive infants with CD4% of > 25% (p-values)

Time Frame	CD4 Count	CD4 %
Baseline to Visit 1	0.34	0.11
Visit 1 to Visit 2	0.19	0.25
Baseline to Visit 2	0.13	0.11

No significant changes were seen for CD4 count and CD4 percentage over the course of the study for the CD4% > 25% group.

4.9.2. Anthropometric Measurements

Weights, heights and head circumference are presented in terms of z-scores. Table 4.19 shows the mean z scores for HIV positive group that was stratified according to CD4% at baseline over time. Comparisons between the groups were made using two sampled t-tests.

Table 4.19 Anthropometric Measurements at each visit for HIV Positive with CD4% < 25% and CD4% >25%

Variable	HIV Positive CD4% < 25%	HIV Positive CD4% > 25%	P value
	Mean (SD)	Mean (SD)	
Baseline			
	n = 12	n = 15	
Weight for age z score	-3.19 (2.19)	-1.90 (1.52)	**0.04***
Height for age z score	-3.68 (3.5)	-2.80 (2.14)	0.21
Wt for Ht z score	-1.28 (2.85)	0.66 (2.45)	**0.04***
HC for age z score	-1.01 (1.54)	-1.08 (1.17)	0.45
Visit 1			
	n = 9	n = 13	
Weight for age z score	-1.28 (1.2)	-0.16 (1.61)	0.36
Height for age z score	-2.34 (1.1)	1.89 (2.21)	0.29
Wt for Ht z score	0.15 (1.53)	0.36 (2.4)	0.41
HC for age z score	-0.45 (1.52)	-0.31 (1.65)	0.42
Visit 2			
	n = 8	n = 12	
Weight for age z score	-0.7 (1.33)	-0.12 (1.59)	0.19
Height for age z score	-0.92 (1.28)	-0.76 (1.21)	0.39
Wt for Ht z score	-0.3 (1.01)	0.41 (1.99)	0.18
HC for age z score	0.65 (1.67)	0.31 (1.36)	0.31

At baseline the CD4% < 25% group had low weight for age z scores. Weight for age z scores were significantly lower in the CD4% < 25% group compared to those in the CD4% > 25% group (p = 0.04). Weight for height z scores for the CD4% < 25% group were significantly lower compared to the CD4% > 25% group (p = 0.04).

Z-Scores improved in both groups for all anthropometric measurements over the course of the study.

At visit 1 and visit 2 no significant differences were seen between the groups for anthropometric measurements.

Table 4.20 presents the change over time for anthropometric measurements for the HIV Positive group with CD4% < 25%.

Table 4.20 Changes over time in anthropometric measurements for the HIV positive with CD4% < 25% (p-values)

	Baseline to Visit 1	Visit 1 to Visit 2	Baseline to Visit 2
Weight for Age	0.06	0.20	**0.03***
Height for Age	0.20	**0.04***	**0.02***
Weight for Height	0.18	0.10	0.27
Head Circumference for Age	0.08	**0.00***	**0.00***

Significant improvements were seen in the CD4% < 25% group for weight for age z scores, height for age z scores and head circumference for age z scores over the course of the study. No significant changes were seen for weight for height z scores.

Table 4.20 presents the change over time for anthropometric measurements for the HIV Positive group with CD4% < 25%.

Table 4.21 Changes over time in anthropometric measurements for the HIV Positive with CD4% > 25% (p-values)

	Baseline to Visit 1	Visit 1 to Visit 2	Baseline to Visit 2
Weight for Age	**0.04***	**0.01***	**0.01***
Height for Age	0.21	0.06	**0.01***
Weight for Height	**0.04***	0.49	0.41
Head Circumference for Age	0.45	0.15	**0.00***

Significant improvements for weight for age z scores were seen for the CD4% > 25% group from baseline to visit 1 (p= 0.04), visit 1 to visit 2 (p = 0.01) and baseline to visit 2 (p = 0.01). Significant increases were

seen for height for age from visit 1 to visit 2 (p = 0.06) and baseline to visit 2 (p = 0.01). Weight for height significantly increased from baseline to visit 1 (p = 0.04). Head circumference for age z scores significantly increased from baseline to visit 2 (p = 0.00).

In general all anthropometric measurements improved significantly over the course of the study.

4.9.3. Developmental Scores

The developmental scores for cognitive development, language development and motor development over time are presented in table 4.22. The data is presented as means and standard deviations. A score of less than 89 places the child in the low average, borderline or extremely low category on the Bayley III and depicts a delay in the particular area of development.

Table 4.22 Developmental Scores for HIV Positive infants with CD4% < 25% and CD4% > 25%

Variable	HIV POSITIVE CD4% < 25%	HIV Positive CD4% > 25%	p - value
	Mean (SD)	Mean (SD)	
Baseline			
	n = 12	n = 15	
Cognitive Composite	77.08 (17.64)	93.33 (11.27)	**0.00***
Language Composite	80.25 (13.59)	93.93 (10.33)	**0.00***
Motor Composite	82.08 (20.85)	102 (12.76)	**0.03***
Visit 1			
	n = 9	n = 13	
Cognitive Composite	80 (12.75)	84.23 (19.98)	0.29
Language Composite	82.11 (11.2)	87.77 (10.64)	0.12
Motor Composite	88.44 (10.79)	93.23 (18.84)	0.25
Visit 2			
	n = 8	n = 12	
Cognitive Composite	88.75 (15.29)	98.75 (12.27)	0.06
Language Composite	85.88 (8.79)	93.25 (7.51)	**0.03***
Motor Composite	90.25 (8.45)	96 (12.05)	0.13

Throughout the course of the study the CD4% < 25% group had very low scores for all developmental outcomes.

The trend was that children with higher CD4 percentages had better scores for all facets of development.

At baseline the CD4% < 25% group had significantly lower scores for cognitive (p = 0.00), language (p=0.00), and motor (p = 0.03) development compared to the CD4% > 25% group.

At visit 1 there were no significant differences between the groups for developmental scores.

At visit 2 the CD4% > 25% group had significantly higher scores for language development (p = 0.03).

Table 4.23 presents the changes that occurred over time for mean cognitive, language and motor composite scores in the HIV Positive group with CD4% < 25%.

Table 4.23 Developmental Changes over time for HIV positive with CD4% < 25% represented by p-values

	Baseline to Visit 1	Visit 1 to Visit 2	Baseline to Visit 2
Cognitive Composite Score	0.38	0.05	0.05
Language Composite Score	0.36	0.15	0.39
Motor Composite Score	0.21	0.41	0.14

Significant improvements were seen in the CD4% < 25% group for cognitive composite scores from visit 1 to visit 2 (p = 0.05) and from baseline to visit 2 (p = 0.05). No significant changes were seen for language and motor composite scores over time in this group.

Table 4.24 presents the changes that occurred over time for mean cognitive, language and motor composite scores in the HIV Positive group with CD4% > 25%.

Table 4.24 Developmental Changes over time for HIV Positive group with CD4% > 25% represented by p-values

	Baseline to Visit 1	Visit 1 to Visit 2	Baseline to Visit 2
Cognitive Composite Score	**0.03***	**0.01***	0.25
Language Composite Score	0.07	0.07	0.44
Motor Composite Score	**0.04***	0.35	0.05

A significant decrease in cognitive composite score was seen from baseline to visit 1 (p= 0.03) in the CD4% > 25% group. This score then significantly increased from visit 1 to visit 2 (p= 0.01). A significant decrease was also seen in the motor composite score from baseline to visit 1 (p=0.04), this score did not increase significantly from visit 1 to visit 2 (p = 0.35).

Table 4.25 presents the percentage of infants with a delay at each time period for the HIV positive and HIV exposed uninfected groups. The infant was considered to be delayed if they fell in the low average, borderline and extremely low categories on the Bayley III.

Table 4.25 Percentage of infants delayed at each visit for developmental outcomes

Outcome Measure	Baseline		Visit 1		Visit 2	
	HIV Positive CD4% < 25%	HIV Positive CD4% > 25%	HIV Positive CD4% < 25%	HIV Positive CD4% > 25%	HIV Positive CD4% < 25%	HIV Positive CD4% > 25%
Cognitive Function	66.67	33.33	66.67	53.85	50	16.67
Language Function	75	33.33	77.78	53.85	62.5	33.33
Motor Function	50	13.33	55.56	30.77	50	33.33

The CD4% < 25% group consistently had a greater percentage of infants with delay in all facets of development compared to the CD4% < 25% group.

The percentage of infants in the CD4% > 25% group with delay increased from baseline to visit 1 in all facets of development. The percentage of infants in the CD4% > 25% group with delay then decreased from visit 1 to visit 2 for cognitive and language function.

4.10. Conclusion

The results for this study show that children with HIV are at more risk for delay in all facets of development when compared to HIV exposed uninfected infants. Even when children initiate HAART, developmental scores do not improve significantly. HIV positive infants who have CD4 percentages of less than 25% have significantly lower developmental scores when compared to HIV positive infants with CD4 percentages of more than 25%.

HIV positive infants have lower weight for age and height for age z scores when compared to HIV exposed uninfected infants. Over time anthropometric scores improved significantly and by six months of follow up there were no significant differences seen between the HIV positive group and HEU group.

At baseline the HIV positive group had significantly more illnesses and hospital admissions when compared to the HIV exposed uninfected group. By six months follow up no significant differences were seen between the two groups.

The results of this study will be discussed in chapter five.

Chapter 5

DISCUSSION

The results of the study will be discussed in detail in this chapter. The limitations of the study will be discussed. Recommendations for changes in clinical practice and for future research will also be made.

5.1. Neurodevelopment of HIV positive infants

5.1.1. Cognitive Development

The HIV positive group had significantly lower scores for cognitive development at baseline and visit one when compared to the HIV exposed uninfected group. This is depicted in Figure 5.1. Several other studies have showed that HIV positive children tend to score significantly lower for cognitive function when compared to HIV exposed uninfected infants and healthy controls (Burns et al, 2008; Van Rie et al, 2008; Tahan et al, 2006; Blanchette et al, 2001; Bruck et al, 2001; Knight et al, 2000; Drotar et al, 1997; Pollack et al, 1996; Boivin et al, 1995; Chase et al, 1995; Gay et al, 1995; Nozyce et al, 1994).

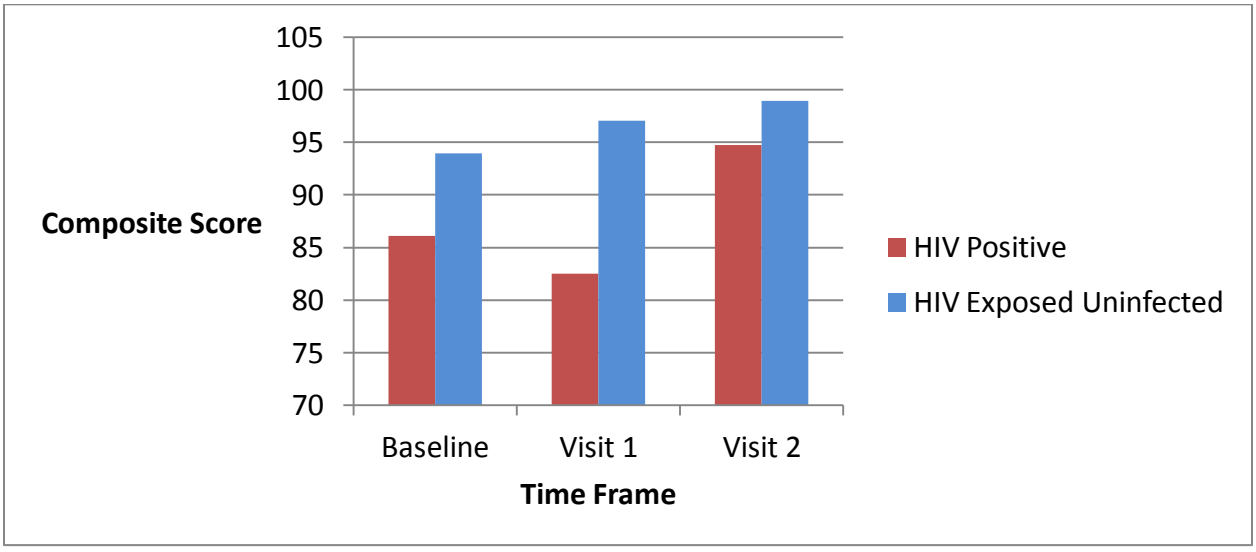


Figure 5.1. Bar graph depicting cognitive composite scores for HIV positive and HIV Exposed Uninfected groups over time

When looking at two South African studies that used an earlier edition of the Bayley Scales of Infant Development, the percentage of infants presenting with cognitive delay is far higher than in this study (Potterton et al 2009b; Ballieu and Potterton 2008). In Potterton et al (2009b) 78% of the sample had delayed cognitive development, Baillieu and Potterton (2008) showed that 97.5% of HIV infected children had a cognitive delay. In the current study at baseline 48.15% of the HIV positive infants had a cognitive delay and at six months follow up 30% of the HIV positive infants had a cognitive delay. Mean composite scores for cognitive development were also higher in this study. This may indicate that care for HIV children is improving and appears to be having a positive impact on cognitive development. When Potterton et al (2009b) and Ballieu and Potterton (2008) conducted their studies very few of their participants were receiving HAART. Criteria for initiating HAART changed in 2010. All children under the age of one year are initiated on HAART regardless of their CD4 count. Therefore, all the HIV infected children in this study were receiving HAART.

At visit two there were no significant differences between the two groups for mean cognitive composite scores. Van Rie et al (2009) found that at baseline their HIV positive group scored significantly lower for cognitive function when compared to the HIV exposed uninfected infants, but by 12 months of follow-up the HIV positive group had similar scores to the HIV exposed uninfected group. A similar finding can be noted in this study - no significant differences were seen between the two groups by six months follow-up.

Over the course of the study cognitive composite scores increased significantly from visit one to visit two ($p = 0.0161$) and the scores fell within normal ranges. The children had been on HAART for at least 6 months at this stage and this may explain the increase in scores seen. From baseline to visit one there was a slight decrease in the mean cognitive composite score that was not significant, however this could be related to high viral loads continuing to persist and high viral loads still being present in the central nervous system (CNS). Other studies have noted that cognitive function tends to decline over time (Pollack et al, 1996; Chase et al, 1995; Gay et al, 1995; Nozyce et al, 1994). This was not noted in this study. The authors of the various studies hypothesized that a decline was seen in cognitive scores due to a language barrier being present as cognitive items became more difficult and as they relied more heavily on language (Gay et al, 1995). Due to this study's population being so young the decline in scores from baseline to visit one could not be attributed to a language barrier. Wolters et al (1997) found that cognitive function stayed stable over time with no significant changes even if the child was on ARV's.

Two case studies reported improvement in cognitive function after HAART was initiated (Silva et al, 2009; Tepper et al, 1998). Thomaidis et al (2010) also found that cognitive deficits continue to persist even with HAART. Two reviews have reported that cognitive deficits continue to persist even when children are initiated on HAART (Burns et al, 2008; Van Rie et al, 2007).

The severity of delay of cognitive function has been associated with lower CD4 counts and higher viral loads as well as with growth failure (Potterton et al, 2009b; Pearson et al, 2000; Pollack et al, 1996; Chase et al, 1995; Newell et al 1995). During the course of this study growth as well as immune function in the HIV positive group improved and this may have resulted in the increase seen in mean cognitive composite scores.

There was a far higher percentage of infants delayed for cognitive development at baseline (48.15%), visit one (59.09%) and visit two (30%) compared to the HIV exposed uninfected group. From baseline to visit one the percentage of infants that were delayed in the HIV positive group increased. Once again this may be related to viral loads were not yet being adequately suppressed and a high viral loads still bring present in the CNS.

When the HIV positive group was stratified according to CD4 percentages at baseline it was found that the group with CD4% < 25% (n = 12) had significantly lower mean cognitive composite scores at baseline compared to the group with CD4% > 25% (n= 15). At visit one and visit two there was no significant difference for mean cognitive composite scores between the two groups. At each visit there was a higher percentage of children with cognitive delay in the CD4% < 25% group compared to the CD4% > 25% group. The percentage of children delayed in both groups had decreased by visit two and only 16.67% of children in the CD4% > 25% group had a cognitive delay.

Significant improvements were seen in the group with CD4% < 25% from visit one to visit two and baseline to visit two. In the CD4% > 25% group a significant decrease in cognitive composite score was seen from baseline to visit 1 but the score improved significantly from visit one to visit two.

It appears that CD4 percentage plays a role in cognitive development. The higher the CD4 percentage when initiating HAART the better the cognitive outcome. Cognitive outcome has been associated with CD4 counts as well as viral loads (Potterton et al 2009b; Pearson et al, 2000; Pollack et al 1996; Chase et

al, 1995; Newell et al, 1995). Poorer CD4 counts are related to worse the cognitive outcome. Therefore, it is essential that infants who are HIV positive are detected early in order for HAART to be initiated and to prevent further immune compromise so that cognitive function is maintained and improved upon.

It appears that HAART may have a positive effect on improving cognitive function in children with HIV. This result is positive when compared to other results that have not shown a significant improvement in cognitive function over time in children with HIV on HAART. Children with lower CD4 percentages tend to function worse cognitively; therefore, the early initiation of HAART is essential in order to preserve cognitive function. If cognitive function is not preserved early on, myelination in the CNS may be affected and the brain may not be protected from an early stage. This may lead to catastrophic consequences as the child ages.

5.1.2. Language Development

Mean language composite scores were significantly lower at baseline, visit one and visit two for the HIV positive group when compared to the HIV exposed uninfected group. This is depicted in figure 5.2 below. At each visit there was always a higher percentage of HIV positive infants with language delay compared to the HIV exposed uninfected infants.

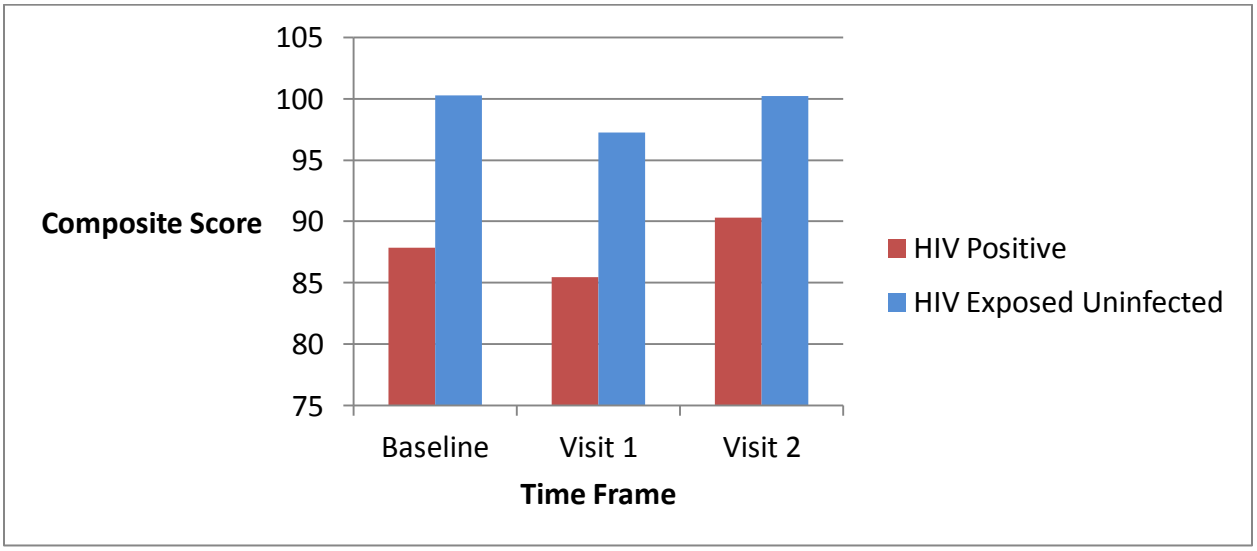


Figure 5.2. Bar graph depicting language composite scores for HIV positive and HIV Exposed Uninfected groups over time

Several studies have shown that language is delayed in HIV positive infants (Brackis-Cott et al, 2009; Van Rie et al, 2008; Coplan et al, 1998; Wolters et al, 1997; Boivin et al, 1995). Baillieu and Potterton (2008) found that 82.5% of their sample had a language delay. In this study, at baseline, 51.85% of the sample had a language delay and at visit two 45% had a language delay. This is far lower than in Baillieu and Potterton's study. In their study very few infants had access to ARV's and their sample was older. In the current study all the children were on HAART at visit two, therefore improved care may be resulting in fewer HIV positive children with a language delay.

In the HIV positive group the percentage of infants with a language delay increased from baseline (51.85%) to visit one (63.34%) and then decreased from visit one (63.34%) to visit two (45%). This may be due to the fact that from baseline to visit one only a period of three months had elapsed, high viral loads may still be present especially in the CNS which would contribute to the language delay. At visit two the percentage of infants with a language delay had decreased and this may indicate that HAART is starting to take effect, however it is important to note that no significant increases were seen in the mean language composite scores over this time period. The HIV positive group's scores remained significantly lower when compared to the HIV exposed uninfected group. Therefore, HAART may not be effective in improving language function but may prevent it from deteriorating as no significant decrease in scores was seen over time. This finding is similar to that of Wolters et al (1997) who found no significant changes over time for language function.

Other studies have shown that as HIV positive children get older language function tends to decline (Coplan et al, 1998; Wolters et al 1997). This however was not seen in this study; therefore HAART may be effective in preventing a decline in language function.

It has been found that language development is related to the severity of disease stage as well as CD4 counts and viral loads (Pearson et al, 2000; Newell et al, 1995). Over time in this study CD4 counts improved and may have contributed to stabilisation of language function being detected.

Language development is also dependent on motor function and cognitive development (Coplan et al, 1998). In this study both cognitive and motor function were delayed and may have contributed to the language delay seen.

A lower percentage of children with delay were seen in this study at baseline, visit one and visit two when compared to other South African studies (Potterton et al, 2009b). This is a positive finding. It may mean that care of HIV infected infants is slowly improving and this may be contributing to improved language performance. However, this finding should be viewed with care as the study population was far younger in this study.

At each assessment in this study the HIV positive group had lower expressive language scaled scores compared to receptive language scaled scores. This is similar to findings from other studies (Baillieu and Potterton, 2008; Foster et al, 2006; Wolters et al, 1997). The reason for expressive language being more delayed than receptive language may be due to the fact that expressive language development relies on motor development (Coplan et al, 1998). Motor development in the HIV positive group in this study was delayed and therefore may have contributed to the delay seen in expressive language.

When the HIV positive group was stratified according to CD4 percentages at baseline it was found that the group with CD4% < 25% had significantly lower mean language composite scores at baseline and visit two compared to the group with CD4% > 25%. At visit one there were no significant differences for mean language composite scores between the two groups. The language composite score in the CD4% > 25% group had decreased. This decrease may be related to high viral loads still being present in the CNS and HAART may not yet have fully taken effect.

At each visit there was a higher percentage of children with language delay in the CD4% < 25% group compared to the CD4% > 25% group. The percentage of children delayed in the CD4% < 25% group had decreased by visit two. The percentage of children delayed in the CD4% > 25% group had increased at visit one but then by visit two had decreased again to what it was at baseline.

No significant improvements were seen throughout the course of the study in both groups. Therefore, HAART may not be effective in improving language function. However, scores did not decrease significantly either, so HAART may be effective in maintaining language function.

It appears that CD4 percentage plays a role in language development. The higher the CD4 percentage when initiating HAART the better the language outcome. Language function is associated with disease severity, CD4 counts and viral loads (Potterton et al 2009b; Pearson et al, 2000; Pollack et al 1996; Chase

et al, 1995; Newell et al, 1995). This has been shown in this study as well. In this study the higher the CD4 percentage at baseline the better the language function. Therefore, it is essential that infants who are HIV positive are detected early in order for HAART to be initiated and to prevent further immune compromise so that language function can be maintained.

It appears that HAART does not result in significant improvements in language function over time. However, language did not deteriorate in this study; therefore HAART may be effective in preventing further declines in language. It is still important to note that even though no significant declines were seen in language function, language scores were still significantly lower when compared to the HIV exposed uninfected group, therefore HIV results in language delay that continues to persist despite the use of HAART. Other intervention is required in order for language function to improve.

5.1.3. Motor Development

At baseline, visit one and visit two mean motor composite scores were significantly lower in the HIV positive group when compared to the HIV exposed uninfected group. This is depicted in figure 5.3. Several studies have shown that motor development is affected in HIV positive children (Baillieu and Potterton, 2008; Foster et al, 2006; McGarth et al, 2006; Pearson et al, 2000; Armstrong et al, 1993).

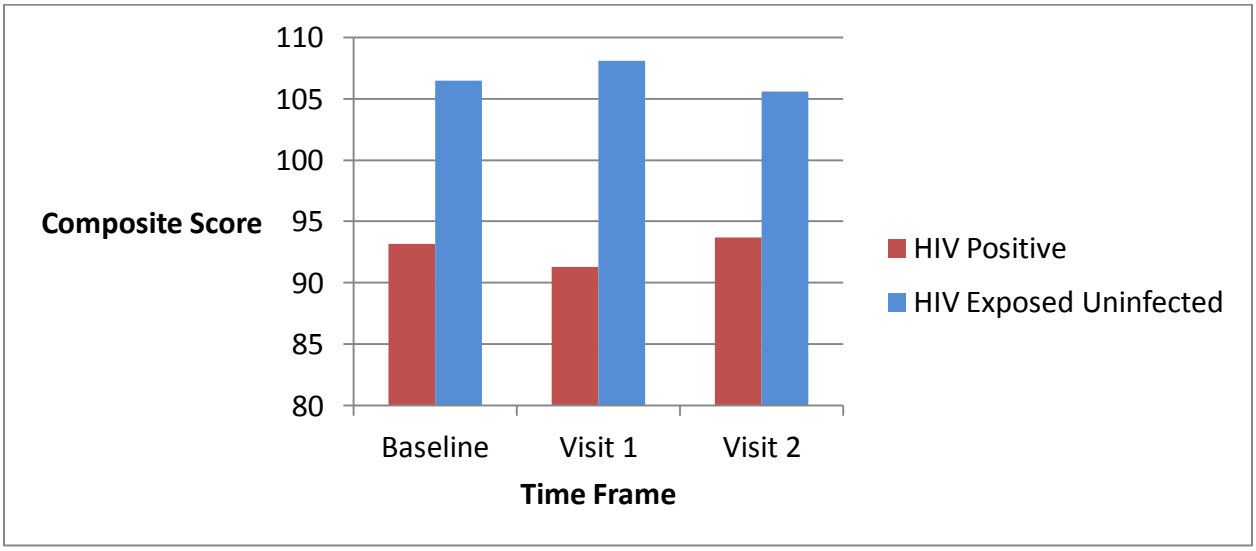


Figure 5.3. Bar graph depicting motor composite scores for HIV positive and HIV Exposed Uninfected groups over time

In two South African studies the frequency of motor delay was found to be higher than 80% (Potterton et al, 2009b; Baillieu and Potterton, 2008) and in another study 66% of HIV positive infants had a motor delay (Ferguson and Jelsma, 2009). In the current study at baseline there were 29.63% of children with a motor delay and at visit two 40% of HIV positive infants had a motor delay. This is far lower than reported in other studies however, similar to the results reported in Potterton and Eales (2001). This study also had very young infants.

Motor development appears to decline over time (Burns et al, 2008; Pollack et al, 1996; Nozyce et al, 1994). In this study no significant changes were seen over time for mean motor composite scores in the HIV positive group. No improvement was seen in mean motor composite scores and this may indicate that HAART has no effect on motor development. However, no decline was seen in scores, therefore HAART may prevent motor function from deteriorating in HIV positive infants.

At baseline, visit one and visit two there was a higher percentage of HIV infected children presenting with delay compared to the HIV exposed uninfected group. The percentage of delay increased from baseline (29.63%) to visit one (40.91%) and did not decrease from visit one to visit two as seen with cognitive and language development. This may indicate that motor development is more severely affected than cognitive and language development. Several studies have reported that motor development appears to be more severely affected than other facets of development (Baillieu and Potterton 2008; Foster et al, 2006; Drotar et al, 1997). The reason that motor development declines over time may be explained by the requirements in the standardised tests that are administered. As the child gets older the test items in the Bayley III become more challenging. More proximal stability is required as well as more strength. Many of the items are now performed against gravity. It has been postulated that often function is poor in HIV positive children in activities that require postural stability, motor co-ordination and eccentric strength (Baillieu and Potterton, 2008; Potterton and Eales, 2001). It is important to note that the test has been normed on healthy children, therefore a decline in scores may be related to a deterioration in motor function. Also the HIV exposed uninfected group did not deteriorate in terms of motor function, thus HIV appears to influence motor development.

Motor developmental delay is also associated with severity of disease stage; CD4 counts and viral loads as well as growth (Potterton et al 2009b; Abubaker et al, 2009; Foster et al 2006; Pearson et al, 2000; Boivin et al, 1995; Chase et al, 1995; Nozyce et al, 1994)

At each assessment in the HIV positive group, gross motor scaled scores were lower than fine motor scaled scores. Several studies have also shown this (Jelsma et al, 2011; Baillieu and Potterton, 2008; Van Rie et al, 2007; Msellati et al, 1993). The reason for gross motor function being more delayed than fine motor function is because HIV positive children are often stunted which impacts on gross motor performance, they have decreased strength as well as tone abnormalities which contribute to gross motor delay (Abubaker et al, 2009; Potterton et al, 2009b; Baillieu and Potterton, 2008).

When the HIV positive group was stratified according to CD4 percentages at baseline it was found that the group with CD4% < 25% had significantly lower mean motor composite scores at baseline compared to the group with CD4% > 25%. At visit one and visit two there were no significant differences for mean motor composite scores between the two groups. At each visit there was a higher percentage of children with motor delay in the CD4% < 25% group compared to the CD4% > 25% group. The percentage of children delayed in both groups had not decreased by visit two. The percentage of children with motor delay in the CD4% > 25% group had increased to 33.33% from baseline percentage of 13.33%. This may indicate that motor function is more severely affected than language and cognitive function in infants with HIV. This finding has been reported in several other studies (Baillieu and Potterton 2008; Foster et al, 2006; Drotar et al, 1997).

No significant improvements were seen in the CD4% < 25% for motor function through the course of the study. In the CD4% > 25% group a significant decrease in motor composite scores were seen from baseline to visit one and baseline to visit two. Once again motor function may be more severely affected than language function in HIV positive infants.

It appears that CD4 percentage does not play such a huge role in motor development. Initially infants with higher CD4 percentages perform better, but once initiated on HAART motor performance is similar regardless of CD4 percentage.

It appears that HAART does not have an effect in improving mean motor composite scores in HIV positive infants. No significant improvements or declines were seen over time therefore it may protect the child from regressing in terms of motor development. However, infants with a CD4% > 25% had a significant decline in motor scores. This result should be viewed with care as the sample was extremely

small. As time passed a higher percentage of infants became delayed in motor development. Clearly there is a need for a different sort of intervention.

5.2. HAART Regimens and HIV Encephalopathy

The children in this study were initiated on a regimen which included a combination of 3TC/ABC/Kaletra. The children remained on this regimen except for one child who was started on 3TC/ABC/D4T at visit 2. Patel et al (2009) discuss the various CNS penetrating ARVs in their study. According to them 3TC has a medium CNS penetration scale. ABC and Kaletra (Lopinavir/Ritonavir)r has a high CNS peneratiom scale. This means that the ARV's the children in this study were receiving were able to cross the blood brain barrier and should therefore help to decrease viral loads present in the CNS thereby minimising damage from HIV.

5.3. Development of the HIV Exposed Uninfected Child

The HIV exposed uninfected group had normal composite scores for cognitive, language and motor development at all time points in the study. There were no significant changes in development over time in the HIV positive group and fewer HIV exposed uninfected infants had delays compared to the HIV positive group.

Several studies have shown that development is normal in HIV exposed uninfected infants (Van Rie et al, 2008; Blanchette et al, 2001; Bruck et al, 2001; Boivin et al, 1995). Alimenti et al (2006) compared neurodevelopment in HIV exposed and HIV unexposed children and when controlling for substance abuse found no significant differences between the two groups. The data in this study shows that HIV exposed uninfected infants obtain normal scores on the Bayley III and are not as delayed as HIV positive infants.

5.4. Anthropometric outcomes in HIV positive infants

HIV infected children have problems with growth (Isanaka et al, 2009). Growth failure often becomes apparent early on and may continue to persist without adequate intervention (Isanaka et al, 2009; Miller

et al, 2001). Growth failure in HIV positive infants is often due to increased energy requirements, gastrointestinal disturbances and infections, mal-absorption problems and endocrine changes (Isanaka et al, 2009; Miller et al, 2001). Growth failure is often associated with poorer immune function, disease progression and increased mortality (Isanaka et al, 2009).

5.4.1. Weight

In this study the HIV positive group had very low weight for age z scores at baseline and scores were well below two standard deviations of the norm. Therefore, the infants in this group were malnourished. At baseline and at visit one the HIV positive group had significantly lower weight for age z scores when compared to the HIV exposed uninfected group. By visit two significant increases in weight for age z scores had occurred, and scores were within normal ranges. There were no significant differences in mean weight for age z scores between the HIV positive and HIV exposed uninfected group at visit two.

This study appears to indicate that HIV may influence weight in infected infants. Several other studies from both developed and developing countries have shown that HIV infected children are malnourished (Abubaker et al, 2009; Potterton et al, 2009b; Van Rie et al, 2008; The European Collaborative Study, 2003; Bobat et al, 2001; Miller et al, 2001). In a South African study by Bobat et al (2001), HIV infected infants were underweight when compared to HIV exposed uninfected infants, weight for age z scores were 2SD below the norm and being underweight continued to persist. In their study infants did not yet have access to ARV's. In another South African study, Potterton et al (2009a) also showed that HIV infected infants were malnourished and weight for age z scores were 2SD below the international standard.

Significant increases in mean weight for age z scores were seen over the course of this study. The increase seen may be attributed to the effects of HAART. At the clinic caregivers are also able to consult with a dietician and receive education regarding good nutrition. This could also explain the improvements seen in weight for age z scores. Several other studies have also shown improvements in weight with the initiation of HAART as well as with improved care of HIV positive infants. Potterton et al (2009a) showed that infants receiving care at an HIV clinic in South Africa had increases in weight for age z scores over a 12 month period. In this study not all infants were receiving HAART. Foster et al (2006) showed significant improvements over time in weight, in their study all infants were receiving ARV's.

Guillen et al (2007) and Song et al (2007) also showed significant increases in weight for age z scores over time with HAART in HIV infected infants. In a review on the effectiveness of ARV treatment in Sub-Saharan Africa, Sutcliffe et al (2008) reported that in the first year of receiving ARV treatment, HIV positive children have significant gains in weight that are maintained over a long period of time. Musoke et al (2010) in a Ugandan study showed that the younger the children are when initiating HAART the more significant increases in weight will be seen. Reddi et al (2007) showed that after one month of being on HAART, significant increases in weight are present. In the current study children were followed for 6 months and significant improvements in weight for age were seen. This result is similar to that of other studies.

After stratifying the HIV positive group according to CD4 percentages at baseline it was found that the group with CD4% < 25% had significantly lower weight for age z scores at baseline compared to the CD4% > 25% group. A significant improvement was seen for both groups for weight for age by visit 2. This result may show that CD4 percentage may affect weight. The more immune compromised the child is the more malnourished they are. Foster et al (2006) showed that HIV positive children with a more advanced disease stage had significantly lower growth parameters. Bobat et al (2001) and The European Collaborative Study (2003) also found that there is an association between viral load, disease stage and growth. They postulate those children with a more severe disease stage and who are more immune compromised are at higher risk for problems with nutrient absorption and therefore have worse growth. This may have been the case in this study. At baseline many of the HIV positive infants had severe illnesses including gastroenteritis; this may have affected weight for age z scores. Once on HAART weight for age z scores in both groups improved and therefore HAART may have influenced the increase seen in weight in infants infected with HIV.

5.4.2. Height

The HIV positive group in this study was very short. At baseline and visit 1 height for age z scores were two standard deviations below the norm. However, there were no significant differences between the HIV positive and HIV exposed uninfected groups at any visit. Over time height for age z scores increased significantly and by visit 2 scores were within normal ranges.

Clearly infants infected with HIV are stunted. Several other studies have shown that children infected with HIV are stunted (Van Rie et al , 2009; Potterton et al, 2009a; The European Collaborative Study,

2003; Bobat et al, 2001;). Bobat et al (2001) showed that South African infants are significantly shorter when compared to HIV exposed uninfected infants. They found that stunting occurs from early on and continues to persist. In Bobat et al's study children did not have access to ARV's which may have contributed to the fact that stunting continued to persist. The European Collaborative Study (2003) had similar findings to Bobat et al (2001). Potterton et al (2009a) also found that South African infants infected with HIV were stunted.

There was a significant increase in mean height for age z scores over the course of this study. This increase may be due to the effects of HAART as well as nutritional advice that was given at the HIV clinic. Potterton et al (2009a) showed an increase in height over a 12 month period in South African HIV infected infants but infants still remained quite short. In their study there was no comparison group with HIV uninfected children. These children received care at an HIV clinic similar to the one in this study and some of the infants also received HAART. Foster et al (2006) also showed a significant increase in height over time in HIV infected children, however their study was retrospective and once again there was no comparison group. Guillen et al (2007) showed significant increases in weight for age z scores for HIV positive children with the use of HAART. In a review by Sutcliffe et al (2008), improvements in height were noted; however the increase in height was not as significant as with weight.

After stratifying the HIV positive group according to CD4 percentages at baseline no significant differences were found between the groups at any time point, however significant improvements for height were seen in both groups. The European Collaborative Study (2003) and Bobat et al (2001) reported that stunting may be attributed to severity of disease stage, however in this study no differences were seen when the HIV positive group was stratified according to CD4 percentages prior to initiation of HAART. Stunting is generally related to poor socioeconomic circumstances (WHO, 1986).

5.4.3. Weight for Height

Weight for height z scores are indicative of wasting in a child. Low weight for height z scores may result from a failure to gain weight or from weight loss (WHO, 1986).

In this study weight for height z scores were significantly lower for the HIV positive group at baseline and visit one when compared to the HIV exposed uninfected group. By visit two, no significant differences were seen between the two groups for weight for height z scores and scores had improved

but not significantly. Mean weight for height z scores in the HIV positive group did not indicate that wasting was present and this is similar to findings in several other studies (Potterton et al, 2009a; The European Collaborative Study, 2003; Bobat et al, 2001). No significant differences occurred over time for weight for height z scores in the study.

The CD4% < 25% group had significantly lower weight for height z scores compared to the CD4 % > 25% group. No significant differences were seen by visit 2. Because both weight and height increased in the HIV positive infants, less of an effect may have been seen for weight for height z scores.

5.4.4. Head Circumference

Head circumference is considered to be a part of general growth and is therefore not a widely used measure. Research concerning head circumference in HIV positive infants is fairly limited.

There were no significant differences between the HIV positive and HIV exposed uninfected group at baseline, visit one and visit two for head circumference. Pollack et al (1996) had a similar finding when comparing HIV positive infants, HIV exposed uninfected infants and HIV unexposed, unaffected infants. Initially head circumference was low in the HIV positive group. Both Van Rie et al (2008) and Chase et al (1995) have reported a decreased head circumference as well as microcephaly in HIV positive children. A significant increase in head circumference was seen by visit two in the HIV positive group. There were no significant differences between the two stratified groups for head circumference at any time point in the study. However, significant increases in head circumference were seen over time. Potterton et al (2009a) also showed low z scores for head circumference that had improved over time. Raskino et al (1999) showed a significant increase in head circumference in HIV positive infants receiving a combination of ZDV and DDI.

The increases seen in head circumference may be related to the effects of HAART. The increases could indicate good brain growth and development. It is important to note that increases in head circumference were not significant and there were no significant differences between the HIV positive and HIV exposed uninfected groups.

5.4.5. General Growth

It is important to consider growth when looking at development. Poor growth is often associated with poor development. Abubaker et al (2009) showed that HIV positive children who are underweight and malnourished perform significantly worse for psychomotor development. Pollack et al (1996) also showed that HIV positive children with poor weight and height have poorer scores on the BSID II. They found that severe growth failure results in severe cognitive and motor delays and that growth failure often precedes onset of neuro developmental delay. Potterton et al (2009a) also shows that weight influences development.

By the end of this study growth parameters were within normal ranges in the HIV positive group and therefore should not have impacted too severely on developmental outcomes by visit two. Even though children in this study were not wasted, muscle atrophy may have started to occur when the children were underweight and stunted and this may not have yet resolved by visit two. Therefore, there may have been a loss of muscle strength which would have impacted on certain test items for motor development especially those requiring muscle activity against gravity and proximal stability.

It appears that HAART has an important effect on growth in HIV positive infants. In this study significant increases were seen for weight for age, height for age and head circumference for age in the HIV positive group. The improvements seen in growth parameters may also be explained by the nutritional advice that caregivers received at the HIV clinic.

It is encouraging to note that growth parameters improved after a fairly short period on HAART. The increases seen in growth may have positive effects on immune function as well as on overall development in the HIV infected child.

5.5. Growth in the HIV Exposed Uninfected Infant

Children in the HIV exposed uninfected group had good weight for age z-scores at all time points in the study. Height for age z scores were low and below 2SD of the norm at baseline and visit 1. By visit two, the mean height for age z score was within normal range and had increased significantly over the course of the study.

Several other studies have shown that HIV exposed uninfected infants are stunted (Arpadi et al, 2009; Filteau, 2009). Height has been found to be influenced by socioeconomic circumstances (WHO, 1986). Children living in poor socioeconomic circumstances are stunted (WHO, 1986). The height gain seen in the study may be attributed to the fact that the majority of HIV exposed infants were formula fed. Formula was being provided to the caregivers free of charge for the first 6 months of the child's life and caregivers were given continuous dietary advice. This may have impacted the results.

5.6. Medical Information

The presence of severity of HIV, the presence of illness as well as CD4 counts, CD4 percentages and viral loads have been shown to impact on cognitive, language and motor development (Potterton et al 2009b; Bertou et al, 2008; Burns et al, 2008; Foster et al, 2006; Smith et al, 2006; Pearson et al, 2000; Chase et al, 1995; Nozyce et al, 1994;).

At baseline the HIV positive group had significantly more illnesses and hospital admissions compared to the HIV exposed uninfected group. At visit one there were no significant differences between the two groups for hospital admissions and illnesses. At visit two, the HIV exposed uninfected group had significantly more illnesses compared to the HIV positive group. These illnesses were things like a cough or rhinitis and were not as severe as the illnesses experienced by the HIV positive group.

By visit two far fewer HIV positive infants were ill and were being admitted to hospital. This may be due to the effects of HAART.

Zwi et al (1999) and Kourtis et al (2007) showed that HIV positive infants have high numbers of hospital admissions. Hospital admissions are often due to oral candidiasis, respiratory infections, anemia, failure to thrive, diarrhea, TB, malaria and meningitis (Kourtis et al, 2007; Zwi et al, 1999). Nesheim et al (2007) and Sutcliffe et al (2008) showed that with HAART the incidence of opportunistic infections is reduced. Hospital admissions in infants receiving HAART is also decreased (Sutcliffe et al 2008; Violori et al, 2008; Foster and Lyall, 2005). This study also showed a decrease in hospital admissions as well as illnesses over time, this decrease is may be related to the effects of HAART.

In the HIV positive groups CD4 counts and CD4 percentages increased over time. There was a significant increase in CD4 counts from baseline to visit two and the increase in CD4 percentage approached significance. During the course of the study viral load decreased and by visit two 23.53% of the infants had an undetectable viral load. HAART may have a positive effect on CD4 counts, CD4 percentages and viral loads. Various studies have reported significant decreases in viral loads and increases in CD4 counts and CD4 percentages (Musoke et al, 2010; Bracher et al, 2007; Janssens et al, 2007; Resino et al, 2006). In a review Sutcliffe et al (2008) reported that CD4 percentages increased and viral load decreased in the first year of life. Reddi et al (2007) reported similar findings in a South African study. McKinney et al (2007) showed that after 96 weeks on HAART, 86% of infants had a suppressed viral load.

5.7. Pregnancy History

Prevention of mother to child transmission is effective in reducing vertical transmission of HIV (Connor et al, 1994; Sharer et al, 1999). This was also seen in the current study. In this study significantly more mothers of HIV exposed uninfected infants received antenatal care and AZT during pregnancy compared to mothers of HIV positive infants.

There were no significant differences between the two groups for the mothers having illness and hospital admissions during pregnancy. CD4 counts prior to delivery in the mothers were also not significantly different. Therefore, these factors may not have impacted on developmental outcomes in the two groups.

5.8. Demographic Information

The HIV exposed uninfected group was younger than the HIV positive group. The main reason for this may be that HIV exposed uninfected infants were detected far sooner than the HIV positive group and were often detected at six to eight weeks of age as the caregivers were attending the follow-up clinic at that time. The HIV positive infants often presented to the clinic at a later stage. Even though a difference was seen in age, both groups were still very young at baseline. Anthropometric measurements and developmental scores are corrected for age therefore the age difference would not have impacted upon the results.

It is encouraging to note that the HIV positive infants are being detected at such an early age so that treatment can start early on.

The HIV positive group had significantly lower birth weights when compared to the HIV exposed uninfected group. Even though there was a difference in birth weights in the two groups, the HIV positive group did not have a mean low birth weight. Therefore, there should not have been any adverse effects on developmental outcomes.

5.9. Loss to follow-up

Loss to follow-up in this study was high at 30.36%. Loss to follow-up occurred for a variety of reasons. The reasons included death, participants relocating and participants being untraceable.

In the HIV positive group four participants had died during the course of the study and deaths had occurred prior to visit one (three month follow-up). This may have meant that these children were rapid progressors and therefore had died sooner. The researcher was unable to trace five participants; three from the HIV exposed uninfected group and two from the HIV positive group. Contact numbers for these participants no longer worked and they had defaulted on their appointments at the Empilweni clinic. The clinic was also unable to trace them. Due to poor socioeconomic circumstances, participants often do not have access to cell phones, or cell phones get stolen and their numbers change. In the HIV positive group one patient relocated. Seven participants relocated in the HIV exposed uninfected group. Most of the relocations occurred after visit one. This may be explained by the fact that free formula was no longer being dispensed to the HIV exposed uninfected infants and the infants were no longer in need of medical care or follow-up from the clinic. Therefore, caregivers could relocate to areas where they were able to find work or children were sent to live with their grandparents in rural areas so that their parents could work.

In this study every effort was made to prevent loss to follow-up. Participants were reimbursed for their transport costs. Appointments for the study were made on the same day as the participant's clinic visit and participants were phoned to remind them about their appointments. If they did not arrive for their appointment they were phoned again to reschedule.

High loss to follow-up is often anticipated in studies conducted in South Africa. Participants often live in very poor social circumstances and this may result in poor follow-up (Rosen et al, 2007; Mills et al, 2006; Jones et al, 2005). Participants often live far away from the hospitals where they receive treatment and therefore transport costs to get to the clinic are high (Meyers et al, 2007, Mills et al, 2006; Jones et al, 2005). South Africa has a high unemployment rate and often participants simply do not have money for taxi fares (Mills et al, 2006; Jones et al, 2005). Death in this study population also results in high loss to follow-up (Rosen et al, 2007).

5.10. Challenges of the Study

- There was a high loss to follow-up in this study. This has been explained in depth above.

- A longer follow-up would have been useful and would have given more insight into neurodevelopment in HIV positive infants receiving HAART. However, this study showed improvements in growth parameters, morbidity as well as blood results over the six month period which was similar to results from other studies. Developmental scores did not change significantly over time but once again this was similar to findings from several other studies. A longer follow-up would have resulted in a far higher loss to follow-up and would not have been feasible.

- The Bayley III has not been normed on South African infants, however the BSID I was (Richter et al, 1992). The BSID I was found to be a valuable and reliable tool in assessing black South African infants. The Bayley III has also been used in several other developmental studies (Hilburn, 2010; Brown, 2009; Kigara, 2008). The fact that the HIV exposed uninfected children had normal scores indicate that the norms of the Bayley III are appropriate for children in South Africa.

- Once the HIV positive group was stratified according to CD4 percentages at baseline, sample size was very small in each group. Therefore it is difficult to draw conclusions from these results. Results need to be viewed with care and only general observations can be made.

- The assessor was not blinded to the HIV status of the children in the study.

5.11. Clinical Recommendations based on the Results

- HAART may prevent delay occurring in HIV positive infants and may preserve neuro-developmental function, therefore it is essential that HIV positive infants are detected early and that HAART is started as soon as possible.

- HIV positive infants are clearly delayed for cognitive, language and motor development. HAART appears to prevent further delay, however does not reverse delay already present. This means that it is essential for therapists to become an integral part of HIV clinics in South Africa. Policies need to be changed in order to include therapists in the staff establishments of HIV clinics.

- Potterton et al (2009a) showed that a basic home stimulation programme provided to HIV positive infants is effective in improving developmental outcomes. Programmes such as these need to be given to all caregivers of HIV infected infants. Therapists need to be present in the HIV clinics in order to administer these programmes.

- Due to budgetary constraints in the Department of Health a therapist in each HIV clinic may not be a feasible option. Counsellors and nurses should therefore be educated on the effects of HIV development and be encouraged to educate parents regarding development and how to stimulate their children appropriately.

- In order for early intervention to occur, all HIV positive infants should be screened for developmental delay.

- Doctors in HIV clinics need to be provided with screening tools so that they can easily detect developmental delays and refer patients early on for adequate rehabilitation.

- HIV exposed uninfected infants do not have severe delays in cognitive, motor and language development. Efforts need to continue in order to reduce MTCT of HIV in South Africa so that children are not put at increased risk for developmental delays which adversely affect school performance and work opportunities later in life.

- Efforts to detect HIV early on in infants should continue and be improved. The earlier an infant is initiated on HAART and before severe immune compromise the better for their development and growth.

5.12. Recommendations for future research

- Studies of a similar nature with longer follow-up should be considered.

- Studies of a similar nature should be undertaken in older children in order to determine effects of HIV on school performance and to determine rehabilitation needs

- Randomised controlled trials on intervention strategies for rehabilitation in HIV positive infants and children need to be conducted in order to establish protocols for rehabilitation needs and to determine the best possible rehabilitation in HIV positive children.

Children in this study who were HIV positive scored significantly lower for all facets of development when compared to an HIV exposed uninfected group. Their growth parameters were also significantly worse at baseline compared to the HIV exposed uninfected group. Developmental scores did not improve over time with the initiation of HAART however, growth parameters did improved significantly. The conclusions of this study will be presented in the next chapter.

Chapter 6

CONCLUSION

The main aim of this study was to compare neurodevelopment in HIV positive infants on HAART to HIV exposed uninfected infants. Part of this study was to also compare anthropometric data, hospital admissions, illnesses and maternal health between the groups. Subjects all attended the HIV clinic (Empilweni Clinic) at Rahima Moosa Mother and Child hospital and came from similar socioeconomic backgrounds. The conclusions of this study are summarised below.

- Infants infected with HIV are significantly more delayed in cognitive, language and motor function when compared to HIV exposed uninfected infants. This is similar to findings from other studies and indicates that HIV positive infants should be screened for developmental delay when attending their clinic appointments.

- Despite the use of HAART, delays continued to persist, therefore there is a need for further intervention and rehabilitation in HIV infected infants.

- Although no significant improvements were seen in developmental scores, no significant decline occurred. Therefore, HAART may prevent further neurological damage and be neuro-protective. It was not, however in the scope of this study to observe brain abnormalities.

- There was a trend for infants with lower CD4 percentages to score lower on the Bayley III compared to infants with higher CD4 percentages. Therefore, it is of utmost important that children infected with HIV are detected early on and that treatment is initiated prior to severe immune compromise.

- During the course of the study anthropometric measurements in the children increased significantly. HAART as well as nutritional advice and support received at the clinic may be effective in preventing stunting and malnourishment in children infected with HIV.

- HIV positive infants had significantly more illnesses and hospital admissions compared to HIV exposed uninfected infants. However, with the use of HAART, hospital admissions and illnesses decreased in the HIV group and by six months follow up there were no significant differences between the two groups.

- In this study maternal health between the two groups were similar, with no significant differences between the groups for maternal illnesses, hospital admissions and CD4 counts prior to delivery. A significant difference was seen in use of AZT during pregnancy. The mothers of the HIV exposed uninfected infants used significantly more AZT than the mothers of the HIV positive infants. This suggests that PMTCT is effective in reducing vertical transmission of HIV.

This study suggests that HAART is effective in reducing illnesses and hospital admissions in HIV positive infants as well as improving growth parameters. HAART does not appear to be effective in improving neurodevelopment, however it may prevent further delay occurring. The HIV positive infants still scored significantly lower on the Bayley III compared to HIV exposed uninfected infants even after being on HAART for six months. Therefore, there is a need for HIV infected infants and children to have improved access to developmental screening services as well as to rehabilitative services. Therapists need to become more involved in HIV clinics and research in the area of rehabilitation in HIV infected children is urgently required.

Chapter 7

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Appendix 1
Interview Questions: Pregnancy History

The neurodevelopment of HIV positive infants on HAART compared to HIV exposed but uninfected infants.

Interview Questions: Pregnancy History

Participant/Study Number:	
Date of Visit:	

1. At which hospital did you have your baby?

2. Where did you book for your antenatal care?

	1. Did not book	2. Unknown

3. During your pregnancy were you ill?

1. Yes	2. No
If Yes: Illness: …… When:……	

4. During your pregnancy were you admitted to hospital?

1. Yes	2. No
If Yes: …… days of admission Reason for admission: ……	

5. Before delivery did you take nevirapine?

1. Yes	2. No	3. Unknown

6. Did you take any other ARV's during the pregnancy?

1. Yes	2. No	3. Unknown

7. During the labour or birth did you take nevirapine?

1. Yes	2. No	3. Unknown

8. What was your CD4 count just before or just after you delivered your baby?

9. Was your child given nevirapine after birth?

1. Yes	2. No	3. Unknown

10. Was it a normal deliver or a caesarian section?

1. NVD	2. Caesarian Section

11. What was your baby's gestational age?

1. Full Term	2. Preterm	3. Unknown

12. What was your child's birth weight?

Appendix II
Data Collection Sheet

The neurodevelopment of HIV positive infants on HAART compared to HIV exposed but uninfected infants.

Data Collection Sheet

Participant/Study Number	
Date of Visit	

1. Interval at which data is being collected?

Baseline	3 months	6 months	9 months	12 months

2. Since the last visit has your baby been to the doctor because he/she was sick?

1. Yes	2. No
If Yes: Reason for visit? ……	

3. Since the last visit has your baby been admitted to the hospital?

1. Yes	2. No
If Yes: Duration: …… days Reason: …… ……..	

4. Since your last visit has your child received any vaccinations/immunizations (check on road to health card)?

1. Yes	2. No
If Yes: Date: …… Vaccination: …… Date: …… Vaccination: ……	

3. Anthroprometric Measurements:

Weight	
Height	
Head Circumference	

4. What medication is your child currently taking?

Medication	**YES**	**NO**
Kaletra (LPV/R)		
Lamivudine (3TC)		
Stavudine (D4T)		
Abacavir (ABC)		
Efavirenz (EFV)		
Nevirapine (NVP)		
Zidovudione (AZT)		
Didanosine (DDI)		
Ritonavir (RTV)		
Other		

5. Is the child taking any other types of medication?

1. Yes	2. No
If Yes: What medication? ……	

6. Blood results

CD4 Count		Date Measured:
CD4 Percentage		Date Measured:
Viral Load		Date Measured:

Appendix III

Ethical Clearance

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

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Nicole Whitehead

CLEARANCE CERTIFICATE	**M10535**
PROJECT	The Neurodevelopment of HIV Postive Infants on Highly Active Antiretroviral Therapy (HAART) Compare to HIV Exposed but Uninfected Infants
INVESTIGATORS	Nicole Whitehead.
DEPARTMENT	Department of Physiotherapy
DATE CONSIDERED	28/05/2010
DECISION OF THE COMMITTEE*	

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

DATE **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr J Potterton

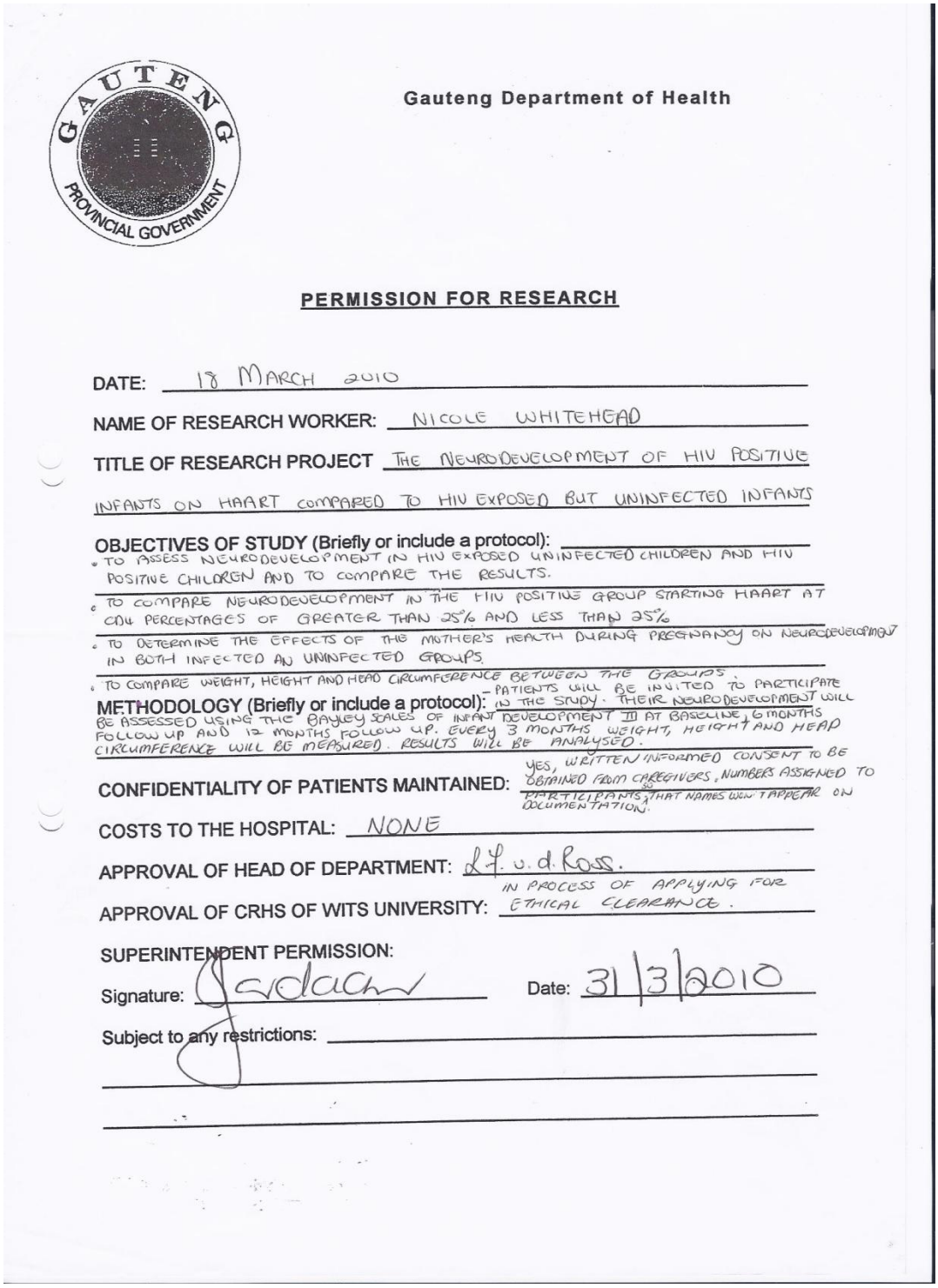
DECLARATION OF INVESTIGATOR(S)

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

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix IV

Permission from Rahima Moosa Hospital



Gauteng Department of Health

PERMISSION FOR RESEARCH

DATE: 18 MARCH 2010

NAME OF RESEARCH WORKER: NICOLE WHITEHEAD

TITLE OF RESEARCH PROJECT: THE NEURODEVELOPMENT OF HIV POSITIVE INFANTS ON HAART COMPARED TO HIV EXPOSED BUT UNINFECTED INFANTS

OBJECTIVES OF STUDY (Briefly or include a protocol):
- TO ASSESS NEURODEVELOPMENT IN HIV EXPOSED UNINFECTED CHILDREN AND HIV POSITIVE CHILDREN AND TO COMPARE THE RESULTS.
- TO COMPARE NEURODEVELOPMENT IN THE HIV POSITIVE GROUP STARTING HAART AT CD4 PERCENTAGES OF GREATER THAN 25% AND LESS THAN 25%
- TO DETERMINE THE EFFECTS OF THE MOTHER'S HEALTH DURING PREGNANCY ON NEURODEVELOPMENT IN BOTH INFECTED AN UNINFECTED GROUPS
- TO COMPARE WEIGHT, HEIGHT AND HEAD CIRCUMFERENCE BETWEEN THE GROUPS.

METHODOLOGY (Briefly or include a protocol): - PATIENTS WILL BE INVITED TO PARTICIPATE IN THE STUDY. THEIR NEURODEVELOPMENT WILL BE ASSESSED USING THE BAYLEY SCALES OF INFANT DEVELOPMENT II AT BASELINE, 6 MONTHS FOLLOW UP AND 12 MONTHS FOLLOW UP. EVERY 3 MONTHS WEIGHT, HEIGHT AND HEAD CIRCUMFERENCE WILL BE MEASURED. RESULTS WILL BE ANALYSED.

CONFIDENTIALITY OF PATIENTS MAINTAINED: YES, WRITTEN INFORMED CONSENT TO BE OBTAINED FROM CAREGIVERS. NUMBERS ASSIGNED TO PARTICIPANTS SO THAT NAMES WON'T APPEAR ON DOCUMENTATION.

COSTS TO THE HOSPITAL: NONE

APPROVAL OF HEAD OF DEPARTMENT: Dr. v. d. Ross.

APPROVAL OF CRHS OF WITS UNIVERSITY: IN PROCESS OF APPLYING FOR ETHICAL CLEARANCE.

SUPERINTENDENT PERMISSION:

Signature: [signature] Date: 31/3/2010

Subject to any restrictions:

Appendix V

Information Sheet: HIV Positive Infants

Information Sheet for HIV positive infants

The neurodevelopment of HIV positive infants on HAART compared to HIV exposed but uninfected infants

Good Day Parent or Caregiver

Thank you for taking the time to read this information sheet.

My name is Nicole Whitehead and I am a physiotherapist. I am currently doing a Masters degree in physiotherapy and for this I need to conduct a study. I am conducting a study on the development of HIV positive children starting highly active antiretroviral therapy (HAART) and comparing them to the development of children who are HIV exposed but uninfected. Research is a way of finding an answer to a question. In this study I want to learn if HAART has an effect on the way your child develops.

I am inviting you and your child to be part of my study.

For this study to be done I will need to assess 27 children who are HIV positive and who are starting HAART and also 27 children who were exposed to HIV but are HIV negative.

The study will involve me assessing your child's development. I will assess your child's development before they start HAART or at the first visit and then every three months for six months. The assessment will take about an hour to do and will occur on the same day as your clinic visit. The assessment will not interfere with the treatment or services that you receive at the clinic and I will pay for your transport costs. The assessment involves me looking at different parts of your child's development to see what they can and can't do for their specific age. The assessment that I do does not hurt the child.

I will also need to see your child every 3 months for six months, at these visits I will measure the child's weight, height and head. I will also need to look in your child's file to see their blood results. I will need to ask a few questions to get information regarding the mother's pregnancy.

The assessments do not hurt and will take place on the same day as your clinic visits. I will also pay for your transport costs. There are no risks to this study.

There are no direct benefits to participating in this study, you will only be able to see and be told how your child is developing. Your child will still be receiving his/her routine care at the clinic. The results of the assessment will be given to you.

Participation in this study is voluntary. If you do not want your child to participate in the study there will be no change to the treatment that your child is already receiving at the clinic. You may stop your child participating in the study at any time without penalty and if you withdraw, your child will continue to receive the same treatment at the clinic.

All personal information will be kept private. Each participant will be assigned a number and there will be no way to identify you or your child on the record sheet. All information will be kept safe in a locked cupboard. The results of the study will be published, but, these results will be published as a group.

If you want to contact me for any information or concerns you can get hold of me on the following numbers: 073 254 7816 / 011 673 8862 / 011 470 9075.

For information regarding your human rights and for reporting complaints or problems you can contact the chair of the Ethics Committee, Prof. C Jones on 011 717 2301.

If you wish for your child to participate in the study, please read and sign the consent form.

Thank You

_____

Nicole Whitehead

Appendix VI

Consent Form: HIV Positive Infants

Consent Form for HIV Positive Infants

The neurodevelopment of HIV positive infants on HAART compared to HIV exposed but uninfected infants

I _____ agree that I and my child _____ will be part of this study.

I have read the information sheet and fully understand it. I have had the opportunity to ask questions which were answered adequately. I understand that this research is completely voluntary and that I can withdraw my child from the study at any stage.

I agree that Nicole Whitehead may look at my child's file to see their blood results as well as to find blood results from the mother's pregnancy.

_____ _____

Participant Date

_____ _____

Researcher Date

_____ _____

Witness Date

Appendix VII

Information Sheet: HI Exposed but negative infants

Information Sheet for HIV exposed but negative infants

The neurodevelopment of HIV positive infants on HAART compared to HIV exposed but uninfected infants

Good Day Parent or Caregiver

Thank you for taking the time to read this information sheet.

My name is Nicole Whitehead and I am a physiotherapist. I am currently doing a Masters degree in physiotherapy and for this I need to conduct a study. I am conducting a study on the development of HIV positive children starting highly active antiretroviral therapy (HAART) and comparing them to the development of children who are HIV exposed but uninfected. Research is a way of finding an answer to a question. In this study I want to learn if HAART has an effect on the way your child develops.

I am inviting you and your child to be part of my study.

For this study to be done I will need to assess 27 children who are HIV positive and who are starting HAART and also 27 children who were exposed to HIV but are HIV negative.

The study will involve me assessing your child's development. I will assess your child's development at the first visit and then every six months for a year. The assessment will take about an hour to do and will occur on the same day as your clinic visit and I will pay you for your transport costs. The assessment will not interfere with the treatment or services that your child receives at the clinic. The assessment involves me looking at different parts of your child's development to see what they can and can't do for their specific age. The assessment that I do does not hurt the child. At the first visit I will also ask you questions regarding your pregnancy.

The assessments do not hurt and will take place on the same day as your clinic visits. I will pay you for your transport costs. There are no risks to this study.

There are no direct benefits to participating in this study, you will only be able to see and be told how your child is developing. Your child will still be receiving his/her routine care at the clinic. The results of the assessment will be given to you.

Participation in this study is voluntary. If you do not want your child to participate in the study there will be no change to the treatment that your child is already receiving at the clinic. You may stop your child participating in the study at any time without penalty and if you withdraw your child from the study your child will continue to receive the same treatment at the clinic.

All personal information will be kept private. Each participant will be assigned a number and there will be no way to identify you on the record sheet. All information will be kept safe in a locked cupboard. The results of the study will be published, but, these results will be published as a group.

If you want to contact me for any information or concerns you can get hold of me on the following numbers: 073 254 7816 / 011 673 8862 / 011 470 9075.

For information regarding your human rights and for reporting complaints or problems you can contact the chair of the Ethics Committee, Prof. C Jones on 011 717 2301.

If you wish to participate in the study, please read and sign the consent form.

Thank You

_____

Nicole Whitehead

Appendix VIII

Consent Form: HIV exposed but uninfected infants

Consent Form for HIV Exposed but uninfected Infants

The neurodevelopment of HIV positive infants on HAART compared to HIV exposed but uninfected infants

I _____ agree that I and my child _____ will be part of this study.

I have read the information sheet and fully understand it. I have had the opportunity to ask questions which were answered adequately. I understand that this research is completely voluntary and that I can withdraw at any stage during the study.

I agree that Nicole Whitehead may look at my child's file and may look for blood results to see information regarding the mother's pregnancy.

_____ _____

Participant Date

_____ _____

Researcher Date

_____ _____

Witness Date

Appendix IX

<u>Demographic Questionnaire</u>

Child's name: ……

Child's Date of Birth: ……

Caregiver's name: ……

Relationship of caregiver to child: ……

Address: ……

……

Telephone Number 1: ……

Telephone Number 2: ……

Participant number: _____