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DEVELOPMENTAL DELAY IN HIV-EXPOSED INFANTS IN HARARE, ZIMBABWE

Jenna Hutchings

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

Johannesburg, 2012

ABSTRACT

The aim of this cross-sectional study was to determine the difference in development (cognition; receptive and expressive language; and fine and gross motor) of Human Immunodeficiency Virus (HIV) -exposed *infected* (HEI) infants with the development of HIV-exposed but *uninfected* (HEU) infants using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). Sixty infants were enrolled in the study; 32 (53.33%) HEU infants and 28 (46.67%) HEI infants. The two groups were well-matched for infant demographics, anthropometry at birth, maternal demographics, as well as socioeconomic status. Statistically significant differences were found in anthropometry and development between the HEI and HEU group. The HEI infants had malnutrition, were stunted and had smaller head circumferences than HEU infants. The BSID-III showed that the mean developmental delay for the HEI group was approximately two months below their mean chronological age for all scales (cognitive; receptive and expressive communication; and, fine and gross motor age). The HEI group showed that 64.29% had cognitive delay, 60.71% had language delay and 53.57% had motor delay, all of which was significantly different from the development of the HEU group for all domains ($p<0.001$). In addition to using the BSID-III, the majority of mothers were able to correctly indicate whether their child was developing at the same, or at a slower rate of development than children of the same age. This study demonstrates that infants who are HIV-exposed and infected are at risk of developmental delay.

DECLARATION

I, **Jenna Elizabeth Hutchings**, declare that this research report is my own unaided work except for the help given by the persons listed under the acknowledgements. It is being submitted in partial fulfilment of the requirements of the degree of Master of Science (Physiotherapy) at the University of the Witwatersrand. It has not been submitted before for any other degree or examination in any other university.

Signed this day in Johannesburg

_____

Signature

__ / __ / ____

Date

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ANC	Antenatal Care
ANT	Amsterdam Neuropsychological Tasks
ART	Antiretroviral Therapy (synonymous with HAART)
ARV	Antiretroviral
ARVs	Antiretroviral medicines
AZT	Azidothymidine or Zidovudine (ZDV)
BAEPs	Brainstem Auditory-Evoked Potentials
BBB	Blood-Brain Barrier
BINS	Bayley Infant Neurodevelopmental Screener
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency 2nd Edition
BSID	Bayley Scales of Infant Development
BSID-I	Bayley Scales of Infant Development, First Edition
BSID-II	Bayley Scales of Infant Development, Second Edition
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
BTVMI	Beery Test of Visual Motor Integration
CDC	Centers for Disease Control and Prevention
CELF-4	Clinical Evaluation of Language Functioning 4th Edition
CNS	Central Nervous System
CPRS	Conner's Parent Rating Scale
C-section	Caesarean section
CT Scan	Computerised Tomography Scan
DAP	Harris-Goodenough-Draw-A-Person Test
DBS	Dried Blood Spot
DDST	Denver Developmental Screening Test
DNA	Deoxyribonucleic Acid
DRC	Democratic Republic of the Congo
DTVMI	Beery-Buktenica Developmental Test of Visual-Motor Integration
EC	Expressive Communication
ECD	Early Child Development
EEG	Electroencephalogram
FM	Fine Motor
FS-2	Functional Status 2nd Edition
FTII	Fagan Test of Infant Intelligence
GM	Gross Motor
GMDS	Griffiths Mental Development Scales
GMDS-ER	Griffiths Mental Development Scales-Extended Revised Version
HAART	Highly-Active Antiretroviral Therapy (synonymous with ART)
HAZ	Height-for-age z-score
HCZ	Head circumference-for-age z-score
HEI	HIV-exposed infected
HEU	HIV-exposed uninfected
HIV	Human Immunodeficiency Virus
HOME	Home Observations for the Measurement of the Environment
IDIYC	Illingworth's Development of the Infant and Young Child
IUGR	Intrauterine Growth Restriction
KABC	Kaufman Assessment Battery for Children 1st Edition
LBW	Low-Birth Weight (<2.5kgs)
mDS	Modified Denver Score
MICI	Measures of Infant-Caregiver Interactions
mKABC-2	A modified Kaufman Assessment Battery for Children 2nd Edition

mo	months
MRI	Magnetic Resonance Imaging
MSCA	McCarthy Scales of Children's Abilities
MTCT	Mother-to-Child Transmission (of HIV)
NMDAR	N-methyl-D-aspartate type receptor
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NtRTIs	Nucleotide Reverse Transcriptase Inhibitors
NVD	Natural Vaginal Delivery
NVP	Nevirapine
OI	Opportunistic Infections
PCR	Polymerase Chain Reaction
PDMS-2	Peabody Development Motor Scale 2nd Edition
PIs	Protease Inhibitors
PITC	Provider-Initiated Testing and Counselling
PLS	Preschool Language Scale
PMTCT	Prevention of Mother-to-Child Transmission (of HIV)
RC	Receptive Communication
RITLS	Rossetti Infant-Toddler Language Scale
RNA	Ribonucleic Acid
RPCM	Raven Progressive Coloured Matrices
SB	Stanford Binet
sd-NVP	Single-dose Nevirapine
SONIT	Snijders-Oomen Nonverbal Intelligence Test
SON-R	Snijders-Oomen Nonverbal Intelligence Test-Revised
TOVA	Test of Variables of Attention
TRG	Test of the Reception of Grammar
UNAIDS	Joint United Nations Programme for HIV/AIDS
UNICEF	United Nations Children's Fund
US	United States
USD	United States Dollar
VEPs	Visual-Evoked Potentials
VSMS	Vineland Social Maturity Scale
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WAZ	Weight-for-age z-score
WHO	World Health Organization
WHZ	Weight-for-height z-score
WISC-3	Wechsler Intelligence Scale for Children 3rd Edition
WISC-4	Wechsler Intelligence Scale for Children 4th Edition
WISC-R	Wechsler Intelligence Scale for Children-Revised
WITS	Woman and Infants Transmission Study
wks	weeks
WPPSI	Wechsler Pre-School and Primary Scales of Intelligence
WRAT-3	Wide Range Achievement Test 3rd Edition
yrs	years

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CHAPTER 1: INTRODUCTION

Sub-Saharan Africa accounts for two-thirds (approximately 22 million people) of the global HIV population (UNAIDS, 2009). Of that, women account for 60% of all HIV infections in this region (UNAIDS, 2009). In sub-Saharan Africa the primary mode of transmission of HIV is through heterosexual intercourse, therefore the majority of these women will be of child-bearing age (15-49 years). In 2009, Zimbabwe was deemed to be one of 25 countries with the largest number of pregnant women living with HIV (UNAIDS, 2010), where Harare had an HIV prevalence of 10-24.9% for pregnant women (UNAIDS, 2009). Pregnant women living with HIV expose their infants to HIV during gestation, the perinatal period and/or while breastfeeding. This is the second most important mode of transmission in Zimbabwe (UNGASS, 2009). Infants who are born to HIV-positive mothers are referred to as being HIV-exposed. It is estimated that more than 30% of HIV-exposed infants are HIV-positive when there has been no intervention (Sharland and Bryant, 2009; Dabis, *et al*., 1993; Boylan and Stein, 1991). In sub-Saharan Africa, Mother-to-Child-Transmission of HIV (MTCT) accounts for more than 90% of all paediatric HIV-cases (UNAIDS, 2010).

HIV is a neurotrophic and neurotoxic virus causing detrimental neuropathological changes resulting from both direct and indirect effects of the virus on the central nervous system (CNS) (Mitchell, 2006; Albright, *et al*., 2003; Miller, 2002; Tardieu, 1998; Schmitt, *et al*., 1991). These changes manifest as physical and cognitive impairments, which adversely affect function. The effect of HIV on an immature CNS (as in the case of vertically-infected infants) is injurious to a greater extent where neurological impairments occur in 15-40% of all cases (Msellati, *et al.*, 1993). Significant delays in cognitive, language and motor development are observed in these children (Abubakar, *et al*., 2009; Potterton, *et al*., 2009; Baillieu and Potterton, 2008; Van Rie, *et al*., 2008; Lindsey, *et al*., 2007; Foster, *et al*., 2006; Blanchette, *et al*., 2001; Drotar, *et al*., 1997; Belman, *et al*., 1996; Pollack, *et al*., 1996; Belman, *et al*., 1994) due to the inability of the immature CNS to cope with the destructive nature of HIV. Perinatal infection occurs at a time when an infant's CNS is going through a rapid process of myelination which is synonymous with the most substantive brain

development (Willen, 2006). Despite the above-mentioned evidence of developmental delay in children infected with HIV through vertical infection, no studies to date have looked at cognition, language and motor development in Zimbabwean infants.

ART has had a tremendous effect in reducing the prevalence of MTCT and decreasing mortality due to suppression of the HIV viral load (UNAIDS, 2010). This has given way to improvements in length of life and thus changed the outlook for people living with HIV from being a terminal disease, to that of a chronic illness (Robertson, *et al*., 2008; Gortmaker, *et al*., 2001). However it has been reported that despite the introduction of ART, the CNS effectively harbours the virus by means of an impermeable blood-brain barrier to the majority of available classes of ARVs (Miller, 2002). The limited access of ARVs into the CNS provides poor therapeutic levels to suppress the virus and so it continues to negatively manifest itself (Jaspan, *et al*., 2008; Eley and Nuttall, 2007; Lindsey, *et al*., 2007). The implications of extended life through ART do not equate to improved quality of life when living with neurological impairment secondary to HIV-related neuronal damage.

Problem Statement

Cognitive, language and motor development of children-exposed to HIV have not been studied in Zimbabwe. National efforts to minimise the effect of HIV in children include the provision of ARVs although paediatric roll-out is still limited. In addition to this, national objectives primarily focus on prevention and life-saving measures. However, this does not necessarily lead to improved quality of life for those children already infected with HIV, and living with neurological impairment.

Aim of Study

The aim of the study was to determine the difference in development (cognition; receptive and expressive language; and fine and gross motor) of HIV-exposed *infected* infants (i.e. infants who are born to HIV-positive mothers and are themselves infected) with the development of HIV-exposed but *uninfected* infants.

Objectives of the Study

- To measure height, weight and head circumference of HIV-exposed *infected* infants and HIV-exposed *uninfected* infants.
- To assess and describe cognitive, receptive and expressive language, fine and gross motor abilities in HIV-exposed *infected* infants with that of HIV-exposed *uninfected* infants.

Significance of the Study

There has been no research in Zimbabwe that has looked at development in HIV-exposed infants and so this problem remains unquantifiable. This study describes cognitive, language and motor development in a sample of Zimbabwean infants who were exposed to HIV through MTCT.

Research in this field may highlight gaps in the management of children who are experiencing developmental delay, not only those who are HIV-infected. An expansion of services may include access to physiotherapy, introduction of pre-schools for early cognitive stimulation, and possibly an expansion of ARVs to include more efficacious regimens for those who are HIV-positive and vulnerable to HIV-related neuropathology.

Finally, there is limited available research that has looked to minimise confounding cofactors that affect development as a result of neurological insult (orphan hood; institutionalisation; exposure to recreational drugs; maternal factors; neurological damage associated with pregnancy, labour and delivery and breastfeeding; socioeconomic status; and/or malnutrition).

Conclusion

Despite other studies being done worldwide on developmental delay in children living with HIV, Zimbabwe faces unique challenges that affect those infants who are born to HIV-positive mothers. There have been no studies hitherto looking at these issues and therefore the aim of this study was to determine the development of HIV-exposed *infected* infants compared with HIV-exposed but *uninfected* infants with a view to identify any differences in cognitive, language and motor development.

CHAPTER 2: LITERATURE REVIEW

This chapter will review the epidemiology of HIV in sub-Saharan Africa with a closer look at MTCT in Zimbabwe. It will then go on to discuss paediatric HIV and management in the developing world. This review will focus mainly on HIV and its implications on a child's development; and so a closer look at HIV and the developing CNS will also be made. Literature from previous studies looking at development of children living with HIV will be discussed. To conclude this section, the risk factors that affect early child development (ECD) will also be presented.

Literature was sourced through comprehensive searches on the following databases: Medline, Cochrane Collaboration, Pubmed, ScienceDirect and CINAHL. The following are the key words that were used in searches: HIV, children, development, encephalopathy, brain development, CNS, HIV vertical transmission.

2.1 Epidemiology

As stated above, sub-Saharan Africa accounts for two-thirds of the global HIV population (22.9 million [21 600 000 – 24 100 000] people in 2010). Globally, 3.4 million children [3 000 000 – 3 800 000] are living with HIV, more than 90% of whom are living in sub-Saharan Africa. In 2010, women accounted for 59% [56-63%] of all HIV infections in this region. (UNAIDS and WHO, 2011.)

The primary mode of transmission of HIV in sub-Saharan Africa is through heterosexual intercourse (UNGASS, 2009), where the majority of women will be of child-bearing age (15-49 years). Adversely, women living with HIV can during gestation, the perinatal period and/or while breastfeeding, expose their infants to HIV, which can lead to a large number of infants being infected with HIV. Therefore MTCT is the second most important mode of transmission in sub-Saharan Africa.

In sub-Saharan Africa, MTCT accounts for more than 90% of all paediatric HIV-cases (UNAIDS, 2010). Infants who are born to HIV-positive mothers are referred to as being HIV-exposed. It is estimated that more than 30% of HIV-exposed infants are HIV-positive when there has been no intervention (Sharland and Bryant, 2009; Dabis, *et al*., 1993; Boylan and Stein, 1991). In 2009, the reported percentage of Zimbabwean infants born to HIV infected mothers who are themselves infected was 30% (UNGASS, 2009), indicating failure of timely access to PMTCT programmes.

In 2009, Zimbabwe was deemed to be one of 25 countries with the largest number of pregnant women living with HIV (UNAIDS, 2010), where Harare had a HIV prevalence of 10-24.9% of pregnant women (UNAIDS, 2009). The history of Zimbabwe's unparalleled socio-economical challenges over the past decade has adversely affected basic social services in general. One of these services is ANC which is a means of advocating for Provider-Initiated Testing and Counselling for HIV (PITC) to effect PMTCT. It is well-known that PMTCT is dependent on access to ANC, an efficacious duration and regimen of ARVs (or ART if the mother is eligible) and skilled attendance during labour and delivery (UNAIDS, 2010; Lehman and Farquhar, 2007). PMTCT is not accessible to many pregnant Zimbabwean women living with HIV. In Harare, this is because of the following factors: women attending City of Harare clinics who wish to register a pregnancy are expected to pay USD30 (this fee was reduced from USD50 at the end of 2010); more than half those HIV-positive, pregnant women accessing ANC in 2008 were unable to obtain ARVs (UNAIDS, 2010); and it is reported that 39% of all births two years prior to 2009 were home-deliveries without skilled attendance (ZHDS, 2009). Zimbabwean infants born to HIV-positive mothers are therefore at high risk of acquiring HIV through vertical transmission due to poor access to ANC, little or no skilled attendance, and poor duration and regimen of ARVs.

2.2 Paediatric HIV

2.2.1 Mother-to-Child Transmission of HIV (MTCT)

MTCT can occur during pregnancy, intrapartum or during breastfeeding (Lehman and Farquhar, 2007; Kourtis, *et al*., 2001; Kuhn and Stein, 1995). Maternal viral load (presence of HIV-RNA in plasma) is a strong independent determinant of the risk of vertical transmission (John and Kreiss, 1996). A high viral load occurs secondary to primary infection of HIV (Humphrey, *et al.*, 2010; Dunn and Newell, 1992), advanced disease (Fawzi *et al*, 2001), or drug resistance (WHO, 2011). Increased risk of vertical transmission is also associated with poor maternal nutrition which can lead to impaired epithelial integrity of the placenta and lower genital tract (Dreyfuss and Fawzi, 2002).

The third trimester is associated with the highest transmission of HIV *in utero* primarily occurring when HIV crosses the placenta (Lehman and Farquhar, 2007). However, studies have been done which have found HIV in cells found in electively aborted foetuses in the first trimester of pregnancy (Lewis, *et al.*, 1990). Factors that are associated with transmission during pregnancy are: maternal genital infections, as well as malaria, which can damage the placenta and allow passage of HIV cells (Gumbo *et al.,* 2010; ter Kuile, *et al*., 2004; Bloland, *et al*., 1995; Inion, *et al*., 2003); and, gender, where female infants are thought to be at double the risk of infection than males (Biggar, *et al*., 2006).

Intrapartum transmission can occur because the infant is exposed to infected maternal blood during delivery (Lehman and Farquhar, 2007). Factors that will influence transmission during delivery are: birth complications; invasive procedures; and poor mucosal integrity of the delivery route (Lehman and Farqhar, 2007).

Breastfeeding is another method of MTCT (Coutsoudis, *et al.*, 2004). HIV-1 RNA has been found in infected breast milk cells. Low to high concentrations of HIV-1 RNA is

highly correlated with viral load in plasma. (Rousseau, *et al.*, 2004). Factors associated with transmission are: early mixed-feeding i.e. before six months of age when the infant's gastrointestinal tract is still immature and susceptible to damage (Coovardia, *et al.*, 2007), abrupt breastfeeding cessation (WHO, 2010b), and mastitis or breast abscess (Gumbo, *et al.*, 2010).

2.2.2 Testing

Infant testing is dependent on knowledge of the mother's HIV status. PITC is recommended for all infants and children known to have been exposed perinatally or those who shown signs and symptoms suggestive of HIV infection (malnutrition or tuberculosis). Children under 18 months of age require virological testing as antibody testing will elicit a false-positive result because maternal HIV antibodies persist during this period (WHO and UNICEF, 2010). Ideally, early infant diagnosis through testing should be initiated within the first two months of life because 30% of infants will die from HIV before their first birthday, 50% by their second birthday (WHO and UNICEF, 2011).

Testing is extremely important to reduce mortality and morbidity through timely provision of ART before clinical disease manifests, as well as to identify HIV-exposed but uninfected infants and thus implement prevention strategies such as counselling on appropriate infant feeding practices to reduce risk of future infection (through breastfeeding), whilst ensuring adequate nutrition and health (WHO, 2011). HIV-exposed infants in Zimbabwe now have access to virological testing using the Dried Blood Spot (DBS) method, although this service is not available at all sites nationwide.

All children under the age of two years with a confirmed HIV-positive status are eligible for ART. Testing is therefore a very important factor in ensuring that a diagnosis is made so that ART can be initiated promptly.

2.2.3 Prevention of Mother-to-Child Transmission of HIV (PMTCT)

PMTCT is primarily dependent on a multitude of factors. The mother's knowledge of her status before or during pregnancy, and/or accessing antenatal clinics where PITC is available, can be complicated by a number of factors such as poverty, psychosocial issues, and variance in HIV management. However, if the mother accesses the service then PMTCT works to minimise the risks of transmission through: maternal ART (if eligible) or ARV prophylaxis to lower her viral load; infant prophylaxis at birth, extended through the breastfeeding period; and, safe feeding practices (where exclusive breastfeeding is promoted in developing countries) and prescription of co-trimoxazole at six weeks for breastfed infants. Table 2.1 shows the Zimbabwean guidelines for PMTCT.

Table 2.0 Zimbabwean PMTCT guidelines

Year Implemented	Preferred 1st Line ART (pregnant women *eligible* for ART)	ARV prophylaxis (pregnant women *not eligible* for ART)
2011	Tenofovir + Lamuvidine + NVP, or	AZT 300mg bi-daily from 14 weeks + sd-NVP in labour + AZT 300mg + Lamuvidine 150mg bi-daily for seven days
	AZT + Lamuvidine + NVP	
	INFANT: NVP daily for six weeks	INFANT: Extended NVP prophylaxis to cover breastfeeding period.
2009/10		AZT from 28 weeks + AZT/Lamuvidine in labour and for seven days
		INFANT: sd-NVP
2008		sd-NVP in labour
		INFANT: sd-NVP

2.2.4 Antiretroviral Therapy (ART)

ART acts on different stages of the HIV life cycle to prevent replication of the virus (Simon, *et al.*, 2006). De Clercq's review (2010) shows that with Azidothymidine/Zidovudine (AZT) being the first antiretroviral drug used 25 years ago, ART has advanced significantly to advocate for three or four drugs to be used in a triple therapy combination. In this report, ART will be the term used to denote highly-active active antiretroviral therapy (HAART), which has been available since 1996 in developed countries (De Clercq, 2009), and since 2004 in Zimbabwe for adult formulations. There are now several classes of ARVs which will be discussed briefly with regard to those available in Zimbabwe:

- *Nucleoside Reverse Transcriptase Inhibitors* (NRTIs), *Nucleotide Reverse Transcriptase Inhibitors* (NtRTIs) and *Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)* inhibit the enzyme reverse transcriptase; and thus prevent HIV-RNA from transcribing itself into HIV-DNA, which effectively prevents replication. NRTIs include AZT, Stavudine, Lamuvidine, and Abacavir. NtRTIs include Tenofovir. NNRTIs include Nevirapine (NVP) and Efavirenz.

- *Protease Inhibitors* (PIs) inhibit the enzyme protease. Protease is necessary for the maturation of RNA viral particles (virions). Inhibiting protease therefore prevents virions from maturing into infectious particles and thus slows replication of the virus. Ritonavir and Lopinavir are PIs. (Simon, *et al*., 2006).

With regard to PMTCT, ART/ARVs can be given to an HIV-positive mother in pregnancy, the intrapartum period and breastfeeding, to reduce the maternal viral load, and thus lower the risk of transmission (Volmink, *et al.*, 2007). The World Health Organization (2010) recommends that pregnant women should be started on ART if they are eligible (i.e. confirmed HIV-positive status, and, CD4 count is ≤350µl; and/or they present with a WHO Clinical Stage of 3 or 4). ARV prophylaxis should be given

to all pregnant women who are not eligible for ART. ARVs are recommended as post-exposure prophylaxis for the infant at delivery and for the entire duration of breastfeeding, regardless of the mother's HIV management (WHO, 2010a).

2.3 The Developing CNS and HIV

HIV is a neurotropic and neurotoxic virus causing detrimental neuropathological changes resulting from both direct and indirect effects of the virus on the CNS (Mitchell, 2006; Albright, *et al*., 2003; Tardieu, 1998; Aylward, *et al.*, 1992; Schmitt, *et al*., 1991). In children, damage to the CNS is mainly due to presence of the virus, and not opportunistic infections, as these are rare, occurring in mainly older children and largely in adults (Belman, 1992). An exception is TB meningitis which is commonly reported in infants younger than one year (Hesseling, *et al*., 2009).

The effect of HIV on an immature CNS (as in the case of vertically-infected infants) is injurious to a greater extent than in adults, where neurological impairments occur in 15-40% of all cases (Msellati, *et al.*, 1993) and manifest as progressive or static encephalopathy (Van Rie, *et al.*, 2007, Belman, 1997). The effects of the virus on the CNS will differ according to the stage of brain development at time of infection (Belman, 1997), and this too, will lead to varying clinical presentations (Belman, 1990). As the last trimester of pregnancy is known to be synonymous with rapid brain development, children who are infected at this time are likely to show more severe CNS disease progression (European Collaborative Study, 1996). Having said this, disease progression of the infant is dependent on the disease stage, CD4 count and viral load of the mother (Ioannidis, *et al*., 2004; Fawzi, *et al*., 2001). Presentations of HIV encephalopathy generally manifest as physical, language and cognitive impairments, which adversely affect function.

Significant delays in cognitive, language and motor development are observed in children infected with HIV (Abubakar, *et al*., 2009; Potterton, *et al*., 2009; Baillieu and Potterton, 2008; Van Rie, *et al*., 2008; Lindsey, *et al*., 2007; Foster, *et al*., 2006;

Blanchette, *et al*., 2001; Drotar, *et al*., 1997; Belman, *et al*., 1996; Pollack, *et al*., 1996) due to the inability of the immature CNS to cope with the destructive nature of the virus.

This section will look at the neuropathogenesis of HIV and the clinical manifestations of the disease on an immature CNS and will attend to the cognitive, language and motor deficits that these children suffer.

2.3.1 Neuropathogenesis

HIV-1 is known to enter the CNS as early as the tenth day after primary infection (Powderly, 2000; Davis, *et al.*, 1992) chiefly by infecting blood monocytes, macrophages and T lymphocytes which all contain CD4 receptors (Albright, *et al.,* 2003; Liu, *et al.*, 2000). This is known as the 'Trojan-Horse' hypothesis (Peluso, *et al.*, 1985) where the infected cells cross the blood-brain barrier (BBB) and/or the cerebrospinal fluid (CSF) brain barrier (Albright, *et al.*, 2003). Ironically, it is these structures that prevent ART from permeating efficaciously into the CNS and effectively halting viral replication and preventing the development of a drug-resistant, mutant virus (Jaspan, *et al*., 2008; Eley and Nuttall, 2007; Lindsey, *et al*., 2007; Miller, 2002).

HIV can remain in the nervous system due to this notion that the CNS (by means of its barriers) is a viral reservoir (Epstein and Gendelman, 1993). In this haven the virus is known to replicate, thereby causing direct damage to the neural tissue of the CNS (Grovit-Ferbas and Harris-White, 2010). The virus then goes on to infect parenchymal microglia and perivascular monocyte-derived macrophages (Wiley, *et al.*, 1986), as well as astrocytes and neurons in paediatric infection (Tornatore, *et al.*, 1994). Unlike the adult disease, astrocytes are infected (Tornatore, *et al.*, 1994) which leads to poor oligodendrocyte function in the production of myelin (Ishibashi, *et al*., 2006), hence retarded or absent myelination.

Secondary effects occur, where the infection of these cells triggers a chronic inflammatory response which causes the pathological changes in the CNS, alternately known as the indirect effects of HIV on the CNS (Eugenin, *et al.*, 2006). This inflammatory response activates migration of more microglia to the site where cytotoxic responses occur such as: release of reactive oxygen species and nitric oxide, and secretion of cytokines (Hegg, *et al.*, 2000), as well as overstimulation by neurotransmitters of the N-methyl-D-aspartate type receptor (NMDAR) system (Mitchell, 2006). The release of these proinflammatory mediators damages the structure of the surrounding cells which impacts on their functioning, leading to neuronal loss as a result of monocyte recruitment (Ivey, *et al.*, 2009). And so the cycle continues by means of a cytotoxic cascade (Pulliam, *et al.*, 1991). This damage creates a variety of CNS abnormalities which are known as HIV encephalopathy.

Pathological changes associated with HIV encephalopathy are: diffuse myelin pallor; astrogliosis; disseminated glial-microglial nodules; dendritic destruction and neuronal loss; and fusion of microglia resulting in multinucleated giant cells (MGC), the hallmark of CNS infection by HIV (Sharer, 1992; Brew, *et al.*, 1988; Navia, *et al.*, 1986a; Navia, *et al.*, 1986b; Sharer, *et al.*, 1985). Neuroimaging shows abnormalities consisting of enlargement of the subarachnoid space and ventricles, calcifications of the basal ganglia and the frontal lobe white matter (Tardieu, 1998; Belman, *et al*., 1986), cerebral atrophy, white matter lesions (De Carli, *et al*., 1993), and demyelination (Angelini, *et al.*, 2000), which correlate with the microscopic findings.

To conclude, CNS infection by HIV happens early after primary infection and results in diffuse damage of neural tissue with devastating clinical manifestations which are the effects of HIV encephalopathy. The neurological impairments are more marked in children who have acquired HIV through vertical transmission due to an immature nervous system. The following section will discuss the clinical presentation of HIV encephalopathy.

2.3.2 Clinical Manifestations of HIV Encephalopathy

HIV encephalopathy as a clinical diagnosis is the umbrella term given to the wide spectrum of presentations seen with CNS infection by HIV (Hilburn, *et al.*, 2010; Sherr, *et al*., 2009; Van Rie, *et al*., 2007; Smith *et al.*, 2006; Brouwers, *et al*., 1995; Chase, *et al.*, 1995; Aylward, *et al.*, 1992; Belman, 1992). It must be noted that there is a distinctly different pattern of clinical presentation seen in children when compared to the dementias seen in adults, due to the effect of the virus on an immature CNS (Smith, *et al*., 2006; Belman, 1997; Chase, *et al.*, 1995).

HIV encephalopathy in children is classified as a World Health Organization (WHO) Clinical Stage 4 which is an Acquired Immune Deficiency Syndrome (AIDS) defining illness. Currently the World Health Organization (p. 37, 2007) states that clinical diagnosis of HIV encephalopathy in children younger than 15 years of age requires identification of "at least one of the following progressing over at least two months in the absence of another illness:

failure to attain, or loss of, developmental milestones
or loss of intellectual ability;
or,
progressive impaired brain growth
demonstrated by stagnation of head circumference;
or,
acquired symmetrical motor deficit
accompanied by two or more of the following:
paresis, pathological reflexes, ataxia and gait disturbances."

WHO recommends that definitive diagnosis of HIV encephalopathy can be made (when other causes have been excluded) if neuroimaging demonstrates atrophy and basal ganglia calcification (WHO, p.37, 2007), which is not feasible for the majority of children living in developing countries.

The occurrence of HIV encephalopathy is reported more frequently among children presenting with symptomatic disease during the first two years of life (Newell, 1998). HIV encephalopathy is likely to present more frequently in this time period as the first

years of life are synonymous with rapid myelination as well as the most substantial development of the CNS (Willen, 2006; Blanchette, *et al*., 2001); the virus is infecting and thus damaging an immature CNS at a critical time point. It is also noted that there is a higher cumulative incidence of encephalopathy in children compared to adults during the first and second years post-infection (Tardieu, *et al*., 2000). This is likely to occur due to 90% of children being infected with HIV through vertical transmission and thus the incidence of HIV encephalopathy coincides with the effects of HIV on an immature CNS. Correlations have been made between low birth weight, smaller head circumference and early occurrence of symptomatic CNS disease (Tardieu, *et al.*, 2000). Although, these correlations need to be verified according to the time of transmission of the infants studied so as to provide explanation for differing clinical presentations between *in utero* infection, infection during labour and delivery or infection through breastfeeding.

Neurological dysfunction is often the earliest sign of HIV infection in infants and young children (Pizzo, *et al.*, 1988) and can manifest as cognitive, language and/or motor delays. In developing countries where access to HIV management is stringent, identification of these signs (and eliminating other causes) aids in the presumptive diagnosis of HIV infection (WHO, 2007b) – permitting infants and children to start ART. HIV encephalopathy has a progressive or static course of disease progression (Civitello, 2003).

Progressive encephalopathy has two subtypes – subacute progressive or plateau (Civitello, 2003). Subacute progressive encephalopathy has a slow, insidious onset and is clinically apparent in infants and young children and is the most severe form of the disease. It presents as the loss of previously acquired, or failure to attain milestones and progressive, generalised motor dysfunction (Belman, *et al*., 1988; Epstein, *et al*., 1988) including oromotor dysfunction. Plateau encephalopathy is characterised by an indolent course of clinical progression where acquisition of milestones occurs at a slower rate than previously acquired skills. Brain growth slows as does cognitive development, and spastic diplegia is common (Civitello, 2003). Acquired microcephaly is a common finding with progressive encephalopathy.

Static encephalopathy is clinically evidenced by a slow rate of development, without loss of skills (Civitello, 2003) with poor brain growth and mild atrophy (Belman, *et al*., 1988; Epstein, *et al*., 1988). Due to the subtle clinical manifestations of this course of the disease, children who develop static encephalopathy in developing countries are often only diagnosed with HIV encephalopathy at school-age due to this form of the disease manifesting as lower cognitive attainment (Mialky, *et al*., 2004).

Literature reporting on the clinical manifestations of HIV encephalopathy in children can be confounded by: inconclusive definitions of HIV encephalopathy where only the extreme spectrum of the disease are observed; inclusion of children with opportunistic CNS infections or CNS tumours secondary to HIV; inclusion of children who may have suffered CNS damage through other factors such as intravenous drug use and/or alcohol abuse which is usually seen in studies from the developed world (Blanchette, *et al*., 2001; Chase, *et al*., 2000; Mellins, *et al.*, 1994; Nozyce, *et al.*, 1994; Ultmann, *et al*., 1985) and/or factors that increase poor early child development (poverty and, poor health and nutrition) which are commonly found in studies from the developing world. These factors will be considered in section 2.5 when discussing the findings of clinical studies.

2.4 Developmental Delay

This section will discuss the delay in cognition, language and motor development associated with HIV encephalopathy.

2.4.1 Cognitive Delay

Neurocognitive impairment has been shown to result from a direct infection of macrophages and microglia in the CNS (McGrath, *et al*., 2006; Angelini, *et al*., 2000; Safriel, *et al*., 2000; Mintz, 1999; Brouwers, *et al.*, 1995). Cognitive delay in HIV-infected children has been well documented in numerous studies with a variety of clinical manifestations. These include: behavioural impairments, learning impairments, lower intellectual function, poor ability in sequential processing, attention-deficit disorders; and spatial memory impairment (Ruel, *et al.*, 2012; Grover, *et al*., 2007; Willen, 2006; Chase, *et al*., 2000; Blanchette, *et al*., 2001; Pearson, *et al*., 2000; Boivin, *et al*., 1995; Gay, *et al.*, 1995; Brouwers, *et al*., 1995; Mellins, *et al.*, 1994; Nozyce, *et al*., 1994).

2.4.2 Language Delay

Language is a complex skill which is dependent on both cognitive and motor function (Wolters, *et al*. 1997). Studies have identified that expressive language is more severely affected than receptive language in HIV-infected children (Van Rie, *et al*., 2008; Wolters, *et al.*, 1997). Common problems observed in children with HIV infection are: feeding problems and impaired articulation (Wolters, *et al*., 1997).

2.4.3 Motor Delay

Motor delay in HIV-infected children is apparent in the early postnatal period (Chase, *et al*., 1995; Nozyce, *et al*., 1994). Due to motor development being synonymous with obvious child developmental milestones (such as head control, sitting, crawling and walking), motor delay can assist in a presumptive diagnosis of HIV infection during this period (Hilburn, *et al*., 2010). Motor impairments consist of: abnormal muscle tone, muscle weakness, poor coordination and hyperreflexia (Drotar, *et al.*, 1997; Chase, *et al*, 1995; Msellati, *et al*., 1993).

Table 2.1 shows a summary of clinical studies that have described the extent of cognitive, language and motor delay in HIV-infected children in sub-Saharan Africa. A list of the abbreviations used in the table will follow the table.

Table 2.1 Studies showing extent of developmental delay in HIV-infected children

Author	Year	Country	Population Size	Age of Children	Percentage of HIV-infected children with delay
Msellati, *et al*.	1993	Rwanda	50+ 136- 32u	6-24 mo	31% (12 mo of age) 40% (18 mo of age)
Boivin, *et al.*	1995	DRC	14+ 20- 16c	<24 mo	All infected infants had social and motor deficits
Drotar, *et al*.	1997	Uganda	59+ 211- 107c	0-24 mo	At 12 mo of age: 26% cognitive 30% motor
McGrath, *et al*.	2006	Tanzania	327	6-18 mo	26% general delay
Bagenda, *et al*.	2006	Uganda	28+ 37- 42e	6-12 yrs	No significant delay or neurological impairment
Baillieu and Potterton	2008	South Africa	40+	18-30 mo	70% cognitive 82.5% language 85% gross motor 12.5% fine motor
Smith, *et al*.	2008	South Africa	39+	Mean 60 mo	33.3% motor dysfunction 33-81% subnormal intelligence quotients
Van Rie, *et al.*	2008	DRC	35+ 35a 90c	18-72 mo	60% cognitive 29% motor 85% expressive language 77% receptive language
Potterton, *et al*.	2009b	South Africa	60+ 62-	<48 mo	52% cognitive 72% motor
Shead, *et al*.	2010	South Africa	16+ 24-	16-42 mo	Significant mental and motor delay
Jelsma, *et al*.	2011	South Africa	21+ 23-	Mean 52.8 mo	All 21 children who were HIV infected were significantly delayed.
Lowick, *et al*.	2012	South Africa	30+ 30c	55-75 mo	90% severely delayed 46.7% mental handicap
Ruel, *et al*.	2012	Uganda	93+ 106-	2-12 yrs	Significant neurocognitive and motor deficits compared to controls

Abbreviations used in Table 2.1

+	HIV-positive (HIV+)	e	HIV-exposed, uninfected (HEU)
-	HIV-negative (HIV-)	mo	months
a	HIV-infected, affected	yrs	years

2.5 Clinical Studies

This section will review the clinical studies on paediatric HIV-related neurological impairment from the early 1980s to present day. Clinical studies from developed countries will be discussed first as these were the first to emerge. A discussion will also be presented on the effect of ART on the development of children infected with HIV. Finally, studies from sub-Saharan Africa will be reviewed as these relate to this study and present challenges different from those in the developed world.

2.5.1 Developed World

Pre-antiretroviral Era

In June, 1981 the United States (US) Centers for Disease Control and Prevention (CDC) issued the first official report on AIDS which discussed five cases of a rare pneumonia (*Pneumocystis carinii* pneumonia) presenting in homosexual men in Los Angeles, California (MMWR Weekly, 1981). Reports from medical communities in New York and California had also been made earlier that year on an aggressive form of Karposi's sarcoma presenting in eight young homosexual men in New York (Hymes, *et al*., 1981). These diseases were later evidenced as AIDS-related. It was a common assumption at this time that AIDS was a homosexual male's disease (Altman, 1981). HIV was however unknown as the pathogen implicated until 1985 (Marx, 1985) and only named as HIV in 1986 (Coffin, *et al*., 1986) but the link between HIV and AIDS was still not clear. Altman (1981) reported on Dr Curran of the CDC as saying "the best evidence against contagion is that no cases have been reported to date outside the homosexual community or in women." Inevitably, in August 1982, a 20-month old male infant from California, who received multiple blood transfusions

after a complicated birth history, died of AIDS (MMWR Weekly, 1982). This was the first official report on paediatric HIV in the US.

Given the above history on the emergence of HIV/AIDS, it is not surprising that the first clinical studies to emerge in 1985 that focused on paediatric HIV-related neurological impairments had their limitations. Methodological issues included: case study design; small sample sizes (a range of four to 16 children); wide age ranges (six months to 11 years); no comparison of cases with controls; diagnoses of AIDS was made from clinical symptoms and signs of defective cell-mediated immunity which ensured an inclusion of children with symptomatic HIV infection (AIDS-related complex, or AIDS); poorly standardised neurodevelopmental assessment; and inclusion of confounding factors for child development such as drug-exposure during pregnancy, premature gestation, small-for-gestational age birth weights, CNS infections (by cytomegalovirus, Epstein-Barr virus, *Haemophilus influenzae* meningitis, and *Toxoplasmosis gondii*), co-infection with *Pneumocystis carinii* pneumonia, history of seizures, orphan hood, and, other medical conditions affecting growth and development (Belman, *et al*., 1985; Epstein, *et al.*, 1985; Ultmann, *et al*.,1985).

Although not methodologically sound, these studies offered much-needed information, as well as public awareness of a deadly virus at a time when very few public health initiatives were being undertaken to research and publicise the disease (Shilts, 1987). The clinical studies in the 1980s were also the first to document the neurological sequelae seen in children with HIV infection, identify a correlation between clinical disease progression with pathological findings (Belman, *et al*., 1988; Belman, *et al*., 1985; Epstein, *et al.*, 1985; Ultmann, *et al*., 1985) and suggest HIV infection as the primary cause of encephalopathy (Epstein, *et al*., 1986). Attempts were made during this time to objectify the medical observations by employing the first edition of the BSID, the Denver Developmental Screening Test, First Edition and the Stanford Binet (Belman, *et al*., 1985; Ultmann, *et al*., 1985). Epstein and colleagues (1985) relied on CT scans and neurological examinations. Belman and colleagues (1988) employed a longitudinal study design and included 68 HIV-positive children from six weeks to 13 years of age. In this study, Belman, *et al*. found evidence of CNS dysfunction in 90%

of the population. However, this high prevalence was documented in an age when referral was dependent on clinical signs of AIDS and thus implicates those children with already established severe progression of the disease. The primary aim of this study, as was the aim of the previous studies in the 1980s, was to document clinical signs and symptoms, and disease progression, and not the prevalence of HIV-related neurological dysfunction. The study by Belman, *et al*. (1988) and the review by Epstein, *et al*. (1988) identified categories of HIV encephalopathy, namely progressive and static. This is interesting as it shows that the authors were sensitised to the variations in disease progression and gave pointers for future research as to pathogenic mechanisms of vertical transmission, timing of infection, and suggested that the most useful approach to paediatric HIV infection is one of prevention.

Some of the hallmark features which the World Health Organization (WHO, 2007b) has adopted to aid in the clinical diagnosis of HIV encephalopathy in children were documented through observation during this period: acquired microcephaly, pyramidal tract signs and encephalopathies (Belman, *et al*., 1988).

Clinical studies started to emerge in the 1990s from Europe and Africa with continued studies from North America. The focus in developed countries shifted from descriptions of the effect of HIV on the CNS to documenting the extent of neurological and developmental impairment (Belman, *et al*., 1996; Gay, *et al*., 1995; Lobato, *et al*., 1995; and European Collaborative Study, 1990). Improvements in methodology to support this aim included: longitudinal design; smaller age ranges from birth to four years with increased sample sizes (Belman, *et al*., 1996; Pollack, *et al*., 1996; Chase, *et al*., 1995; Gay, *et al*., 1995; Mellins, *et al*., 1994; Nozyce, Hittelman, *et al*., 1994; Condini, *et al*., 1991; and, European Collaborative Study, 1990); employing the use of the BSID-I, a standardised assessment tool (Belman, *et al*., 1996; Pollack, *et al*., 1996; Chase, *et al*., 1995; Gay, *et al*., 1995; Mellins, *et al*., 1994; and, Nozyce, Hittelman, *et al*., 1994); introduction of control groups (Belman, *et al*., 1996; Pollack, *et al*., 1996; Chase, *et al*., 1995; Gay, *et al*., 1995; Mellins, *et al*., 1994; Nozyce, Hittelman, *et al*., 1994; Condini, *et al*., 1991; European Collaborative Study, 1990; and Diamond, *et al*., 1990); and minimising confounding factors (Belman, *et al*., 1996).

However, limitations were present and included: failure to state how HIV diagnosis was made (Lobato, *et al*., 1995); lack of uniformity in diagnostic procedures (European Collaborative Study, 1990) due to the available diagnostic tests at the time having poor sensitivity and specificity for the age-range studied; blinding to the HIV-status of the child was redundant as clinical signs of HIV infection were used to diagnose the children in some of these studies, and therefore would be obvious to the assessor (Belman, *et al*., 1996; Nozyce, Hittelman, *et al*., 1994; European Collaborative Study, 1990; and Diamond, *et al*., 1990); and, some studies failed to objectify their findings by employing the use of a standardised assessment tool (Lobato, *et al*., 1995; Blanche, *et al*., 1990; European Collaborative Study, 1990). Despite using neurological examination exclusively, Blanche and colleagues (1990), and the European Collaborative Study (1990) were in agreement with their findings that approximately a third of children with HIV showed higher risks of suffering HIV-related neurological impairment, and this concurs with a study conducted by Belman, *et al*. (1996) which used neurological examination in conjunction with the BSID-I and found that 25% of children infected with HIV had neurological impairment. It is also important to note that the discrepancies observed in quantifying the extent of neurological and developmental impairment between studies conducted in the 1980s and the 1990s exist due to differences in the: aims of the research conducted; and methodology employed, namely study design (case studies versus longitudinal prospective studies) and sample size. It must also be stated that in the early 1990s, as in the 1980s, these studies were limited by the inconclusive knowledge of HIV available.

Some important findings on paediatric HIV-related neurological and developmental impairments emerged at this time. Children with symptomatic HIV infection are more at risk of developmental impairment than asymptomatic HIV-infected children (Nozyce, *et al*., 1994) indicating that disease progression is correlated with increased morbidity and mortality (Belman, *et al*., 1996; Lobato, *et al*., 1995). A diagnosis of HIV-encephalopathy indicates a mean survival time of 22 months with natural progression of the disease, where the highest risk of HIV-encephalopathy (4%) occurs in the first year of life (Lobato, *et al*., 1995). The mean rate of development in the first 24 months of life is slower in HIV-infected children than in HIV-exposed uninfected children (Chase, *et al*., 1995; Gay, *et al*., 1995). Belman, *et al*. (1996) also established that

HIV-exposed uninfected infants' neurological development is not different from that of HIV-uninfected controls.

Antiretroviral Era

In the decade following the 1990s, studies started to be published in the United States and Puerto Rico using data from the Woman and Infants Transmission Study (WITS) (Nozyce, *et al*., 2006; Smith, *et al*., 2006; Llorente, *et al*., 2003; Macmillan, *et al*., 2003; Chase, *et al*., 2000; Smith, *et al*., 2000), the Pediatric AIDS Clinical Trials Group (Lindsey, *et al*., 2007; Pearson, *et al*., 2000), and from the Adolescent Master Protocol (Rice, *et al*., 2012). These studies were primarily concerned with describing the type of neurodevelopmental impairment. One study looked at the risk of neurodevelopmental impairment associated with timing of HIV infection (Smith, *et al*., 2000). Common themes that were found in these studies were that HIV infection increases the risk for neurodevelopmental impairment, namely cognitive and motor domains (Blanchette, *et al*., 2001; Macmillan, *et al*., 2001; Chase, *et al.*, 2000; Smith, *et al*., 2000), and behavioural and cognitive domains reported by Nozyce *et al* (2006). Other studies reported on severity of impairments being associated with outcomes in HIV-infected children (Smith, *et al*., 2006; Llorente, *et al*., 2003; Pearson, *et al*., 2000) with a reduction in mortality and severity with the use of ART (Lindsey, *et al*., 2007). Foster and colleagues (2006) reported on HIV-positive children in the United Kingdom less than three years of age and found persistent neurodevelopmental impairment despite ARVs/ART. Although it is important to note that some of the children included in this retrospective case note review were treated in the pre-ART era, while others received ART (Foster, *et al*., 2006).

A recent study has identified the need to report on language impairment in HIV-positive children and found no significant effect of HIV infection status on the odds of language impairment (Rice, *et al*., 2012). This is contrary to a cross-sectional study conducted by Koekkoek *et al* (2008) in the Netherlands where HIV-infected children in a similar age-range showed poorer verbal fluency than age-norms. The study by Rice *et al* (2012) was of cross-sectional design, which meant that language function was

assessed at one time-point, and the groups were not well-matched (the HIV-exposed group was younger and living in lower income households) – two factors that are known to introduce bias when interpreting the results.

The methodology employed in these studies suggests improved accuracy in the validity of the results obtained. These factors include: longitudinal design (except for those studies by: Rice, *et al*., 2012; Koekkoek, *et al*., 2008; Foster, *et al*., 2006; and, Blanchette, *et al*., 2001), larger sample sizes as a result of access to multiple research sites, use of valid and reliable outcome measures in addition to brain scanning and neurological assessment, and more structured inclusion and exclusion criteria.

All except one study (Chase, *et al*., 2000) showed that children with HIV infection received ARVs according to accepted guidelines (at the time of data collection) on the standard of care for paediatric HIV patients (Rice, *et al*., 2012; Koekkoek, *et al*., 2008; Lindsey, *et al*., 2007; Foster, *et al*., 2006; Nozyce, *et al*., 2006; Smith, *et al*., 2006; Llorente, *et al*., 2003; Macmillan, *et al*., 2003; Blanchette, *et al*., 2001; Pearson, *et al*., 2000; Smith, *et al*., 2000). The advancements in pharmacological management during the data collection period of these studies introduced error which could not be controlled. Three options of ARV regimens were generally available during the time periods of data collection for these trials. Therefore, depending on the year that the child was assessed dissimilarities between HIV-positive children will exist because of how the virus impacts on development in the presence of differing efficacy of these pharmacological interventions. The most obvious example of this effect is the study conducted by Lindsey *et al* (2007).

A summary of the clinical studies from the developed world that have been discussed in this section can be viewed in Table 2.2 on the next page. Abbreviations used in this table will follow for ease of reference.

Table 2.2 Clinical studies from the developed world

Author	Year	Country	Research Design	Population Size (n)	Age of Children	Tools	Neurological and Developmental Impairments (HIV+)	Main Findings
Belman, *et al.*	1985	USA	Case Review	6+	6 mo - 5 yrs	- CT scan, EEG, VEPs and BAEPs - DDST - BSID-I - SB	All	The children in this study were documented as suffering from developmental and/or neurological impairment.
Epstein, *et al.*	1985	USA	Case Review	4+	9 mo - 11 yrs	- CT scan - Neurological Examination	All	Progressive encephalopathy manifests as loss of milestones in younger children and loss of higher cortical function in the older child. All children showed neurological impairment.
Ultmann, *et al.*	1985	USA	Case Review	16+	10 mo - 6 yrs	- BSID-I - SB - DDST	All	All children show developmental and neurological impairment.
Epstein, *et al.*	1986	USA	Longitudinal	36+	2 mo - 11 yrs	- Serial Neurological Examination - BSID-I - VSMS - BTVMI - DAP - SB - CT Scans	Motor and expressive language developmental delay were more common and of greater severity than receptive language and cognitive deficits.	Progressive encephalopathy occurs in greater than 50% of children with HIV infection. Progressive encephalopathy is due to primary infection of CNS with HIV.
Belman, *et al.*	1988	USA	Longitudinal	68+	6 wks-13 yrs	- BSID-I - SB - PLS - KABC-1	90% CNS dysfunction.	Variable severity of dysfunction and neurologic course.
Blanche, *et al.*	1990	France	Longitudinal	94+	1 mo-9 yrs	- Neurological Examination	Higher incidence of HIV encephalopathy in 33% of children diagnosed with AIDS.	One-third of children had AIDS defining illness and higher incidence of encephalopathy. The majority had longer survival and less severe clinical symptoms.
European Collaborative Study	1990	Eight European Centres	Longitudinal	39+ 164e	Birth-4 yrs	- Neurological Examination	31% of children showed delay.	Lower prevalence of developmental delay than reported in US studies.
Condini, *et al.*	1991	USA	Longitudinal	18+ 18e	18-30 mo	- Brunet-Lèzine's Tests	Mean length of utterance is less advanced in HIV+ children.	HIV infection impairs genesis rather than later development of language in infected but not ill children.
Mellins, *et al.*	1994	USA	Longitudinal	24+ 30e 23c	4-30 mo	- BSID-I - Neurological Examination	Significantly lower mental and psychomotor scores.	HIV+ and perinatal drug-exposure indicates worse psychomotor and mental scores.

Author	Year	Country	Research Design	Population Size (n)	Age of Children	Tools	Neurological and Developmental Impairments (HIV+)	Main Findings
Nozyce, Hittelman, *et al.*	1994	USA	Longitudinal	21+ 65e 95-	Birth-2 yrs	- BSID-I - Kent Scoring Adaptation	HIV+ children had significantly lower mental and psychomotor scores.	Children with HIV who are symptomatic are at greater risk for developmental impairment than asymptomatic. HIV-exposed uninfected children are not affected by mother's HIV status.
Chase, *et al.*	1995	USA multi-centre	Longitudinal	24+ 27e	4 mo-30 mo	- BSID-I	50% developmentally delayed. Deceleration of mental development in late infancy.	Early and persistent motor delay is common in HIV+ children. Mental development stagnates in late infancy. Variable presentations observed.
Gay, *et al.*	1995	USA	Longitudinal	28+ 98e	Birth-2 yrs	- BSID-I	66% cognitive 50% motor	Mean rate of development in first 24 months is significantly slower in HIV+ children. The delay also increases with age.
Lobato, *et al.*	1995	USA multi-centre	Longitudinal	1811+	Birth-13 yrs	- Medical Record Review	23% of children had HIV encephalopathy	Highest risk of HIV encephalopathy in first year of life (4%). Diagnosis of HIV encephalopathy indicates a 22 month median survival time with natural progression of the disease. Therefore increased morbidity and mortality with HIV encephalopathy.
Belman, *et al.*	1996	USA	Longitudinal	32+ 99e 116c	Birth-2 yrs	- Neurological Examination - BSID-I	25% showed neurological impairment.	Significantly more neurological problems in HIV+ children especially those who have serious clinical disease. HIV-exposed uninfected children's development was not different from controls
Pollack, *et al.*	1996	USA	Longitudinal	22+ 42e 27-	Birth-2 yrs	- BSID-I	Impaired cognitive and motor development in HIV+ infants.	Developmental delay first appreciated at 12 months of age. Delay in HIV+ children is positively correlated with decreased linear growth. Growth and development correlated with HIV viral load.
Chase, *et al.*	2000	USA multi-centre	Longitudinal	114+ 481-	4 mo-30 mo	- BSID-II	Cognitive and motor delays.	HIV infection is significantly associated with increased risk of abnormal mental and motor development.
Pearson, *et al.*	2000	USA multi-centre	Longitudinal	722+	Birth-16 yrs	- BSID-II - MSCA - WISC-R - WAIS-R - CT and MRI Scans		Neuropsychological and motor outcomes are predictors of long-term outcomes in HIV+ children.

Author	Year	Country	Research Design	Population Size (n)	Age of Children	Tools	Neurological and Developmental Impairments (HIV+)	Main Findings
Smith, *et al.*	2000	USA multi-centre	Longitudinal	114+	Birth-30 mo	- BSID-I	Poorer motor and mental development in early infected infants.	Early HIV infection increases the risk for poor neurodevelopmental functioning in the first 30 months of life.
Blanchette, *et al.*	2001	Canada	Cross-Sectional	25+ 25e	Mean 24.7 mo (HIV+) Mean 18.5 mo (HIVe)	- BSID-II - CT Scan	Mild impairments in mental development and significantly delayed motor development.	CT abnormalities were associated with developmental delay, particularly motor development.
Macmillan, *et al.*	2001	USA multi-centre	Longitudinal	147+ 383c	Birth-30 mo	- BSID-II	Lower mental and motor scores for HIV+ group.	HIV infection is persistent and is associated with slow neurodevelopment and decreased head growth. Infants exposed to in utero hard drugs show some postnatal recovery.
Llorente, *et al.*	2003	Six sites in USA including Puerto Rico	Longitudinal	157+	4 mo-30 mo	- BSID-I		Low BSID scores at 4 months are independent and viable predictors of mortality.
Foster, *et al.*	2006	United Kingdom	Retrospective Case Note Review (1989-2001)	62+	<3 yrs	- Neurological Assessment - GMFCS - BSID-II - GMDS - MSCA	40% developmental delay 22% abnormal neurological signs	More neurodevelopmental impairment in children presenting with severe HIV disease and immune compromise. Persistent neurodevelopmental impairment despite antiretroviral therapy.
Nozyce, *et al.*	2006	USA multi-centre	Longitudinal	274+	2-17 yrs	- CPRS - WISC-3III - WPPSI	Behaviour: 28% psychosomatic, 25% learning, 19% impulsive-hyperactive, 16% conduct, 8% anxiety. Cognitive: lower IQ scores than established norms.	Stable HIV+ children had more behavioural problems and lower developmental and cognitive scores than established norms.
Smith, *et al.*	2006	Seven sites in USA including Puerto Rico	Longitudinal	117+ 422-	3-7 yrs	- MSCA	HIV+ children without an early AIDS-defining illness performed as well as HIV- children. HIV+ children with class C status scored significantly lower in all domains of cognitive development.	An early AIDS defining illness increased the risk of chronic static encephalopathy during pre-school and early school age years.

Author	Year	Country	Research Design	Population Size (n)	Age of Children	Tools	Neurological and Developmental Impairments (HIV+)	Main Findings
Lindsey, *et al.*	2007	USA multi-centre including Puerto Rico	Longitudinal	**Cohort 1:** 54+; 221- **Cohort 2:** 91+; 838- **Cohort 3:** 98+; 558-	Birth-3 yrs	- BSID-I - BSID-II	Cohort 1: HIV+ groups had significantly lower motor and mental scores at 6 mo and 24 mo. Cohort 2: HIV+ groups had significant mental and motor delays but the difference decreased with age.	Reduction of mortality and morbidity with use of HAART. Positive, but limited impact of PI-based HAART on neurodevelopmental trajectories in the first years of life.
Koekkoek, *et al.*	2008	The Netherlands	Cross-Sectional	22+	6-17 yrs	- SON-R - ANT	Poor verbal fluency than age-norms. Poor executive function and slowed information processing.	Subtle neurocognitive impairments may exist in school-age children.
Rice, *et al.*	2012	USA 15 sites including Puerto Rico	Cross-Sectional	306+ 162e	7-16 yrs	- CELF-4 - WISC-4	34% Language impairment in HIV+ children compared to 37% in HEU children	Comparable rates of language impairment (LI) between the HIV+ group and the HEU group. No significant effect of HIV infection status on the odds of LI.

Abbreviations

+	HIV-positive (HIV+)
-	HIV-negative (HIV-)
a	HIV-uninfected, affected
c	controls
e	HIV-exposed, uninfected (HEU)
u	unknown status
ANT	Amsterdam Neuropsychological Tasks
BAEPs	Brainstem Auditory-Evoked Potentials
BINS	Bayley Infant Neurodevelopmental Screener
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency 2nd Edition
BSID-I	Bayley Scales of Infant Development 1st Edition
BSID-II	Bayley Scales of Infant Development 2nd Edition
BTVMI	Beery Test of Visual Motor Integration
CELF-4	Clinical Evaluation of Language Functioning 4th Edition
CPRS	Conner's Parent Rating Scale
CT Scan	Computerised Tomography Scan
DAP	Harris-Goodenough-Draw-A-Person Test
DDST	Denver Developmental Screening Test
DTVMI	Beery-Buktenica Developmental Test of Visual-Motor Integration
EEG	Electroencephalogram
FS-2	Functional Status 2nd Edition
FTII	Fagan Test of Infant Intelligence
GMDS	Griffiths Mental Developmental Scales
GMDS-ER	Griffiths Mental Development Scales-Extended Revised Version
HOME	Home Observations for the Measurement of the Environment
IDIYC	Illingworth's Development of the Infant and Young Child
KABC	Kaufman Assessment Battery for Children 1st Edition
mDS	Modified Denver Score
MICI	Measures of Infant-Caregiver Interactions
mKABC-2	A modified Kaufman Assessment Battery for Children 2nd Edition
MRI	Magnetic Resonance Imaging
MSCA	McCarthy Scales of Children's Abilities
PDMS-2	Peabody Development Motor Scale 2nd Edition
PLS	Preschool Language Scale
RITLS	Rossetti Infant-Toddler Language Scale
RPCM	Raven Progressive Coloured Matrices
SB	Stanford Binet
SONIT	Snijders-Oomen Nonverbal Intelligence Test
SON-R	Snijders-Oomen Nonverbal Intelligence Test-Revised
TOVA	Test of Variables of Attention
TRG	Test of the Reception of Grammar
VEPs	Visual-Evoked Potentials
VSMS	Vineland Social Maturity Scale
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WISC-3	Wechsler Intelligence Scale for Children 3rd Edition
WISC-4	Wechsler Intelligence Scale for Children 4th Edition
WISC-R	Wechsler Intelligence Scale for Children-Revised
WPPSI	Wechsler Pre-School and Primary Scales of Intelligence
WRAT-3	Wide Range Achievement Test 3rd Edition

2.5.2 Effect of ART on the Development of HIV-Infected Children

The first antiretroviral, AZT, was available within the first decade of the discovery of HIV (De Clercq, 2009). Numerous regimens including AZT monotherapy became available in the decade following 1987: use of two NRTIs, or NNRTIs without PIs (multi-ART); and the combined use of three or more ARVs with one or more highly-active compound (ART).

Of all these regimens, timely intervention with ART is the most effective strategy employed to date to improve the prognosis for children infected with HIV, and decrease mortality (Llorente, *et al*., 2003; van Rossum, *et al*., 2002). Significant improvements in child nutritional and growth status have been made with the use of ART (Jaspan, *et al*., 2008; Eley, *et al*., 2006; Verweel, *et al*., 2002). Positive, but limited improvements in neurodevelopmental functioning have been reported in numerous studies, however, these improvements did not reverse the existing neurodevelopmental impairment (Lindsey, *et al*., 2007; Foster, *et al*., 2006; Coplan, *et al.*, 1998; Raskino, *et al*., 1999; Pizzo, *et al*., 1988). Despite ART, neurodevelopmental impairments persist due to existing regions of the CNS having sustained injury at critical periods of brain development (Foster, *et al*., 2006; Willen, 2006), as well as the blood-brain barrier (BBB) effectively preventing adequate permeation of ART into the CNS to suppress viral replication (Letendre, *et al*., 2008; Miller, 2002). Letendre *et al* (2008) found that the only ARVs effective in permeating the BBB are: NVP, AZT and Abacavir. In the management of infants, utilising CNS-penetrating regimens are not always possible. Single-dose NVP (sd-NVP) is widely used in sub-Saharan Africa in the prophylactic treatment of infants in the management of PMTCT; however there is controversy over its use due to the emergence of NNRTI resistance mutations developing readily (Arrivé, *et al*., 2007; Kassaye, *et al*., 2007). One study reports the prevalence of NVP resistance in children following single-dose administration as 52.6% (Arrivé, *et al*., 2007). However other studies report that this resistance disappears after time (Kassaye, *et al*., 2007).

It is therefore indicated that universal access to PMTCT services is the only way to prevent HIV-related neurodevelopmental impairment by preventing transmission of HIV altogether. For those children who are already infected, early intervention with ART is indicated so as to minimise the detrimental effects of HIV on the developing CNS.

2.5.3 Developing World

A number of studies have been conducted in Africa. However, too few in proportion to the 90% of children affected by HIV who are living in sub-Saharan Africa (UNAIDS, 2010) where poorly resourced and inaccessible health systems have contributed significantly to the spread of HIV (ter Kuile, *et al*., 2004). A possible explanation for the few studies is mainly due to high rates of mortality associated with perinatal HIV infection where approximately 50% of these children died within the first two years of life (Newell, *et al*., 2004). ART was only available in Zimbabwe in 2004, and even then, paediatric formulations were still not available until the end of 2005 (UNGASS, 2009). With ART becoming increasingly available, sub-Saharan Africa now faces the same concerns that the developing world faced two decades ago. How can these under-resourced countries accommodate HIV-associated disability (Abubakar, *et al*., 2008)?

Some of the first studies to be published were conducted in Uganda, the Democratic Republic of the Congo (DRC) and Rwanda (Drotar, *et al*., 1997; Boivin, *et al*., 1995; Msellati, *et al*., 1993). These studies all employed a longitudinal design, a small age-range, and utilised outcome measures. Msellati and colleagues (1993) devised their own measure which was based on the Denver Developmental Screening Test (DDST) and included only 15 items (three to five gross motor items; two to three fine motor items; two to three social contact items; and three language items). This measure was also not validated either. The limitations of these studies are similar to those seen in the same decade in the developed world: diagnosis in children younger than 15 months was limited to clinical signs and symptoms of HIV (Msellati, *et al*., 1993).

All these studies found delays in development, where Drotar *et al* (1997) reported that 26% of HIV-infected infants showed cognitive delay, and 30% showed motor delays at 12 months of age; and, Msellati *et al* (1993) reported neurologic manifestations in 31% (12 months of age) and 40% (18 months of age) of children infected with HIV. These findings correlate with clinical studies done in the developed world (Belman, *et al*., 1996; Blanche, *et al*., 1990; European Collaborative Study, 1990). Boivin *et al* (1995) did not find differences in language development of preschoolers, whereas the Rwandan study did (Msellati, *et al*., 1993). Again, it is important to bear in mind that Msellati *et al* (1993) only utilised three language items in their modified DDST measure, compared with Boivin *et al* (1995) who used the DDST in entirety.

Contrary to Msellati *et al* (1993) reporting cognitive delays in their Rwandan infants, Bagenda *et al* (2006) found no significant cognitive or neurological differences between HIV-infected and uninfected children in Uganda. The study by Bagenda and colleagues (2006) recruited the same children from the study by Drotar *et al* (1997) who had reached school-age to assess cognitive development (Abubakar, *et al*., 2008). A possible explanation for the discrepancies between these studies is that children from the first Ugandan study (Drotar, *et al*., 1997) did not have access to ART. Therefore this study (Bagenda, *et al.*, 2006) may be confounded by survival bias where children with more severe impairments would have died before reaching school-age.

A study in Tanzania in the new millennium (McGrath, *et al*., 2006) was the first to explore the effect of timing of MTCT on neurodevelopment. This study is comparable to a study done in the United States by Smith and colleagues (2000) who also used the BSID-I. Both these studies found that early infection presented an increased risk of neurodevelopmental impairment. McGrath *et al* (2006) found that those infants who tested HIV-positive within the first 21 days had a 14.9 times higher rate (relative risk) of becoming developmentally delayed in all aspects of mental functioning, and an eight-point-seven times higher rate of motor development, when compared with

uninfected children. However the authors (McGrath, *et al*., 2006) acknowledge that their study introduced error as some of the infants could have been infected by breast milk in the first 21 days of life, and thus the risk of developmental delay may be underestimated. This study found a general developmental delay of 26% in HIV-positive children compared to only 12% in the uninfected group (McGrath, *et al*., 2006).

Studies in South Africa looked at: describing the neurological and neurocognitive deficits in HIV-infected children and the short-term effect of ART (Smith, *et al*., 2008), quantifying the extent of neurodevelopmental delay (Baillieu and Potterton, 2008), identifying the neurodevelopmental status of HIV-infected children in Soweto (Potterton, *et al*., 2009b) and subsequently employing an intervention programme to address deficits (Potterton, *et al*., 2009a); as well as studying the effects of HIV on the neurodevelopment of institutionalised children (Jelsma, *et al*., 2011; Shead, *et al*, 2010).

With increasing use of ART in paediatric populations in sub-Saharan Africa, researchers have identified the need to continue to research the effects of HIV on neurodevelopment in populations which are increasing in prevalence, for example preschoolers (Lowick, *et al.*, 2012; Van Rie, *et al*., 2008). Lowick *et al* (2012) found that 90% of the HIV-infected children in Soweto, South Africa, exhibited general developmental delay despite ART. However a high number of children (76.7%) in the comparison group also demonstrated delay. A possible confounding variable was that the authors were unable to determine the status of the *apparently* healthy comparison group, as well as being unable to control for other risk factors of early child development (see section 2.6). Van Rie *et al* (2008) found that 60% of HIV-infected children in the DRC showed severe cognitive delay, 28.6% showed severe motor delay, and 84.6% and 76.7% of HIV-infected children showed delay in language expression, and comprehension, respectively. Comparisons cannot be made between these studies as they both employed different assessments of child development. Given the limitations of these studies, it is apparent that children with HIV are significantly more affected than their uninfected peers. More studies are needed to

explore the effects of intervention on improving neurodevelopment in these children because as ART becomes more accessible, children will be facing reduced quality of life with extended life through ART. Potterton *et al* (2009a) found a positive effect of a basic home stimulation programme on the neurodevelopmental status of young children infected with HIV.

A recent study conducted in Zimbabwe (Kandawasvika, *et al*., 2011) found that the risk of neurodevelopmental impairment among HIV-exposed infected infants was double that among their non-infected peers (OR 2.1) when using the Bayley Infant Neurodevelopmental Screener (BINS). Kandawasvika and her colleagues also reported that the prevalence of neurodevelopmental impairment in all children assessed was nine-point-four percent. They also confirmed that head circumference was associated with an OR 2.22 risk of neurodevelopmental impairment when controlling for other factors; head circumference is a simple assessment that can be employed in practice to identify children at risk of neurodevelopmental impairment.

All studies which measured motor development (Lowick, *et al*., 2012; Ruel, *et al.*, 2012; Jelsma, *et al*., 2011; Shead, *et al*., 2010; Potterton, *et al*., 2009b; Baillieu and Potterton, 2008; Smith, *et al*., 2008; Van Rie, *et al*., 2008; McGrath, *et al*., 2006; Drotar, *et al*., 1997; Boivin, *et al*., 1995; Msellati, *et al*., 1993) and most of the studies that assessed language development (Lowick, *et al*., 2012; Baillieu and Potterton, 2008; Smith, *et al*., 2008; Van Rie, *et al*., 2008; Msellati, *et al*., 1993) reported significant differences between the HIV-infected children and the uninfected children.

Sub-Saharan Africa has far greater challenges (poverty, malnutrition and poor healthcare) than more developed countries – these challenges greatly impact on the ability to examine children infected with HIV. However, it is clear from the studies presented that children living with HIV in developing countries are still at risk of HIV-related neurodevelopmental impairments despite the introduction of ART (Van Rie, *et al.*, 2008) especially with early HIV infection (McGrath, *et al*., 2006) and with severity of disease stage (Ruel, *et al*., 2012). A summary of these studies can be seen in

Table 2.3 on the next page. Abbreviations used in this table will follow for ease of reference.

Table 2.3 Clinical studies from the developing world

Author	Year	Country	Research Design	Population Size (n)	Age of Children	Tools	Neurological and Developmental Impairments	Main findings
Msellati, *et al.*	1993	Rwanda	Longitudinal	50+ 136- 32u	6-24 mo	- mDS - IDIYC	31% delay (12 mo of age) 40% delay (18 mo of age)	HIV+ children are more at risk of developmental delay than HIV- children. Stage of HIV infection relates to severity of delay.
Boivin, *et al.*	1995	DRC	Longitudinal	14+ 20- 16c	<24 mo	- DDST	All infected infants had social and motor deficits	CNS infection by HIV occurs in asymptomatic children.
Drotar, *et al.*	1997	Uganda	Longitudinal	59+ 211- 107c	Birth-24 mo	- BSID-1 - FTII - MICI - HOME	At 12 mo of age: 26% cognitive 30% motor	HIV results in motor and cognitive delay in HIV+ children independent of other risk factors.
Bagenda, *et al.*	2006	Uganda	Cross-Sectional	28+ 37- 42e	6-12 yrs	- KABC-1 - WRAT-3	Not applicable.	No significant delay, or neurological or cognitive impairment.
McGrath, *et al.*	2006	Tanzania	Longitudinal	327+	6-18 mo	- BSID-1	26% general delay	Higher risk of developmental delay in children infected at birth.
Baillieu and Potterton	2008	South Africa	Cross-Sectional	40+	18-30 mo	- BSID-2	70% cognitive 82.5% language 85% gross motor 12.5% fine motor	Significant delays in cognitive, motor and language development is found in HIV+ children. Motor delay was more apparent in these children. Factors critical to gross motor function may also lead to language impairment.
Smith, *et al.*	2008	South Africa	Longitudinal	39+	Mean 60 mo	- GMDS - TRG - RPCM - DAP - DTVMI	33.3% motor dysfunction 33-81% subnormal intelligence quotients	Language deficits (mild disability range) were evident in all age groups. HIV+ children are are vulnerable to neurological and cognitive impairments. Neurological and cognitive deficits observed in these children remained static despite six months of HAART.
Van Rie, *et al.*	2008	DRC	Cross-Sectional	35+ 35a 90c	18-72 mo	- BSID-2 - PDMS-2 - SONIT - RITLS	60% cognitive 29% motor 85% expressive language 77% receptive language	Young HIV+ children are the more severely affected than older HIV+ children. More motor and language expression delay in HIV+ children than control group.

Author	Year	Country	Research Design	Population Size (n)	Age of Children	Tools	Neurological and Developmental Impairments	Main findings
Potterton, *et al.*	2009b	South Africa	Longitudinal	60+ 62-	<48 mo	- BSID-2	52% cognitive 72% motor	Severe developmental delay in HIV+ children for motor and cognitive development. Motor development was more affected than cognitive development. Weight-for-age, age and HAART were important predictors of cognitive and motor development.
Shead, *et al.*	2010	South Africa	Longitudinal	16+ 24-	16-42 mo	- BSID-2	Significant mental and motor delay	Greater delays in mental and motor development seen in HIV+ children. Motor development was more affected than mental development.
Jelsma, *et al.*	2011	South Africa	Longitudinal	21+ 23-	Mean 52.8 mo	- PDMS-2	All 21 children who were HIV infected were significantly delayed.	HIV+ children were significantly delayed than their HIV- counterparts. Fine motor development was worse in HIV+ children. HIV status and place of residence are predictors for total motor quotient.
Kandawasvika, *et al.*	2011	Zimbabwe	Longitudinal	65+ 188e 287- 58u	Birth-12 mo	- BINS	Prevalence of neurodevelopmental impairment for the entire sample was 9.4%.	Higher risk for neurodevelopmental impairment for infants infected with HIV by 3 months of age.
Lowick, *et al.*	2012	South Africa	Cross-Sectional	30+ 30c	55-75 mo	- GMDS-ER	90% severely delayed 46.7% mental handicap	Significant delays evident in HIV+ children compared to controls.
Ruel, *et al.*	2012	Uganda	Cross-Sectional	93+ 106-	6-12 yrs	- TOVA - mKABC-2 - BOT-2	Significant poorer scores in attention deficit. Worse scores in sequential processing, simultaneous processing, planning and reasoning. Poorer manual dexterity and speed/agility.	Significant neurocognitive and motor deficits compared to controls despite these children having CD4 cell counts and percentage above WHO thresholds.

Abbreviations

+	HIV-positive (HIV+)
-	HIV-negative (HIV-)
a	HIV-uninfected, affected
c	controls
e	HIV-exposed, uninfected (HEU)
u	unknown status
ANT	Amsterdam Neuropsychological Tasks
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DAP	Harris-Goodenough-Draw-A-Person Test
DDST	Denver Developmental Screening Test
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EEG	Electroencephalogram
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MICI	Measures of Infant-Caregiver Interactions
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MRI	Magnetic Resonance Imaging
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PDMS-2	Peabody Development Motor Scale 2nd Edition
PLS	Preschool Language Scale
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RPCM	Raven Progressive Coloured Matrices
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TOVA	Test of Variables of Attention
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WPPSI	Wechsler Pre-School and Primary Scales of Intelligence
WRAT-3	Wide Range Achievement Test 3rd Edition

2.6 Risk Factors for Early Child Development (ECD)

ECD is defined as the period below the age of eight years including the prenatal period (UN CRC, 2005). However, most of the available research on ECD shows data collected for children younger than five years. In these critical years a number of factors can contribute to the healthy development of children (protective factors), or place them at risk (risk factors) (Walker, *et al.*, 2011). The CNS is also developing rapidly in this timeframe, and is itself a bidirectional entity that influences, and is influenced by, the environment (Mustard, 2006). Exposure to developmental risk factors can permanently alter the structure and function of the brain (Walker, *et al.*, 2011). Facets of a child's development that can be affected are: sensory-motor, cognitive-language and social-emotional (Baker-Henningham and Boo, 2010). As these facets are synonymous with CNS development, they contribute to the foundation for: basic learning, school success, economic participation, social citizenry and health (WHO, 2007a).

In 2007 it was estimated that 200 million children under five years of age were not fulfilling their developmental potential (Walker, *et al.*, 2007b). The main causes of adverse development are: poverty, poor health and nutrition, and deficient care (Grantham-McGregor, *et al*., 2007). Children who are exposed to these causes are at risk of not reaching their developmental potential (Engle, *et al.*, 2011). Walker and colleagues (2007b) identify many risks namely, biological, psychosocial and socioeconomic factors which are associated with the causes. These risk factors can co-occur and this has a cumulative effect on the facets of ECD, as the facets are interdependent. The risk factors with the highest prevalence and strongest evidence base are: stunting (linear growth retardation), iodine and iron deficiencies, and inadequate cognitive and social-emotional stimulation (Walker, *et al.*, 2007b). In addition to these, less documented risks are: maternal depression, intrauterine growth restriction and infectious diseases, such as malaria and HIV (Walker, *et al.*, 2007b).

Identification of the causes and risk factors is important as it will facilitate identification of those children at risk. Interventions can then be implemented early to ensure that risks are prevented or minimised and protective factors are promoted. Often the intervention is the inverse of the risk factor. However, knowledge not only of these risk factors but also of the critical time-points for intervention is important to minimise the detrimental effects for ECD (Engle, *et al.*, 2011). The major economic gains in productivity on a national level that can be made from investment in interventions promoting ECD are vast. However, in spite of this, few developing countries have made significant steps to positively affect ECD which perpetuates intergenerational transmission of poverty, poor health and nutrition, and deficient care for children most in need (Grantham-McGregor, *et al.*, 2007).

This paper will discuss the interplay of: poverty; poor health and nutrition, and deficient care; and the associated risk factors, in relation to ECD. For the purpose of clarity, the factors will be discussed individually despite many co-occurring.

2.6.1 Poverty

Children living in poverty have increased exposure to biological and psychosocial risk factors for ECD, namely poor health and nutrition, and deficient care. Availability of food, poor living conditions, poor health, limited access to education (maternal and child education), maternal depression, poor parenting, and many other risks are enhanced by poverty and fuel the poverty cycle for the next generation (Walker, *et al*., 2011). Therefore, the developmental consequences of poverty can result in all facets of a child's development being affected. For example, a social problem caused by poverty, such as low maternal education, and maternal depression, can lead to inadequate stimulation and poor understanding of nutrition which in turn could lead to a child being exposed to inadequate learning opportunities (and thus decreased earning capacity in adulthood) and malnutrition (Walker, *et al*, 2011).

Deficient Care

The primary caregiver is fundamental in the care of the child. It is their interaction with the child that will facilitate or hinder ECD. It is obvious that many risk factors will impact on this relationship (Baker-Henningham and Boo, 2010). Inadequate cognitive and social-emotional stimulation is mainly a consequence of poor quality child-caregiver interactions and lack of access to services (Engle, *et al*., 2007). Factors that will increase the likelihood of cognitive and social-emotional deficits which are resultant of deficient care are: maternal depression, low maternal education, access to learning and institutionalisation (Walker, *et al.*, 2011).

2.6.2 Nutrition

The relationship between nutrition and health is positively correlated and interdependent. This section will discuss the impact of maternal nutrition and health on foetal development, as well as childhood nutrition (including breastfeeding) and its effects on ECD. It is also important to understand that poverty will significantly impact on nutrition, as well as health, at all stages of foetal and childhood development.

Intrauterine Growth Restriction

Nutrition can significantly affect all aspects of a child's development, particularly, cognition and motor development. Maternal nutrition before conception and during pregnancy plays a vital role in the growth of the placenta and the foetus (King, 2003; Barker and Clark, 1997). The effects of maternal nutritional deficiencies together with maternal infections during pregnancy can cause intrauterine growth restriction (IUGR) (Walker *et al*, 2011). There is also evidence that suggests that nutrition has the most significant role in the intrauterine environment (Barker and Clark, 1997). This environment is more important than genetics of the foetus in the aetiology of chronic diseases in later life (Wu, *et al.*, 2004) such as Type 2 Diabetes (Godfrey and Barker, 2000) and Coronary Heart Disease (Osmond, *et al.*, 1993).

Most births are low birth weight (LBW) as a result of IUGR (Walker, *et al.*, 2011). Studies that have looked at LBW infants (<2500g) up to the age of three years, show deficits in: problem-solving abilities, behaviour and cognitive and motor development (Walker, *et al.*, 2004; Gardner, *et al.*, 2003; Lui, *et al.*, 2001; Grantham-McGregor, *et al.*, 1998; Gorman and Pollitt, 1992; Villar, *et al.*, 1984). One study reported that food supplementation for pregnant mothers in their third trimester and for infants up to six months of age did not benefit growth of children with LBW (Waber, *et al.*, 1981). This supports that foetal and infant growth and development is dependent on maternal nutrition (Wu, *et al.*, 2004), whereby growth is most susceptible to deficiencies of nutrients (protein and micronutrients) during implantation (day five to ten post-fertilisation) and the period of rapid placental development (first trimester of gestation) (Waterland and Jirtle, 2004).

Breastfeeding

Exclusive breastfeeding leads to improvements in school grades by 18 years of age and is linked to a ten to 15% difference in income (Victora, *et al.*, 2005). WHO/UNICEF recommends exclusive breastfeeding for the first six months of life, and thereafter breastfeeding with nutritionally adequate complementary feeding up until two years of age (WHO/UNICEF, 2003). The effect of breastfeeding enhances cognitive development, as well as child-mother bonding, and is a known to be a protective factor for ECD (Walker, *et al.*, 2011). Although exclusive breastfeeding is practiced in most developing countries in more than a third of infants below six months of age, it is the duration that is most important in enhancing ECD, as early supplementary bottle-feeding is known to be associated with poorer motor and cognitive function (Clark, *et al.*, 2006).

Stunting

Chronic malnutrition predisposes a child to stunting (linear growth retardation) and can begin *in utero* (WHO, 2007a). Stunting affects 34% of children younger than five years in developing countries (Walker, *et al.*, 2011). Evidence suggests that stunting is predictive of poor psychological functioning, low level school-attainment and

decreased likelihood of formal employment by 20-22 years of age (Carba, *et al.*, 2009; Walker, *et al.*, 2007a; Alderman, *et al.*, 2006). Inequalities in development caused by stunting are shown to be dramatically improved if interventions are enacted within the first two years of life (Crookston, *et al.*, 2010) and include cognitive and social-emotional stimulation (Winick, *et al.*, 1975).

Micronutrient Deficiencies

Micronutrients are vitamins or minerals that are essential in minute amounts for normal growth and development of organs. Two micronutrients – iodine and iron, are significantly important in ECD because of their effect on CNS development (Walker, *et al*., 2007b). Iron-deficiency anaemia affects cognition, motor and social-emotional development. Alternately, deficiencies during pregnancy only affect the infant's cognitive and emotional development (Walker, *et al.*, 2007b). Iodine has a significant effect on cognition and behaviour, where in severe cases it causes irreversible mental retardation (Walker, *et al.*, 2007b).

Supplementation and fortification of staple foods, with iron has had limited effects on reducing these adverse effects when iron deficiency is severe or chronic. However timely supplementation or fortification, before iron deficiency is apparent, is likely to be more effective, and this includes supplementation during pregnancy (Engle, *et al*., 2007). Worldwide interventions have been undertaken to reduce iodine deficiencies and directly reduce mental retardation by salt iodisation (UNICEF, 2004). Timing of iodine supplementation has been shown to be most effective in the first and second trimesters of pregnancy (Qian, *et al.*, 2005).

2.6.3 Health

Poor health has significant implications on ECD. During pregnancy, maternal infections can affect the development of foetal immune systems independently of the vertical transmission of pathogens (Dauby, *et al.*, 2012).

Infections

Infections, such as malaria, affect the placenta and contribute to placental insufficiency leading to LBW, prematurity and intrauterine growth restriction (Desai, *et al*., 2007). LBW and IUGR are factors which can affect ECD, as discussed earlier. It has also been shown that infants exposed to placental malaria *in utero* are more susceptible to acquiring HIV through mother-to-child transmission (Steiner, *et al.*, 2010). Infants born to mothers with placental malaria also had an increased risk of acquiring malaria postnatally (Dauby, *et al*., 2012), which can cause neurological and cognitive impairments (Walker, *et al.*, 2007b).

Paediatric HIV infection has significant implications on ECD because the virus is known to be both neurotropic and neurotoxic (Mitchell, 2006; Albright, *et al.*, 2003; Tardieu, 1998; Schmitt, *et al.*, 1991). Infants who are infected through vertical transmission are noted to have cognitive, language and motor impairments (Abubakar, *et al.*, 2009; Potterton, *et al.*, 2009; Baillieu and Potterton, 2008; Van Rie, *et al.*, 2008; Lindsey, *et al.*, 2007; Foster, *et al.*, 2006; Blanchette, *et al.*, 2001; Drotar, *et al.*, 1997; Belman, *et al.*, 1996; Pollack, *et al.*, 1996). HIV infection is associated with stunting and wasting (weight-for-length) in the first three months of life (Venkatesh, *et al.*, 2010). In addition to the effects of HIV on health, there is evidence that shows that children who are not themselves infected with HIV are exposed to psychosocial risk factors for ECD, where they are missing developmental opportunities because they are having to care for a parent, or are themselves the head of a household due to orphan hood (ANNECA, 2006).

Increasing evidence is showing the importance of identifying risks for ECD, not only because of the effects on a child's developmental potential, but also because it can lead to public health issues and poor economic growth.

Many risk factors for ECD are caused by poverty, poor nutrition and health and deficient care. IUGR, stunting, micronutrient deficiencies, infections and inadequate cognitive and social-emotional stimulation have been discussed because these are the risk factors which are found to have the most significant outcome on ECD. Identification of these risk factors, as well as knowledge on the critical time-points will lead to timely intervention and thus promote ECD.

2.7 Conclusion

This chapter has reviewed the literature and provided a background to: the epidemiology of HIV; treatment and management of paediatric HIV; the developing CNS and HIV infection; clinical studies of paediatric HIV from the developed and developing worlds; and risk factors for ECD. It is hoped that this background provides rationale for the present study.

CHAPTER 3: METHODS

This chapter will discuss the research setting, ethical considerations, study design, subjects, materials and measurements, the procedures used to collect data and data analysis.

3.1 Research Setting

This study was conducted at Newlands Clinic and Parirenyatwa Opportunistic Infections (OI) Clinic in Harare, Zimbabwe. These clinics provide outpatient care and treatment to adults and children living with HIV/AIDS.

Newlands Clinic is a family-centred, nurse-led clinic that operates in a Private-Public Partnership. In addition to the medical care provided by doctors and nurses (trained in counselling), ancillary services such as Dentistry, Physiotherapy and Woman's Health services are provided free of charge. There is also an onsite laboratory and pharmacy.

Parirenyatwa OI Clinic is a public institution where adults and children attend appointments with doctors, nurses and trained counsellors. There is an onsite pharmacy. As there is no onsite laboratory, this site shares the facilities of the Parirenyatwa Hospital which is located on the same premises, or sends samples to the National Reference Laboratory. Ancillary services can also be accessed in the main hospital.

3.2 Ethical Considerations

Ethical Clearance was obtained from the Ethics Committee of the University of the Witwatersrand (Appendix I). In addition to this, approval was obtained from the Medical Research Council of Zimbabwe (Appendix I) to conduct the study at Newlands Clinic and Parirenyatwa OI Clinic.

Informed consent was obtained from the mothers prior to assessment where each mother signed a consent form. Data of the participants was anonymised by assigning a study number, which was recorded on all documentation so that identification could not be made from revealing demographic data (name, date of birth and address). Mothers were given the opportunity to opt-out at any stage if they no longer wanted to participate in the study without any prejudice to their continued care at the clinic where they received medical care

3.3 Study Design

This was a cross-sectional study of HIV-exposed infants from six weeks to 12 months of age. HIV-positive mothers with infants who met the inclusion criteria were invited to participate if their infants were accessing Newlands Clinic or Parirenyatwa OI Clinic and were tested using DNA-PCR. All patients attending these clinics are black African infants, from similar socioeconomic and cultural backgrounds and are representative of an urban, black Zimbabwean population.

3.4 Subjects

HIV-positive mothers with infants between six weeks to 12 months of age attending Newlands Clinic or Parirenyatwa OI Clinic who were tested (DNA-PCR) for HIV, were invited to participate. The study consisted of 60 (28 HEI; 32 HEU) infants. Infants were excluded from the study if: their mother was not present for the assessment; they tested negative more than six weeks before assessment and were still being breastfed; they were premature (less than 37 weeks gestation); they suffered any CNS infections; they had apparent congenital deformities; or if they were receiving physiotherapy.

3.5 Materials and Measurements

3.5.1 Immunology and Virology

Where available, CD4 counts and percentages, viral loads and clinical staging of HIV were recorded on the Data Collection Sheet (Appendix IV) for both mothers and infants enrolled in this study. Diagnosis of HIV infection in infants was made using DNA-PCR testing available at both clinics.

3.5.2 Anthropometric Measurements

Vertex-to-heel recumbent length was measured with the infant supine – boards were placed at the top of the head and at the feet (knees and hips straight) and the distance was measured in centimetres using a tape measure. The measurements were rounded to the nearest zero-point-one centimetre. Weight was measured with the infant naked on a calibrated, electronic digital scale. Head circumference was recorded with a tape measure placed over the eyebrows, above the tops of the ears and to the occiput. All measurements were taken by the principal investigator.

3.5.3 Bayley Scales of Infant and Toddler Development (Third Edition)

The BSID-III was used to assess development of the infants in this study. The BSID-III is a revision of the second edition of the BSID which was published in 1993. Employing the BSID-III in assessing development ensures an outcome of the presence or absence of developmental delay; it is therefore not diagnostic as to the cause of delay (Bayley, 2006). This tool can be used to assess development in infants from one month to 42 months of age. Development was assessed by administering three scales that focus on the following areas of development: cognition; language (receptive and expressive); and motor (fine and gross). Once each area is assessed, a raw score is obtained for each scale. The raw score is the sum of the number of items achieved in each scale. Raw scores cannot compare performance between

scales, or compare a child with other children. Raw scores are used to obtain derived scores, namely scaled scores and composite scores. Scaled scores are derived from the total raw scores obtained according to age. Scaled scores are scaled from one to 19 with a mean of ten and a standard deviation of three. Composite scores are a transformation of a distribution of scores computed from the scaled scores. Composite scores range from 40 to 160, with a mean of 100 with a standard deviation of 15 (Bayley, 2006). Although none of the BSID editions (I-III) have been normed on Zimbabwean children, the tool was employed for its superior ability to identify developmental delay as seen in many other studies in sub-Saharan Africa (Shead, *et al*., 2010; Potterton, *et al*., 2009b; Baillieu and Potterton, 2008; Van Rie, *et al.*, 2008; McGrath, *et al*., 2006; Drotar, *et al*, 1997).

3.6 Procedure

All infant and mother pairs enrolled in this study were assigned a study number prior to assessment by the principal investigator so that all data were coded. Data obtained from the mother and infant pairs in this study were collected at each site by the principal investigator and a research assistant at one time-point.

On the day of assessment, the mothers of all infants were interviewed by the research assistant using the Maternal Interview (Appendix III) which obtained data of interim history (intercurrent illnesses, feeding, development and maternal health). The information obtained from the mother regarding intercurrent illnesses was also used to assess whether the infant was in a healthy state to be assessed. The mothers of any infants who had been ill within the past two weeks (recent illness) were asked to come back after the infant had been well for two weeks. These mothers were provided with bus fare if the return date did not coincide with an existing appointment. The research assistant recorded the following on the Data Collection Sheet (Appendix IV): infant's anthropometric measurements (height, weight and head circumference) and immunisations; mother and infant CD4 counts and percentages (respectively) and viral loads; as well as all medications used by the mother and infant since pregnancy. These data were obtained from medical records and the child's health card, where available. The infant was then assessed by the principal investigator to obtain the

anthropometric measurements, as well as to assess for cognitive, language and motor development of the infant using the BSID-III.

To ensure standardised assessment, each infant was assessed using the BSID-III whilst seated at a standard table and on their mother's lap. This ensured that they were able to access the toys when presented to them. The mother was asked not to talk during the assessment, or to interact with the infant unless asked to by the principal investigator. The principal investigator administered the scales in the following order: cognitive, language (receptive followed by expressive) and finally the motor scale. Each assessment took approximately 40 minutes to administer. Due to the ages of the infants assessed, there was no need to translate any scales. However, the research assistant helped with instructions to the mothers if needed.

3.7 Data Analysis

This study recruited 60 (28 HEI; 32 HEU) infants from six weeks to 12 months of age. This sample size was calculated using a 90% power calculation to detect a difference between the groups of 15 on the BSID-III when using a mean of 100 with a standard deviation of 15. Conversion tables from the BSID-III were used to convert the raw scores into scaled scores and composite scores to provide individual quantitative scores and qualitative descriptions of development. Descriptive statistics were employed to analyse the raw data. Differences between the two groups were compared using independent t-tests: Chi-Squared Test and, Fischer's Exact Test where values were less than five. These data are presented in tables to show the means and standard deviations, frequencies and percentages. Data were analysed using STATA (version 10.0 for Windows), where the level of significant for all statistical tests employed were set at p=0.05.

3.8 Conclusion

This chapter has discussed the research setting, ethical considerations, study design, subjects, materials and measurements, the procedures used to collect data, and statistical methods employed to analyse the data.

CHAPTER 4: RESULTS

This chapter will present the results of this study. Sixty infants were enrolled in the study; 32 (53.33%) infants were HEU and 28 (46.67%) were HEI. The data collected for the infants will be presented first, followed by that for the mothers. Finally, the results of the developmental assessments will be presented. Descriptive statistics were used to analyse the data and will be shown in tables with frequencies and percentages, or means and standard deviations.

4.1 Infant Data

4.1.1 Demographics

The HEU and HEI groups were compared using a two sample t-test with equal variance. Demographic data for the infants in each group are presented in Table 4.0. Relevant information was obtained from the Maternal Interview (Appendix III), the Data Collection Sheet (Appendix IV) and the BSID-III Record Form.

Table 4.0 Infant demographic data

Variable	HEU n=32		HEI n=28		p-Value
Females (%)	14 (50.00)		14 (50.00)		0.628
Males (%)	18 (56.25)		14 (43.25)		
	Mean	**SD**	**Mean**	**SD**	**p-Value**
Age (months)	4.31	±2.31	5.50	±2.83	0.079
Birth Weight (kg)	2.920	±0.39	2.795	±0.47	0.292

Table 4.0 shows that there was no significant difference for gender, age or birth weight between each group thus showing that the groups were similar. Birth weight could only be analysed from data of 31 HEU infants and 23 HEI infants, as there were missing data for six infants.

4.1.2 Anthropometric Data

Anthropometric data (height, weight and head circumference) were recorded for each infant on the date that the developmental assessments using the BSID-III were done. Z-scores were calculated using WHO Anthro (Version 3.3.2). A z-score of <-2.00 indicates that infants are underweight (WAZ), stunted (HAZ), wasted (WHZ) or have microcephaly (HCZ).

Table 4.1 Anthropometric data taken on the date of the developmental assessment

Variable	HEU	HEI	p-Value
WAZ	-0.33 (±1.38)	-2.67 (±1.64)	<0.001
HAZ	-0.80 (±0.94)	-2.28 (±1.54)	<0.001
WHZ	0.04 (±1.28)	-1.49 (±1.61)	<0.001
HCZ	0.52 (±0.99)	-0.92 (±1.56)	<0.001

(Values presented are means and standard deviations)

Table 4.1 shows that there are statistically significant differences ($p<0.001$) between the groups for WAZ, HAZ, weight-for-height z-scores (WHZ) and head circumference-for-age z-scores (HCZ). HEI infants are underweight (-2.67) and stunted (-2.28) with smaller head circumferences (-0.92), however, their WHZ scores seem to be within normal limits (-1.49).

4.1.3 Infant Medical Information

Medical information for each infant was obtained from their medical records and Child Health Card and recorded on the Data Collection Sheet (Appendix IV). Where information was not available in the records, missing information was extracted from the mothers' report on their infants' medical history during the Maternal Interview (Appendix III). The findings are reported in Table 4.2 on the next page.

Table 4.2 Medical information for infants

Variable		HEU n=32		HEI n=28		p-Value
ARV prophylaxis received	**Yes**	31	(96.88%)	16	(57.14%)	<0.001
	No	1	(3.13%)	12	(42.86%)	
Co-trimoxazole	**Yes**	22	(68.75%)	28	(100.00%)	<0.001
	No	10	(31.25%)	0	(0.00%)	
Feeding	**Exclusive BF**	25	(78.13%)	25	(89.29%)	0.038
	Mixed BF	0	(0.00%)	2	(7.14%)	
	Formula	7	(21.88%)	1	(3.57%)	
Place of Birth	**Hospital/Clinic**	28	(87.50%)	23	(82.14%)	0.721
	Home	4	(12.50%)	5	(17.86%)	
Illnesses	**Yes**	2	(6.25%)	13	(46.43%)	0.001
	No	30	(93.75%)	15	(53.57%)	
Hospital Admissions	**Yes**	1	(3.13%)	13	(46.43%)	<0.001
	No	31	(96.88%)	15	(53.57%)	
Immunisations	**Yes**	31	(100.00%)	26	(96.30%)	0.466
	No	0	(0.00%)	1	(3.70%)	
ARVs	**Yes**	0	(0.00%)	10	(35.71%)	N/A
	No	32	(100.00%)	18	(64.29%)	

(Values presented are frequencies and percentages)
(N/A = not applicable)

There is a statistically significant difference between the groups for ARV prophylaxis received, co-trimoxazole, feeding history, illnesses and hospital admissions. More infants who received ARV prophylaxis were in the HEU group. More children who had illnesses were in the HEI group and these infants also had more hospital admissions than the HEU group. The entire HEI group received co-trimoxazole because they were HIV infected. The feeding history shows that the HEU group were either exclusively breastfed or formula-fed. None of these children were mixed fed unlike the HEI group.

4.1.4 Infant Immunology and Virology

CD4 counts and percentages show the state of the immune system where low CD4 percentages (less than 25%) indicate severe immunosuppression in children. The

viral load shows the amount of the virus in the body, where a viral load of more than five picogrammes of the p24 protein (an indirect measure of virology) in the blood shows that the virus is replicating without control which indicates disease progression and poor prognosis (Mellors, *et al.*, 1997). Data for the HEI group were collected on each infant's Data Collection Sheet (Appendix IV). CD4 percentages and counts, are presented in Table 4.3 for infants in the HEI group. Due to resource-constraints, only 15 infants had CD4 percentages and four children had p24 values.

Table 4.3 CD4 percentage, count and viral load for HEI infants

Variable	HEI
CD4 Percentage n=15	17.91 (±9.97)
CD4 Count n=14	1149.43 (±756.46)
Viral Load (p24) n=4	293.20 (±443.84)

(Values presented are means and standard deviations)

Of the 15 infants with CD4 percentages, 12 (80%) had a CD4 percentage of less than 25%, and only three (20%) had CD4 percentages of 25% and above. The viral loads recorded for the four infants in this study were all above five copies per millilitre of blood.

4.2 Maternal Data

4.2.1 Maternal Demographics

A Maternal Interview (Appendix III) was conducted with each mother to obtain data regarding the mother's HIV status; her pregnancy, labour and delivery, and breastfeeding period; as well as socioeconomic background. These data were used to identify any potential risk factors to the infant during pregnancy or delivery, as well as to determine each family's socioeconomic status.

Table 4.4 Maternal demographics according to the status of their infants

Variable	HEU		HEI		p-Value
Age (years)	29.88	(±5.87)	27.79	(±5.26)	0.155
Level of Education completed (age)	15.44	(±2.27)	14.86	(±2.19)	0.320
Average number of people living in household	4.91	(±1.49)	4.86	(±1.88)	0.911
Earnings per month (USD)	164.53	(±194.38)	184.67	(±186.77)	0.762

(Values presented are means and standard deviations)

As seen in Table 4.4, there were no significant differences between the groups for maternal age, maternal education, average number of people living in the household or earnings per month.

Earnings per month for each family could only be calculated using data from 34 participants because 26 mothers (13 HEU infants; 13 HEI infants) refused to answer the question. Table 4.5 presents these data.

Table 4.5 Family earnings per month

Earnings per month	HEU n=19		HEI n=15		p-Value
Extreme Poverty (USD1 per day)	3	(15.79%)	1	(6.67%)	0.583
Poverty (USD2 per day)	3	(15.79%)	4	(26.67%)	
Above the Poverty Line	13	(68.42%)	10	(66.67%)	

(Values presented are frequencies and percentages)

There is no statistically significant difference (p=0.583) between the two groups, which shows they are similar according to socioeconomic status. It is also interesting to note that two-thirds of the participants are living above the poverty line (two US dollars per day). Table 4.5 shows that six families in the HEU group and five families in the HEI group are living below the poverty line (extreme poverty, and poverty), and 23 families are living above the poverty line.

4.2.2 Maternal HIV History

Information was obtained from medical records regarding each mother's medical history. This was recorded on the Data Collection Sheet (Appendix IV). Where information was not available in the medical records, these data were obtained from each mother's report during the Maternal Interview (Appendix III). Table 4.6 presents these data.

Table 4.6 Maternal HIV history according to the status of their infants

Variable		HEU n=32		HEI n=28		p-Value
Awareness of HIV Status	**Before Pregnancy**	24	(77.42%)	4	(14.29%)	<0.001
	After Pregnancy	7	(22.58%)	24	(85.71%)	
ANC	**Booked**	29	(90.63%)	19	(67.86%)	0.028
	Unbooked	3	(9.38%)	9	(32.14%)	
ART during pregnancy	**Yes**	26	(81.25%)	1	(3.57%)	<0.001
	No	6	(18.75%)	27	(96.43%)	
AZT during pregnancy	**Yes**	3	(9.38%)	7	(25.00%)	0.165
	No	29	(90.63%)	21	(75.00%)	
sd-NVP at onset of labour	**Yes**	5	(15.63%)	12	(42.86%)	0.024
	No	27	(84.38%)	16	(57.14%)	
Infections during pregnancy	**Yes**	1	(3.13%)	2	(7.14%)	0.594
	No	31	(96.88%)	26	(92.86%)	
ART after birth	**Yes**	29	(90.63%)	4	(14.29%)	<0.001
	No	3	(9.38%)	24	(85.71%)	
Mode of Delivery	**NVD**	24	(75.00%)	26	(92.86%)	<0.001
	Elective C-Section	8	(25.00%)	0	(0.00%)	
	Emergency	0	(0.00%)	2	(7.14%)	

(Values presented are frequencies and percentages)

Table 4.6 shows that there were significant differences between the two groups with regard to: awareness of HIV status; ANC; ART received during pregnancy; and mode of delivery. The difference between mothers who received ART after birth is also significant between the two groups ($p<0.001$) as only four mothers of HEI infants

received ART (one of whom started ART during pregnancy) at the time of data collection.

Twenty-four (85.71%) of the HEI infants' mothers only found out their HIV status after pregnancy which is statistically different (p<0.001) from the HEU group where the majority – 24 (77.42%) mothers, knew their status before pregnancy. Twenty-nine (90.63%) mothers with HEU infants, the majority in this group, received ANC compared to only 19 (67.86%) mothers in the HEI group (p=0.028). Only one mother (3.57%) in the HEI group received ART during her pregnancy compared to 26 (81.25%) of mothers with HEU infants (p<0.001). Twenty-six mothers (92.86%) in the HEI group had natural vaginal deliveries (NVD) and two (7.14%) had emergency caesarean (C-) sections which is statistically different from the 24 (75.00%) mothers in the HEU group who had NVD and eight (25.00%) who had elective C-sections (p=0.00). Use of ART, elective C-sections and avoiding breastfeeding is the gold standard procedure for PMTCT during labour, delivery and birth, and the postnatal period (Sturt, *et al.*, 2010).

Twenty-seven (26 HEU infants, and one HEI infant) mothers received ART during pregnancy. For the 33 mothers who did not receive ART during pregnancy, Table 4.7 shows those who received prophylaxis, and the type given:

Table 4.7 Type of prophylaxis given to mothers according to the status of their infants

Prophylaxis	HEU		HEI		p-Value
None (%)	1	(16.67%)	13	(48.15%)	<0.001
AZT only (%)	0	(0.00%)	2	(7.41%)	0.214
sd-NVP only (%)	2	(33.33%)	7	(25.93%)	0.069
AZT + sd-NVP (%)	3	(50.00%)	5	(18.52%)	0.454

(Values presented are frequencies and percentages)

There is a statistically significant difference (p<0.001) between mothers receiving no ARV prophylaxis (none) and the HIV status of their infants. Thirteen mothers did not

receive any prophylaxis (92.86%) and their infants are HEI. However no significant differences occurred between the groups for those mothers who received: AZT only; or, sd-NVP only; or, both AZT and sd-NVP.

4.2.3 Maternal Immunology and Virology

CD4 Counts for 25 mothers of the HEU infants (seven unknown), and only for five mothers of the HEI infants (23 unknown) were used to calculate the means and standard deviations shown in Table 4.8 below. Viral loads were unknown for eight mothers of HEU infants, and for all mothers of HEI infants. Therefore, there are no conclusions that can be made from these data.

Table 4.8 CD4 counts and viral loads for mothers

Variable	HEU		HEI		p-Value
	Mean	SD	Mean	SD	
CD4 Count	358.76	(±143.10)	446.00	(±255.03)	0.2863
Viral Load	11.59	(±44.56)	NA	NA	NA

(Values presented are means and standard deviations)
(NA = not available)

4.3 Developmental Analysis

4.3.1 Cognitive, Language and Motor Development (Composite Scores)

Developmental delay was calculated from the composite score (which is obtained from a scaled score which is computed from the child's raw score according to their age). A composite score of less than 85 represents delayed development, and a composite score of 85 and above, represents no delay. The two groups were compared using Chi-Squared tests.

Table 4.9 Composite scores for cognitive, language and motor development

Variable	HEU		HEI		p-Value
Cognitive Composite	100.31	(±12.75)	75.89	(±17.69)	<0.001
Language Composite	96.28	(±10.13)	77.18	(±16.33)	<0.001
Motor Composite	106.16	(±10.20)	79.71	(±20.91)	<0.001

(Values presented are means and standard deviations)

Table 4.9 shows that there are statistically significant differences in cognitive, language and motor development between the HEU and HEI groups, where infants who are HEI are significantly delayed (<85) in all scales ($p<0.001$). This is reported in more detail in sections 4.3.2-4 below.

4.3.2 Cognitive Delay

Eighteen HEI infants (64.29%) were found to have cognitive delay, where only one HEU infant had a cognitive delay (3.12%). Thirty-one HEU infants (96.88%) showed no cognitive delay compared with ten HEI infants (35.71%). Fischer's Exact Tests were performed to analyse these data and showed significant differences in cognitive delay between the groups ($p<0.001$).

4.3.3 Language Delay

Seventeen HEI infants (60.71%) were found to have language delay, where only four HEU infant had a language delay (12.50%). Twenty-eight HEU infants (87.50%) showed no language delay compared with 11 HEI infants (39.29%). Fischer's Exact Tests were performed to analyse these data and showed significant differences in language delay between the groups ($p<0.001$).

4.3.4 Motor Delay

Fifteen HEI infants (53.57%) were found to have motor delay, where no HEU infant had motor delay (0.00%). Thirty-two HEU infants (100.00%) showed no motor delay

compared with 13 HEI infants (46.43%). Fischer's Exact Tests were performed to analyse these data and showed significant differences in motor delay between the groups ($p<0.001$).

4.3.5 Developmental Delay in Months

Developmental age for each infant was calculated using the raw score obtained from each scale (Cognition, Language and Motor) and Table B.7 from page 220 of the BSID-III Administration Manual (Bayley, 2006) (Appendix V). In order to obtain the difference in months, and essentially a delay, the difference between the mean chronological age and the mean developmental age was calculated and these findings (in months) are recorded in Table 4.10 below:

Table 4.10 Difference (months) between chronological age and developmental age

Variable		HEU	HEI	p-Value
Cognitive		0.28 (±1.14)	2.21 (±2.04)	<0.001
Language	**RC**	0.44 (±1.47)	2.75 (±2.25)	<0.001
	EC	0.53 (±1.48)	2.36 (±2.64)	0.001
Motor	**FM**	0.09 (±0.96)	1.68 (±1.98)	<0.001
	GM	-0.28 (±1.05)	1.57 (±2.25)	<0.001

(Values presented are means and standard deviations)

As seen in Table 4.10 all scales revealed statistically significant differences for the mean chronological age and the mean developmental age (months) between the HEU infants and the HEI infants ($p\leq0.0001$). HEI infants show a mean cognitive delay of 2.21 months for cognitive development, 2.75 months for receptive communication (RC), 2.36 months for expressive communication (EC), 1.68 months for fine motor (FM) and 1.57 months for gross motor (GM) development.

4.3.6 Frequency of Infants According to Qualitative Descriptions of Composite Scores

Infants were stratified according to qualitative descriptions from Table 6.4 in the BSID-III Technical Manual (Bayley, 2006, p.114). This table has been replicated, as seen in Table 4.11 below.

Table 4.11 Qualitative descriptions of composite scores

Composite or Composite Score Equivalent	Classification
130 and above	Very Superior
120-129	Superior
110-119	High Average
90-109	Average
80-89	Low Average
70-79	Borderline
69 and below	Extremely Low

The below tables (Tables 4.12-14) show the frequencies and percentages according to the qualitative descriptions above for cognition, language and motor composite scores. Fischer's exact tests were performed to show statistical significance.

Table 4.12 Frequency of infants according to qualitative descriptions - cognition

	HEU n=32	HEI n=28	p-Value
Extremely Low	1 (3.13%)	10 (35.71%)	<0.001
Borderline	0 (0.00%)	3 (10.71%)	
Low Average	3 (9.38%)	9 (32.14%)	
Average	18 (56.25%)	5 (17.86%)	
High Average	8 (25.00%)	1 (3.57%)	
Superior	2 (6.25%)	0 (0.00%)	

Table 4.12 shows that just over a third of the infants in the HEI group show extremely low cognition. Only a fifth of these infants are considered to have cognitive scores of average and high average. The inverse is true for the HEU group where the majority

of these infants, 28 (87.5%), have cognitive scores that fall in the average, high average and superior categories. Only four (12.50%) HEU infants have scores that fall into low average or extremely low cognition. The difference between the HEU group and the HEI group is statistically significant (p<0.001).

Table 4.13 Frequency of infants according to qualitative descriptions - language

	HEU n=32	HEI n=28	p-Value
Extremely Low	0 (0.00%)	9 (32.14%)	<0.001
Borderline	4 (12.50%)	8 (28.57%)	
Low Average	2 (6.25%)	4 (14.29%)	
Average	23 (71.88%)	7 (25.00%)	
High Average	3 (9.38%)	0 (0.00%)	

Twenty-one (75.00%) of the HEI infants showed low average, borderline and extremely low language scores compared to only six (18.75%) infants in the HEU group as shown in Table 4.13 above. There is statistically significant differences between the two groups (p<0.001) for language scores.

Table 4.14 Frequency of infants according to qualitative descriptions - motor

	HEU n=32	HEI n=28	p-Value
Extremely Low	0 (0.00%)	9 (32.14%)	<0.001
Borderline	0 (0.00%)	3 (10.71%)	
Low Average	2 (6.25%)	5 (17.86%)	
Average	18 (56.25%)	9 (32.14%)	
High Average	7 (21.88%)	2 (7.14%)	
Superior	5 (15.63%)	0 (0.00%)	

Table 4.14 shows that motor ability in the HEU group is of average and above for 30 (93.75%) infants compared to only 11 (39.28%) infants in the HEI group. Five (15.63%) of infants in the HEU group show superior motor scores. The difference between the groups is of statistical significance (p<0.001); the HEI group has the majority of its infants in the low average, borderline and extremely low categories, and the HEU group has the majority of its infants in the average, high average and superior categories.

4.3.7 Subjective Measure of Developmental Delay

In the Maternal Interview (Appendix III) mothers were asked to report whether their infant had the same, slower or faster development than children of the same age. However, it was not indicated to the mother as to which area of development she was commenting on. Fischer's exact tests were used to analyse the data after the composite scores had been categorised as: delayed (<85); normal (85-115); or, superior (116 and above).

The following tables show statistical significance (p=0.00) when looking at cognition (Table 4.15), language (Table 4.16) and motor development (Table 4.17) of the infants and comparing it to the mother's response.

Table 4.15 Maternal observation when compared to cognitive score

Cognitive Score	Maternal Observation			p-Value
	Same	Slower	Faster	
Delayed	5 (26.32%)	12 (63.16%)	2 (10.53%)	<0.001
Normal	28 (80.00%)	3 (8.57%)	4 (11.43%)	
Superior	5 (83.33%)	0 (0.00%)	1 (14.29%)	

(Values presented are frequencies and percentages)

Table 4.16 Maternal observation when compared to language score

Language Score	Maternal Observation			p-Value
	Same	Slower	Faster	
Delayed	6 (28.57%)	13 (61.90%)	2 (9.52%)	<0.001
Normal	31 (81.58%)	2 (5.26%)	5 (13.16%)	
Superior	1 (100.00%)	0 (0.00%)	0 (0.00%)	

(Values presented are frequencies and percentages)

Table 4.17 Maternal observation when compared to motor score

Motor Score	Maternal Observation			p-Value
	Same	Slower	Faster	
Delayed	4 (26.67%)	11 (73.33%)	0 (0.00%)	<0.001
Normal	27 (72.97%)	4 (10.81%)	6 (16.22%)	
Superior	7 (87.50%)	0 (0.00%)	1 (12.50%)	

(Values presented are frequencies and percentages)

The above tables (Tables 4.15-17) show that the majority of mothers are correct in identifying that their infant has: the same development (normal) and slower development (delayed) when compared to another child of the same age. However, few mothers were able to identify that their infant was developing at a faster (superior) rate of development, but were still able to identify that there were no delays.

4.4 Conclusion

The findings from this study show that the two groups were well-matched for infant demographics, anthropometry at birth, maternal demographics, as well as socioeconomic status.

Statistically significant differences were found in anthropometry and development between the HEI and HEU group. The HEI infants had malnutrition, were stunted and had smaller head circumferences than infants who were HEU. The BSID-III showed that the average developmental delay for the HEI group was approximately two months below their average chronological age for all scales (cognitive, receptive and expressive communication, and, fine and gross motor age). The HEI group showed that 64.29% had cognitive delay, 60.71% had language delay and 53.57% had motor delay.

In addition to using the BSID-III to identify developmental delay, each mother was asked during the Maternal Interview (Appendix III) how they thought their infant was developing. The results showed that the majority of mothers were able to correctly indicate whether their child was developing at the same, or at a slower rate of development than children of the same age.

This study confirms that infants who are HIV-exposed and infected are at risk for developmental delay.

CHAPTER 5: DISCUSSION

As a group, HEI infants performed worse than HEU infants on tests of cognitive, language and motor development. These results are consistent with other studies from sub-Saharan Africa (Lowick, *et al*., 2012; Ruel, *et al*., 2012; Jelsma, *et al*., 2011; Shead, *et al*., 2010; Potterton, *et al*., 2009b; Baillieu and Potterton, 2008; Smith, *et al*., 2008; Van Rie, *et al*., 2008; McGrath, *et al*., 2006; Drotar, *et al*., 1997; Boivin, *et al*., 1995; Msellati, *et al*., 1993) and the more developed world (Rice, *et al*., 2012; Koekkoek, *et al*., 2008; Lindsey, *et al*., 2007; Foster, *et al*., 2006; Smith, *et al*., 2006; Llorente, *et al*., 2003; Blanchette, *et al*., 2001; Macmillan, *et al*., 2001; Chase, *et al*., 2000; Pearson, *et al*., 2000; Smith, *et al*., 2000; Belman, *et al*., 1996; Pollack, *et al*., 1996; Chase, *et al*., 1995; Gay, *et al*., 1995; Nozyce, Hittelman, *et al*., 1994; Mellins, *et al*., 1994; Condini, *et al*., 1991; European Collaborative Study, 1990).

This chapter will justify the study design, discuss the results and compare the findings with studies that have been done previously. It will also be useful to discuss the limitations, implications and recommendations for the development of future studies.

5.1 Study Design

This study investigated the difference in development of infants from six weeks to 12 months of age who were HIV-exposed. This age range was chosen as few studies in sub-Saharan Africa have looked at this age-group with certainty of HIV status (McGrath, *et al*., 2006). The BSID-III was a suitable tool to assess development in this age-group as it is an individually administered instrument designed to measure developmental delay of infants and toddlers (Albers and Grieve, 2007). It is also well-known that the BSID has been employed for its sensitivity, validity and reliability in assessing development in many previous studies of children with HIV (Shead, *et al*., 2010; Potterton, *et al*., 2009b; Baillieu and Potterton, 2008; Van Rie, *et al*., 2008; Lindsey, *et al*., 2007; Foster, *et al*., 2006; McGrath, *et al*., 2006; Llorente, *et al*., 2003; Blanchette, *et al*., 2001; Macmillan, *et al*., 2001; Chase, *et al*., 2000; Pearson, *et al*.,

2000; Smith, *et al*., 2000; Drotar, *et al*., 1997; Belman, *et al*., 1996; Pollack, *et al*., 1996; Chase, *et al*., 1995; Gay, *et al*., 1995; Nozyce, Hittelman, *et al*., 1994; Mellins, *et al*., 1994; Belman, *et al*., 1988; Epstein, *et al*., 1986; Ultmann, *et al*., 1985). The authors are of the view that it was not necessary to translate the BSID-III into chiShona (local language in Harare) as the age-range of infants included in the study dictated predominate, non-verbal use of language.

Given the young age of these infants, it was important to ensure that each infant's mother was present at the assessment. The presence of someone other than the mother could indicate that the child had experienced some form of trauma (orphan hood or inconsistent caregivers). This may have introduced confounding variables, where delays in development may be attributed to risk factors of early child development (Baker-Henningham and Boo, 2010; Engle, *et al*., 2007). Other studies with a similar age range failed to exclude infants if mothers were not present at assessment, and so, their results may show developmental delay due to risk factors other than HIV (Potterton, *et al*., 2009b; Baillieu and Potterton, 2008; McGrath, *et al*., 2006; Drotar, *et al*., 1997; Boivin, *et al*., 1995; Msellati, *et al*., 1993).

The Maternal Interview (Appendix III) was used to obtain information on the mother and infant's HIV history, as well as obstetric history. This was introduced into the study to identify other factors that may have contributed to neurodevelopmental impairment other than HIV (Abrams, *et al*., 2003). Maternal health is also thought to influence the course of paediatric infection (Tovo, *et al*., 1994). As timing of HIV infection is associated with differing clinical presentations in infants (McGrath, *et al*., 2006), it was hoped that the information obtained from the mother's HIV history would provide insight into the timing of HIV infection for each infant. This information was also obtained to identify possible risk factors associated with MTCT of HIV as this would be useful in PMTCT (Kuhn and Stein, 1995). The only conclusion that can be drawn from this information is that the majority of HIV-negative infants were born to mothers who were aware of their status before pregnancy and were receiving ART during pregnancy – the reverse was true for the HIV-infected group.

HIV-exposed infants who tested negative were assessed on the day of their DNA-PCR test to ensure that they were HIV-negative at the time of the BSID-III assessment. This was deemed necessary by the authors so as not to include infants who had undergone HIV-testing more than six weeks earlier, as continued breastfeeding in the HIV-exposed uninfected group provides further exposure to HIV infection (Coutsoudis, *et al.*, 2004). Not many other studies in sub-Saharan Africa with a similar age-range (Kandawasvika, *et al.*, 2011; Drotar, *et al*., 1997; Boivin, *et al*., 1995; Msellati, *et al*., 1993) report this concern when comparing their HIV-infected group with the uninfected group.

5.2 Comparison of the Groups

5.2.1 Demographics

There were no significant differences between the groups for infant demographics (gender, age) or maternal demographics (age, level of education completed). Attempts were made using the Maternal Interview to compare the socioeconomic background (average number of people living in household, income) of the groups, however interpretation of these results should be made with caution as the author is not trained in this field of expertise. The author acknowledges that the results may be confounded by variables which are difficult to control for, such as poverty, poor health and nutrition, and deficient care (Grantham-McGregor, *et al*., 2007). However, the mothers and infants in this study were from similar geographic areas of Harare and accessed the same clinics, which may indicate similar socioeconomic backgrounds.

5.2.2 Anthropometric Measurements

At Birth

Although there has been less documentation, LBW is a risk factor for poor child development of cognition, behaviour and motor (Walker, *et al*., 2004; Gardner, *et al*., 2003; Lui, *et al*., 2001; Grantham-McGregor, *et al*., 1998; Gorman and Pollitt, 1992; Villar, *et al*., 1984). The groups were similar at birth according their birth weight where the HEU group had a mean weight of 2920 grammes (±390g) and the HEI group had a mean weight of 2795g (±470g). Due to more than 80% of data missing for length and head circumferences at birth, it was impossible to compare the groups according to these variables. Failure to obtain these measures might introduce discrepancies between the groups.

At Assessment

Abubakar *et al* (2009) report that WAZ and disease staging of children infected with HIV can be used in sub-Saharan Africa to identify those in need of psychomotor rehabilitation. Poor WAZ has been associated with motor impairment in HIV-infected and uninfected populations (Abubakar, *et al*., 2009). Pollack *et al* (1996) reported that: linear growth failure precedes cognitive and motor delay; growth failure is positively correlated with cognitive and motor delay; and onset of neurodevelopmental delay is earlier in infants with growth delay than in those without. Acquired microcephaly, indicating impaired growth of the brain, was reported in early studies of paediatric HIV (Belman, *et al*., 1988; Belman, *et al*., 1985; Epstein, *et al.*, 1985; Ultmann, *et al*.,1985).

Significant differences in anthropometric measurements between the groups were observed in this study. The HEI group were underweight, stunted and had smaller head circumferences. The results of this study are similar to other studies which found that HIV-infected children had significant differences in anthropometric measurements compared to their uninfected peers (Potterton, *et al*., 2009b; Foster, *et al*., 2006; Pollack, *et al*., 1996).

5.2.3 Development

Previous literature has reported a range of delays in children with HIV infection. This study is no exception. However, this study, like that by Van Rie and colleagues (2008) found that cognition was more affected than motor development. More studies in sub-Saharan Africa have shown motor delay to be more affected than cognitive delay (Shead, *et al*., 2010; Potterton, *et al*., 2009b; Baillieu and Potterton, 2008; Drotar, *et al*., 1997). A possible explanation for the variation observed could be attributed to differences in child-rearing practices.

Developmental assessment of children requires the use of specialised tools and training on administering these measures. In the Maternal Interview (Appendix III) mothers were asked to comment on whether they thought their children were developing at the same, slower or faster rate than peers. Sixty-three-point-one-three percent of mothers accurately identified a delay in cognition, 61.90% in language and 73.33% in motor development. Eighty percent, 81.58% and 72.97% of mothers accurately identified similar development to peers in cognition, language and motor development, respectively. Few mothers were able to accurately identify superior development. Limitations of these results apply as the mothers were not asked to specify which area of development they were commenting on.

Developmental delay in this study was reported if an infant obtained a composite score of less than 85. A composite score of less than 69 deemed the child to have extremely poor development (Bayley, 2006).

Cognitive Development

Eighteen (64.29%) HEI infants had developmental delay in cognition. Ten of these infants had extremely low cognition. Only one (3.13%) HEU infant was delayed. Other studies in sub-Saharan Africa that used the BSID reported cognitive delay in HIV-infected children as the following range: 26% (Drotar, *et al*., 1997); 52% (Potterton, *et al*., 2009b); 60% (Van Rie, *et al*., 2008); and, 70% (Baillieu and Potterton, 2008).

Cognition of HIV-infected children is likely to be more impaired than uninfected peers due to the neuropathological and structural changes associated with HIV infection of the CNS. However, various other factors can contribute to cognitive delay in children such as stunting (Carba, *et al*., 2009; Walker, *et al*., 2007a; Alderman, *et al*., 2006), deficient care (Walker, *et al*., 2011) and duration of exclusive breastfeeding (Walker, *et al*., 2011; Clark, *et al*., 2006). It is necessary to interpret the findings with caution as this study included children with stunting and was not able to measure the duration of exclusive breastfeeding due to the cross-sectional design. Despite these limitations, HIV infection does not occur in isolation, and so while attempts were made to minimise confounding factors, this study provides an indication as to developmental delay in HIV-exposed infants.

Language Development

Development of language is complex. It is reliant on both cognitive and motor development (Wolters, *et al*., 1997). Language delay occurred in 17 (60.71%) of HEI infants, where nine of these infants showed extremely poor language development. Only four (12.5%) HEU infants were delayed in language acquisition. Delay in language has been reported in only two studies in sub-Saharan Africa which used descriptive analysis of the data: 82.5% (Baillieu and Potterton, 2008); and 85% expressive language, 77% receptive language (Van Rie, *et al*., 2008). This study found that the mean receptive language age (2.75 months delay ±2.25 months) of the HEI group was more delayed than their mean expressive language age (2.36 months delay ±2.64 months), when compared to their mean chronological age. This finding is

different from other studies which found greater delay in expressive language in children with HIV infection (Van Rie, *et al*., 2008; Wolters, *et al.*, 1997). However these studies examined language development in older children.

Motor Development

Fifteen (53.57%) HEI infants showed developmental delay of motor function, where nine of these infants had extremely poor development. No HEU infants were delayed in motor development. The results on motor development in HIV-infected infants are comparable to other studies in sub-Saharan Africa: 29% (Van Rie, *et al*., 2008); 30% (Drotar, *et al*., 1997); 72% (Potterton, *et al*., 2009b); and, 85% (Baillieu and Potterton, 2008). The HEI group was underweight and stunted, therefore motor development could have been affected by these co-factors (Abubakar, *et al*., 2009; Pollack, *et al*., 1996).

5.2.4 Immunology, Virology and Antiretroviral Therapy

It was not possible in this study to obtain CD4 counts and percentages and viral loads for all the mothers and HEI infants in this study. Monitoring of HIV progression in Zimbabwe is limited to clinical and immunological assessment. Virology is not routinely monitored in Zimbabwe. The impact of ART was difficult to assess due to the study design. Ten (35.71%) of the infants included in this study were receiving ART.

5.3 Limitations

Every attempt was made to ensure that the authors minimised confounding variables as best as possible. However, limitations in this study exist.

- The BSID-III has not been normed, or validated on Zimbabwean children.
- The cross-sectional design impaired the ability of this study to identify the timing of HIV transmission, as well as the impact of ART on development. Timing of HIV transmission is associated with differing neuropathological and clinical manifestations of the disease.
- Severity of HIV disease could not be obtained for mothers and HEI infants due to the lack of data on immunological and virological markers. These data could have provided data to assist in determining the correlation between disease severity and developmental delay.

5.4 Implications

HIV-exposed infected infants are more at risk of cognitive, language and motor delay than HIV-exposed uninfected infants. The implication of disability occurring in HIV-infected children poses an additional burden for the family, as well as public health care systems. With the advent of ART, and its increasing availability in sub-Saharan Africa, these infants are more than likely going to have similar life expectancies as their uninfected peers. Despite this, the focus of HIV management is still centred on life-saving measures. Healthcare professionals working in sub-Saharan Africa need to advocate chiefly for PMTCT to prevent paediatric HIV. And, in the case of infants already infected, healthcare professionals and policy makers need to advocate for integrated, multidisciplinary management with timely identification and intervention. Without provision of allied health professionals (such as occupational therapy, speech and language therapy and physiotherapy) HEI children are likely to experience a significantly decreased quality of life as compared to their uninfected peers.

5.5 Clinical Recommendations

- PMTCT needs to be scaled up in sub-Saharan Africa, as vertical transmission of HIV is avoidable.
- In the case of infants infected with HIV then initiation of ART should be prompt after diagnosis
- Early-intervention and multidisciplinary management of children infected with HIV should be common practice, and involve allied health professionals.
- Utilisation of more efficacious regimens of ART for permeating the BBB so as to effectively halt viral replication of HIV in the CNS.

5.6 Recommendations for Future Research

- Conducting longitudinal studies at multiple sites in sub-Saharan Africa to obtain larger sample sizes.
- Identifying timing of HIV infection as this is likely to impact on the severity of the disease. This may potentially facilitate identification of distinctive clinical presentations.
- Obtaining immunological and virological data for all mothers and infants.
- Recording ARV/ART history for mothers and infants, as this variable is likely to impact on the course of the disease and the severity of impairment.
- Developing a context-specific, global developmental screening tool to be used by nurses and doctors.

The main conclusions which can be drawn from this study will be presented in the following chapter.

CHAPTER 6: CONCLUSION

The purpose of this cross-sectional study was to determine developmental delay in 60 HIV-exposed (28 infected, 32 uninfected) infants from six weeks of age to 12 months of age. Cognitive, language and motor development was assessed using the BSID-III.

The two groups were well-matched for infant demographics, anthropometry at birth, maternal demographics, as well as socioeconomic status. Statistically significant differences were found in anthropometry and all domains of development between the HEI and HEU group. This has been reported globally in studies on the development of HIV-infected children. This study showed that HEI infants were malnourished and stunted and had smaller head circumferences than HEU infants. It was also interesting to note that this study found that cognitive development was more affected than language and motor development, which is different to the majority of studies done in sub-Saharan Africa.

This study demonstrates that infants who are HIV-exposed and infected are more at risk of developmental delay than HEU infants. Timely identification of these children, as well as multidisciplinary intervention, is required to ensure that these children are able to reach their maximum developmental potential.

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APPENDIX I: ETHICAL CLEARANCE

M110484

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

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Mrs Jenna Hutchings

CLEARANCE CERTIFICATE	**M110484**
PROJECT	Developmental Delay in HIV-Exposed Infants Attending Newlands Clinic in Harare, Zimbabwe
INVESTIGATORS	Mrs Jenna Hutchings.
DEPARTMENT	Department of Physiotherpay
DATE CONSIDERED	06/05/2011
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 03/06/2011 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Joanne 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...

Telephone: 791792/791193
Telefax: (263) - 4 - 790715
E-mail: mrcz@mrczimshared.co.zw
Website: http://www.mrcz.org.zw

Medical Research Council of Zimbabwe
Josiah Tongogara / Mazoe Street
P. O. Box CY 573
Causeway
Harare

Ref: MRCZ/B/192 **14 June 2011**

Jenna Hutchings
Newlands Clinic
56 Enterprise Road
Newlands
Harare

RE: Request for approval of Amendments: Developmental Delay in HIV-Exposed Infants.

We refer to your correspondence dated 13 June 2011 on the above mentioned subject.

Please be advised that The Medical Research Council of Zimbabwe has **reviewed** and **approved** the following changes:

- Adding Parirenyatwa OI clinic, Mazoe Street, as a study site on the protocol.
- Increase of sample size to 60 infants, 30 HIV positive and 30 HIV negative.
- Change of title to accommodate the additional site.
- Inclusion criteria specifying that infants who are breastfeeding and test negative will not be assessed >six weeks after DNA-PCR testing.

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
14 JUN 2011
APPROVED
P. O. BOX CY 573 CAUSEWAY, HARARE

Yours Faithfully

.....

MRCZ SECRETARIAT
FOR CHAIRPERSON
MEDICAL RESEARCH COUNCIL OF ZIMBABWE

APPENDIX II: INFORMED CONSENT

DEVELOPMENTAL DELAY IN HIV-EXPOSED INFANTS IN HARARE, ZIMBABWE.

INFORMED CONSENT

Introduction

Good day, my name is Jenna Hutchings, I am a paediatric physiotherapist working at Newlands Clinic. I would like to invite you to consider participating in a research study entitled - *Developmental Delay in HIV-exposed Infants in Harare, Zimbabwe*. This study will take place at Newlands Clinic and Parirenyatwa OI Clinic in Harare, Zimbabwe. You and your child were chosen as a possible participant because you are receiving treatment at one of these clinics. Please read this form and ask any questions that you may have before agreeing to participate in the study.

Study Purpose

The purpose of the study is to look at the growth and development of babies from six weeks of age to 12 months of age who have been born to mothers who are HIV-positive. It will also look to see if there is a difference in the development of babies who are HIV-infected compared with those who are not infected with HIV.

Study Procedures

If you agree to participate in this study, we would like your permission to collect information by:

- interviewing you about your pregnancy, labour and delivery.
- interviewing you about your child's medical history to see how s/he has been growing and developing
- assessing your child's development once using the Bayley Scales of Infant and Toddler Development, third edition (BSID-III) which will show his/her cognitive, language and motor development to-date. (This assessment will take approximately 50 minutes to administer.)
- measuring your infant's height, weight and head circumference on the day of assessment.

The study will not influence your or your child's normal medical follow-up. You are free to choose whether or not to allow the use of your and/or your child's information and/or the information obtained from the assessment of your child's development. Your and your child's treatment at the clinic will continue as normal even if you do not want to participate in this study. However, if you do agree to participate there may be some questions that you answer that highlight that you and your child cannot participate in this study, e.g. if your child was born early (premature). In this case, the principal researcher will let you know and you and your child will not be required to complete the remaining assessments.

Risks and Discomforts

The study has no risks.

Benefits and/ Compensation

By participating in this study you may benefit from improved management of your child. Your and your child's participation may also help other people in the future. You will not be paid to participate in this study. However, if you attend the clinic on a day when you do not already have a scheduled appointment, you will be reimbursed for transport according to the going-rate to and from the clinic. We cannot and do not promise that you will receive any benefits from this study.

In the Event of Injury

There is no foreseeable study-related injury.

Alternative Treatments

If your child is found to have a delay in his/her development (cognition, language, motor) then your child will be referred to rehabilitation in the most appropriate public health service.

Confidentiality

The records and data obtained in this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify you (your child) as a participant. No information with your (child's) name or identity will leave the clinic. Your (child's) name will not appear on any of the records. No one will be able to link you with information in your (child's) file with the exception of the principal investigator (Mrs. J Hutchings) who knows which code belongs to you.

DEVELOPMENTAL DELAY IN HIV-EXPOSED INFANTS IN HARARE, ZIMBABWE.

INFORMED CONSENT

Nhanganyaya
Maswera sei, zita rangu ndinonzi Jenna Hutchings, ndiri physiotherapist wevana vadiki anoshandira kuNewlands Clinic. Ndoda kukukokai kuti mushande mutsvakiridzo yandiri kuita inonzi *Developmental Delay in HIV-exposed Infants kuHarare, Zimbabwe.* Tsvakiridzo iyi ichaitirwa paNewlands Clinic neParirenyatwa OI Clinic. Imi nemwana wenyu masarudzwa kuti muve vamwe vangangokwanisa kushanda mutsvakiridzo iyi nekuti munorapwa pazvipatara izvi. Nyatso verengai gwaro rino uye bvunzai pane zvose zvamunenge musiri kunzwisisa musati mabvuma kushanda mutsvakiridzo ino.

Donzvo nechinangwa chetsvakiridzo iyi
Chinangwa chetsvakiridzo iyi ndechekuongorora makuriro evana kubvira pavanenge vachiri pazera remavhiki matanhatu kusvikira pavachange vava pazera remwedzi gumi rine maviri. Ava vana vanofanira kunge vakazvarwa navanamai vaneutachiona weHIV. Tsvakiridzo iyi ichange ichitsvaka musiyano mumakuriro, pakati pevana vane utachiona weHIV nevana vasina utachiona.

Zvichaitwa
Kana mukati imi munoda kushanda mutsvakiridzo iyi, tinokumbirawo mvumo yekutsvaka ruzivo nenzira dzinotevera:

- Ndichakubvunzai mibvunzo yakanangana nenguva yamanga muine pamuviri, nguva yamakanzwa kuti mava kuda kunosununguka uye nguva yekuzosununguka mwana.
- Ndichakubvunzai nezveupenyu hwemwana nemarwariro aakamboita munguva yapfuura mumashure kuti ndizive makuriro aari kuita.
- Ndichaongorora makuriro emwana kamwe chete ndichishandisa anonzi "*maBayley Scales of Infant and Toddler Development, third edition (BSID-III)*" ongororo iyi ichaita kuti ndikwanise kuziva kuti mwana akura kusvika papi maererano emafungiro aava kuita, mutauro wake kuti wava papi uye kuti nyama dzomuviri wake dziri kuenderana kusvika papi. (Ongororo iyi ichatora nguva inosvika maminiti makumi mashanu.)
- Ndichada zvekare kutarisa kuti mwana murefu kusvika papi, uye kuti ane uremu unosvika papi, uye nekuzoziva kuti musoro wake wakakura kusvikira papi.

Tsvakiridzo ino haina chaicha sandura mumarapirwo agara achiitwa mwana. Makasununguka kuti zvese zvatinenge tawana kubva kwamuri kana kunemwana zvisashandiswe kana musisade. Kunyangwe mukaramba kushanda mutsvakiridzo iyi mucharamba muchiwana mishonga nerubatsiro rwese rwamagara muchiwana kubva kuNewlands Clinic, nekuParirenyatwa OI Clinic. Kunyange zvazvo mabvuma kushanda nesu panenge pane mimwe mibvunzo yamuchapindura icharatidza kuti imi nemwana wenyu hamukwanisi kushanda mutsvakiridzo iyi, sekuti mwana wenyu anenge akazvarwa nguva isati yakwana. Pakadaro Mutsvakiridzi anokuzivisai imi nemwana wenyu kuti hamufanira kupedzisa dzimwe ongororo dzinenge dzasara.

Zvibingamupinyi (Risks and Discomforts)
Hapana zvimhingamipinyi zviripo zvaungasangana nazvo kana ukati unoda kushanda mutsvakiridzo iyi.

Zvinobatsira (Benefits and/or Compensation)
Mukashanda mutsvakiridzo iyi, zvinogona kubatsira kuti mwana awane kurapwa kuri nane. Ruzivo rwatichawana mukunge taita ongororo yemwana nemi zvinokwanisa kuzobatsirao vamwe mune ramangwana. Hapana mari yamuchawana mukashanda mutsvakiridzo iyi. Asi mukauya kuchipatara muchingofambira kuzoshandira mutsvakiridzo iyi muchadzorerwa mari yebhazi yamunenge mashandisa kuuya kuchipatara uye yamuchada kuzodzokeresa kumba. Hatikwanise kukuvimbisai kuti kushanda mutsvakiridzo iyi kuchakubatsirai.

Kana mukakuvara muchishanda mutsvakiridzo ino
Hapana patinotarisira kuti tsvakiridzo iyi ingakonzera kuti mukuvare.

DEVELOPMENTAL DELAY IN HIV-EXPOSED INFANTS IN HARARE, ZIMBABWE.

INFORMED CONSENT

Voluntary Participation
Participation in this study is voluntary. If you decide not to participate in this study, your decision will not affect your future treatment and / or relations with this clinic. If you decide to participate, you are free to withdraw at any time without affecting this relationship. You have the right to decline to answer questions you are not comfortable with.

Offer to Answer Questions
Before you sign this form, please ask any questions about this study that is not clear to you. You may take as much time as necessary to think about it.

Contracts and Questions
The researcher conducting this study is Mrs. J Hutchings. You may ask any questions you have now, or if you have questions later, you are encouraged to contact Newlands Clinic, 56 Enterprise Road, Newlands, Harare. Telephone: (04) 776433.

Authorisation
You are making a decision whether or not to take part in this study. Your signature shows that you have: read and understood the information provided above; had all your questions answered; and, have decided to participate. All pages will be stamped to indicate form validity as approved by the MRCZ.

If you have any questions or concerns regarding the study and would like to talk to someone other than the investigator, including questions about the research, study questions, your rights as a research participant or research related injuries; or if you feel that you have been treated unfairly and would like to talk to someone other than a member of the research team, please feel free to contact the Medical Research Council of Zimbabwe on Telephone 791792 or 791193. You will be given a copy of this form to keep for your records.

Statement of Consent
I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

Name of Participant _____ [Please PRINT]

Signature of Participant _____

Date _____ Time _____

Signature of Investigator _____

Date _____ Time _____

Witness (if applicable) _____

DEVELOPMENTAL DELAY IN HIV-EXPOSED INFANTS IN HARARE, ZIMBABWE.

INFORMED CONSENT

Rumwe rubatsiro
Kana mwana akaonekwa kuti ari kunonoka kukura (mafungiro, kana mutauro kana kuti mashandiro emhumhu yake) achanyorerwa tsamba yekuti agokwanisa kuwana rubatsiro kubva kunevamwe vana chiremba muzvipatara zvehurumende.

Confidentiality
Zvese zvatichawana kubva kwamuri mutsvakiridzo ino hazviudzwe mumwe munhu zvinoenderana nebumbiro remutemo wetsvakiridzo iyi. Patichazenge tonyora kana kuudza veruzhinji maererano nezvatinenge tawana mutsvakiridzo iyi, hapana chichanyorwa kana kutaurwa chinogona kuti mwana wenyu kana kuti imi mugozozivikanwa kuti makashanda mutsvakiridzo iyi. Zvese zvichawanikwa mutsvakiridzo iyi zvinokwanisa kuti zvizivikanwe kuti ndimi manga muri mutsvakiridzo iyi zvichachengetwa zvakavharirwa pachipatara chino. Magwaro ese achachengetwa anenge asina zita remwana. Hapana umwe munhu anokwanisa kuzoziva kuti imi ndimi amai vemwana ane gwaro rinotaridza kuti ongororo iyi yakaitwa kunze kwemuongorori (Amai J Hutchings).

Voluntary participation
Munokwanisa kuramba kushanda mutsvakiridzo iyi, uye munokwanisazve kubvuma kushanda mutsvakiridzo iyi mozoramba pamunonzwa kuti hamuchada kushanda mutsvakiridzo iyi. Zvamunenge masarudza kuita hazvikanganisi marapirwo amunogara muchiwana pamakiriniki aya. Mune kodzero yekuramba kupindura mibvunzo yamunenge musingadi kupindura.

Mibvunzo
Ongororai gwaro rino nemazvo uye bvunzai mibvunzo yese yamungaite musati masarudza kuti munoda kushanda mutsvakiridzo iyi kana kuti kwete.

Muongorori
Muongorori ari kuita tsvakiridzo iyi anonzi J. Hutchings. Bvunzai mubvunzo yese yamungaite. Kana mukazoita mibvunzo munguva inotevera munokurudzirwa kuti mutaure neveNewlands Clinic, 56 Enterprise Road, Newlands, Harare. Telephone: (04) 776433.

Authorisation
Muri kusarudza kuti muri kuda here kana kuti kwete kushandira mutsvakiridzo iyi. Kuisa runyoro rwenyu kunotaridza kuti maverenga mukanzwisisa zvose zviri pagwaro rino uye mibvunzo yenyu yose yapindurwa mukagutsikana kuti muri kuda kushanda mutsvakiridzo ino. Mapeji ose egwaro rino achaiswa chidhindo kutaridza kuti tine mvumo kubva kuMRCZ. Kana muine mibvunzo ine chekuita netsvakiridzo iyi kana kuti ine chekuita negwaro rino yatadza kupindurwa nemuongorori kubatanidzira mibvunzo ine chekuita nekodzero dzenyu, uye kana muchiwona sekuti kodzero dzenyu dzatsikirirwa muchida kutaura nemumwe asiri wevarikuita zvetsvakiridzo munokwanisa kutaure nevekuMedical Research Council of Zimbabwe panhamba dzinoti 791792 or 791193. Muchapihwa rimwe gwaro rakafanana nerino rekuti muchengete.

Statement of Consent
Ndaverenga gwaro rino rinotsanangura kushanda kwangu uye zvimhingamupinyi nezvinobatsira pakushanda mutsvakiridzo iyi. Mibvunzo yangu yapindurwa zvinogutsa. Ndinobvuma kushanda mutsvakiridzo ino.

_____	_____
Zita renyu	Zita remuongorori
_____	_____
Signature yenyu (kana anokumirirai)	Signature yemuongorori
Zuva ranhasi _____ Nguva _____	Zuva ranhasi _____ Nguva _____

_____
Mumiriri (kana achidiwa)

APPENDIX III: MATERNAL INTERVIEW

Developmental Delay in HIV-Exposed Infants in Harare, Zimbabwe.

Participant / Study Number:	
Date of Visit:	
Participant Age:	

MATERNAL INTERVIEW

General

What is your age? _____ What level of education did you complete? _____

How many are in your household? _____ How much does your household earn per month? _____

HIV-related questions

1. Was this pregnancy planned? (Go to Q2) Yes ☐ No ☐
2. When were you first aware of your HIV status? Date __ /__ /____

Before pregnancy	☐	(Go to Q3)	After birth	☐	(Go to Q10)
During pregnancy	☐	(Go to Q3)	Only when infant became sick	☐	(Go to Q12)
During labour / delivery	☐	(Go to Q7)	Age of infant _____		(If >6 mths Go to Q12)

3. When did you seek medical care for HIV?

Before pregnancy	☐	(Go to Q4)	During labour / delivery	☐	(Go to Q7)
During pregnancy	☐	(Go to Q4)	After birth Reason:	☐	(Go to Q7)

4. What was your CD4 count during pregnancy? _____ (Go to Q5)
5. Did you receive ARVs during pregnancy? Yes ☐ (Go to Q6) No ☐ (Go to Q7)
   If yes, what?:_____
6. How many tablets (on average) did you forget each month during pregnancy?
   1-2 ☐ (Go to Q8) 3+ ☐ (Go to Q7)
7. Did you receive a single dose of Nevirapine during labour or delivery? (Go to Q8)
   Yes ☐ No ☐
8. Did your child receive ARV Prophylaxis at birth? Yes ☐ (Go to Q9) No ☐ (Go to Q10)
9. Did your child receive: sd-NVP ☐ + AZT $^{7}/_{7}$ ☐ or, Ext daily NVP ☐ (Go to Q10)
   Reason:_____
10. Has this child received any ARVs to date? Yes ☐ (Go to Q11) No ☐ (Go to Q11)
11. Did you receive ARVs during breastfeeding? Yes ☐ (Go to Q12) No ☐ (Go to Q12)
12. Did this child receive Cotrimoxazole? Yes ☐ No ☐
    If yes, at what age? _____months. Stopped? Yes ☐ No ☐
13. a) Did you exclusively breastfeed this child? Yes ☐ (Go to Q13b) No ☐
    If no, when did you start mixed feeding? _____months
    b) When did the child stop breastfeeding? _____ months

General Pregnancy Questions

1. What month did you go into labour (gestational age)?_____
2. Did you register this pregnancy at a clinic? Yes ☐ No ☐
   Where?_____ If no, why? _____
3. What was your weight before pregnancy? _____ kgs
4. What is your height? ____ cms
5. How many children (including this child) do you have? ____
6. What are their ages?_____
7. How many miscarriages have you had? _____
8. Did you have any illnesses/infections/injuries during this child's pregnancy? Yes ☐ No ☐
   _____
9. Is this child a part of a multiple pregnancy (twins/triplets…)? Yes ☐ No ☐
10. How much weight did you gain during pregnancy?_____

Participant / Study Number:	
Date of Visit:	
Participant Age:	

Labour / Delivery

1. Was your birth managed by a qualified birth attendant? Yes ☐ No ☐
2. Mode of delivery?
   Natural Vaginal Delivery ☐ Elective Caesarean Section ☐ Emergency C-Section ☐
3. Was this child incubated and/or ventilated at birth? Yes ☐ No ☐
4. Did this child have a prolonged stay (more than 2 days) in hospital after birth? Yes ☐ No ☐
   If yes, why? _____

Development in the First Year

1. Did this child have any hospital admissions for meningitis, malnutrition, fits (kugwina), jaundice (yellow baby), diarrhoea (>3 loose stools per day), infections, injuries or problems requiring hospitalisation, a) in the first 30 days of life Yes ☐ No ☐
   b) in the first year of life? Yes ☐ No ☐
   If yes, details _____
2. Please check the following indicating a comparison of this child's growth and development when compared with children of the same age:
   Slower ☐
   Same ☐
   Faster ☐
3. What age did this child sit, crawl, stand, walk and talk?
   Sit _____ months
   Crawl _____ months
   Stand _____ months
   Walk _____ months
   Talk _____ months

Additional: _____

APPENDIX IV: DATA COLLECTION SHEET

DATA COLLECTION SHEET

Participant Number:		Date of Visit:		Participant Age:	

INFANT MEASUREMENTS

APGAR: _____ Medication History: _____

	Birth	1 __/___	2 __/___	3 __/___	4 __/___	5 __/___	6 __/___	7 __/___	8 __/___	9 __/___	10 __/___	11 __/___	12 __/___
Height (cms)													
Weight (kgs)													
Head circum. (cms)													
CD4 %													
CD4 count													
Viral Load													
Hospital Admissions													
Illnesses													
Immunisation													

MOTHER

CD4 count during pregnancy: _____ CD4 labour and delivery: _____ CD4 at birth: _____ CD4 breastfeeding: _____

Viral Load (VL) during pregnancy: _____ VL labour and delivery: _____ VL at birth: _____ VL breastfeeding: _____

Medication during pregnancy: _____

Hospital Admissions/Illnesses: _____

APPENDIX V: RAW SCORE EQUIVALENTS FOR DEVELOPMENTAL AGE

Table B.7 Raw Score Equivalents for Developmental Ages for the Cognitive, Receptive Communication, Expressive Communication, Fine Motor, and Gross Motor Subtests

Developmental Age in Months and Days	Cognitive	Receptive Communication	Expressive Communication	Fine Motor	Gross Motor	Developmental Age in Months and Days
<0:16	0–5	0–4	0–2	0–3	0–4	<0:16
0:20	6	5	3	–	5	0:20
1:00	–	–	–	4	6	1:00
1:10	7	–	–	–	–	1:10
1:20	–	–	–	–	7	1:20
2:00	8	–	4	5	8	2:00
2:10	9	6	–	–	9	2:10
2:20	10	–	5	6	10	2:20
3:00	11–12	–	–	7	11	3:00
3:10	13–14	7	–	8–9	12–13	3:10
3:20	15–16	–	6	10	14	3:20
4:00	17–18	–	–	11–12	15–16	4:00
4:10	19–20	8	–	13–14	17	4:10
4:20	21–22	–	–	15	18–19	4:20
5:00	23–24	–	7	16–17	20	5:00
5:10	25	9	–	18	21	5:10
6	26–28	10	8	19–20	22–26	6
7	29–30	11	9	21–22	27–30	7
8	31–33	–	10	23–24	31–33	8
9	34–35	12	11	25	34–36	9
10	36–37	13	12	26–27	37–38	10
11	38–39	14	13	28	39–41	11
12	40–41	–	14–15	29	42–43	12
13	42–43	15	16	30	44	13
14	44–45	16	17	–	45–46	14
15	46–47	17	18	31	47	15
16	48–49	18	19	32	48–49	16
17	50–51	19	20–21	33	50	17
18	52–53	20	22	34	51–52	18
19	54–55	21–22	23–24	–	53	19
20	56	23	25	35	54	20
21	57–58	24	26–27	36	55	21
22	59–60	25	28	37	–	22
23	61–62	26	29	38	56	23
24	63	27	30	–	57	24
25	64–65	28	31	39	–	25
26	66	29	32	40	58	26
27	67–68	–	33	41	59	27
28	69	30	–	42	–	28
29	70	31	34	43	60	29
30	71	32	35	–	–	30
31	72	33	36	44	61	31
32	73	34	–	45	–	32
33	74	–	37	46	62	33
34	75	35	38	47	–	34
35	76	36	39	48	63	35
36	77	–	–	–	–	36
37–39	78	37	40–41	49–50	64–65	37–39
40–42	79	38–39	42–43	51–53	66	40–42
>42	80–91	40–49	44–48	54–66	67–72	>42