THE EXTENT OF DELAY OF LANGUAGE, MOTOR AND COGNITIVE DEVELOPMENT IN HIV POSITIVE INFANTS

Nicole Baillieu

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ABSTRACT

In South Africa, a total number of 5.7 – 6.2 million individuals had acquired HIV infection by 2004 (Department of Health, 2004). It is estimated that 3.3 million females, 2.8 million males, and 104 963 babies had been infected with HIV in South Africa by 2004 (Department of Health, 2004). It has been found that HIV-positive children have significantly greater neurological dysfunction in eight domains (activity, language, cranial nerve, fine motor, gross motor, cerebellar, sensory and primitive reflexes) than their HIV negative counterparts (Belman et al, 1996). There has been very little research conducted in Africa regarding the extent of delay of language, motor, and cognitive development in HIV positive infants.

The main aim of this study is to determine the extent of delay in acquisition of language, cognitive and motor skills of HIV positive children

The Bayley Scales of Infant Development II (BSID II) were used to determine performance in each section of the child's age group. These results were transferred to the facet scoring section, which analyse in greater detail, with respect to cognitive, language and motor development. Baseline BSID II assessments of HIV infected children currently enrolled in a longitudinal study of neurodevelopmental delay were analysed to determine which facets of development are most delayed. The Mental and Psychomotor Developmental Indices (MDI and PDI) of the BSID II were used to determine the extent of mental and motor delays in this sample.

Mean cognitive development was 7.63 months delayed, which was statistically significant ($p<0.01$) and 97.5% of the sample were functioning below the expected cognitive age. Mean motor development was 9.65 months delayed ($p<0.01$), and 97.5% of the sample were functioning below expected motor age. Gross motor skills were more affected than fine motor skills, and 85% of the sample demonstrated gross motor delays on descriptive analysis. Language was descriptively analysed, revealing language delays in 82.5% of the sample.

The infants in this study demonstrated significant mental and motor delays, as well as delays in language. It is postulated that motor delays may be attributed to decreased

strength, as the most adversely affected skill in this sample was gross motor development. The cognitive delays noted may be due to disease progression and structural damage to the brain, as well as socio-economic factors. The language delays noted could be due to neurological impairment, cognitive delay or environmental deprivation.

Children with HIV have significant delays in mental and motor development, and language is delayed in most children with HIV. The results of this study are similar to findings in other parts of the world, which indicates a global trend in HIV and neurodevelopmental delay. The results of this study are important, particularly for those involved in motor and language rehabilitation, as an awareness of potential problems in these infants is needed in order to provide them with the best management and care possible.

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DECLARATION

I declare that this research report is my own unaided work, except to the extent indicated in the reference citation and 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.

Nicole Baillieu

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LIST OF ABBREVIATIONS

AIDS	-	Acquired Immune Deficiency Syndrome
BSID	-	Bayley Scales of Infant Development
CNS	-	Central Nervous System
CPG	-	Central Pattern Generators
CS	-	Corticospinal
CSF	-	Cerebrospinal Fluid
GH	-	Growth Hormone
HIV	-	Human Immunodeficiency Virus
MDI	-	Mental Developmental Index
NMDA	-	N-Methyl-D-Aspartate
PDI	-	Psychomotor Developmental Index
PE	-	Progressive Encephalopathy
UNAIDS	-	Joint United Nations Programme for HIV/AIDS

OPERATIONAL DEFINITIONS:

HIV-1:

There are two major types of HIV: HIV-1 and HIV-2. Although similar to HIV-1, HIV-2 has a different sequence of nucleotides in its genome. Studies suggest that both HIV-1 and HIV-2 evolved from Simian Immunodeficiency virus (SIV), but from different simian species. HIV-1 diverged from chimpanzee SIV and HIV-2 from sooty mangabey SIV. HIV-2 is less transmissible than HIV-1 both vertically and between partners, and progression to end-stage AIDS is slower. HIV-2 is more commonly found in countries in West Africa (Pratt, 2003)

Facet Scores:

The facet scores were developed to provide information about the infant's performance in four areas of development: Cognitive, Language, Motor and Social. Items from the Mental and Motor Scales of the BSID have been assigned to the facet scores according to area of development. Item difficulty is regressed on age to assign items to developmental ages within each facet (Black and Matula, 2000). The social facet has very few items, and therefore has not been included in this research.

Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI):

The MDI and PDI are the most reliable ad valid scores in the BSID-II. These index scores are a normalized distribution of the standardization sample's raw scores converted to a scale with a mean of 100 and a standard deviation of 15. The index scores range from 50 – 150 (Black and Matula, 2000).

TABLE OF CONTENTS

LIST OF FIGURES

Chapter 1: INTRODUCTION

Globally it was estimated that in 2004, there were 39.4 million people worldwide living with Human Immunodeficiency Virus (HIV). Of these people, 17.6 million were women, and 2.2 million were children. Almost 12 % (4.9 million) were newly infected in 2004 (UNAIDS Update, 2004). In South Africa, a total number of 5.7 – 6.2 million individuals had acquired HIV infection by 2004 (Department of Health, 2004). It is estimated that 3.3 million females, 2.8 million males, and 104 963 babies had been infected with HIV in South Africa by 2004 (Department of Health, 2004). The HIV epidemic amongst children is closely linked to that amongst women, since the majority of paediatric infections are the result of vertical transmission from mother to child (Thorne and Newell, 2000).

Twenty years have elapsed since the original description of the assault of HIV on the central nervous system (Epstein et al, 1985). The nervous system is among the most frequent and serious targets of HIV (Simpson et al, 1996). Involvement of the nervous system in HIV-infected patients can come about as a result of direct HIV action, opportunistic infection caused by the immunodeficiency, or both (Fragoso et al, 1999). The pathogenesis of brain injury in HIV-1 infected patients remains incompletely understood, and is confounded by factors such as timing of infection, variable treatments, and lack of access to brain tissue for evaluation. (Fuller et al, 2004).

The most frequent manifestations of HIV-associated progressive encephalopathy are: cognitive impairment, developmental delays, corticospinal tract lesions, acquired microcephaly, movement disorders, and ataxia. Progressive motor dysfunction is common, and often results in a loss of milestones (Belman, 1992). It has been found that HIV-positive children have significantly greater neurological dysfunction in eight domains (activity, language, cranial nerve, fine motor, gross motor, cerebellar, sensory and primitive reflexes) than their HIV negative counterparts (Belman et al, 1996). Chase et al (1995) and Pearson et al (2000) found that a lower CD4 count, and elevated viral RNA load were associated with increased severity of disability, and that slower attainment in milestones in both motor and mental development is associated

with vertically transmitted HIV infection in infants and children younger than 30 months.

Significant delays in mental and motor development of HIV-infected infants have been found over the first two years of life (Gay et al, 1995; Smith et al, 2000). Because neural development does not cease after 2 years of age, further delays can be expected to evolve over time. In particular, myelination of the frontal and parietal regions of the brain continues throughout childhood and even into early adulthood. These regions are responsible for higher cortical functions, and destruction of the myelination processes of these areas by HIV will cause significant delays in higher functioning (Gay et al, 1995).

The neuropathogenesis of language problems in HIV is unknown (Wolters et al, 1995). Children with HIV have language problems, with expressive language function significantly more affected than receptive language; damage to the basal ganglia may be associated with language dysfunction, particularly in the expressive forms. Verbal expression is highly correlated to motor function, thus motor deficits, including those in muscle coordination and motor programming may affect oral-motor skills and contribute to feeding problems, articulation errors and speech difficulties (Wolters et al, 1997).

The Bayley Scales of Infant Development (BSID) measure the mental and motor development, and test behaviour of children from 1 – 42 months of age. The scales were first published in 1969, with the age range for assessment being 2 – 30 months. The 2nd edition was published in 1993, when the age range was extended down to 1 month, and up to 42 months of age. Infant's mental and motor development can be placed on a bell curve according to the raw scores obtained, and development may be classified as significantly delayed (raw score <70), mildly delayed (70 – 85), within normal limits (85 – 115), or accelerated development (115>). One of the primary uses of the Bayley Scales is to examine development of infants who are suspected to be delayed (Black and Matula, 2000). The Bayley Scales have been found to be sensitive to developmental changes in the first two years of life of infants who are medically fragile (Niccols et al, 2002), and these findings support the clinical validity of the scale, which can be applied to those with HIV.

There has been very little research conducted in Africa regarding the extent of delay of language, motor and cognitive development in HIV positive infants. Overall development of HIV infected infants has been found to be delayed, but there is a need for the assessment of the above-mentioned skills to determine any emerging trends, to facilitate a better understanding of where the biggest developmental problems lie. Government policy does not include allied health professionals in their staffing requirements for HIV units, and patient care (Department of Health, 2003). This could be due to a lack of awareness on the subject, and therefore this study could facilitate better awareness of the need for this service. Treatment regimens could then be formulated to target these areas specifically, in order to prevent delay and further deterioration.

The Aims and Objectives of this study were:

GENERAL AIM OF THE STUDY:

The main aim of this study was to determine the extent of delay in acquisition of language, cognitive, and motor skills of HIV positive children.

STUDY OBJECTIVES:

i) To assess the development of language, cognitive, and motor skills in HIV positive infants.
ii) To determine the emerging trends in neurodevelopmental delay in HIV infected children in South Africa.
iii) To determine the skill that is most adversely affected by HIV infection.
iv) To attempt to determine the ages at which developmental problems begin to manifest.

Chapter 2: LITERATURE REVIEW

Knowledge of the development and function of the normal central nervous system is important in gaining an understanding of its vulnerability in infants, and therefore how it can be affected by HIV infection. This literature review serves to discuss normal development of the central nervous system, and the major components used to assess its integrity, namely cognitive, motor and language function. This will be discussed in relation to HIV, its effect on the developing nervous system, and therefore the outcomes on cognitive, language and motor development. The role that socioeconomic status plays in development will also be discussed. The literature was obtained through comprehensive searches on major data bases (Pubmed, Medline, MD Consult). Keywords used in the searches were: HIV, CNS, Encephalopathy, Normal Development, Vertically Transmitted HIV, Developmental Psychology, Brain Development.

2.1 Vertically Transmitted HIV

More than 95% of all people living with HIV infection live in the developing world, mostly in sub-Saharan Africa (Thorne and Newell, 2000). The HIV epidemic amongst children is closely linked to that amongst women, since the majority of paediatric infections are the result of vertical transmission from mother to child (Thorne and Newell, 2000). Vertically transmitted HIV occurs in an immature and developing organism by transplacental or intrapartum transmission from mother to child (Belman, 1992; Rausch and Stover, 2001). Rates of vertical transmission, in the absence of interventions range from 25-40% in Africa (European Collaborative Study, 1996). Maternal-, obstetric- and infant-related factors have been associated with the risk of vertical transmission, with the most important maternal factor being viral load (European Collaborative Study, 1996).

Obstetric risk factors associated with an increased risk of mother-to-child transmission include vaginal delivery, ascending infection after prolonged rupture of membranes, chorioamnionitis, materno-foetal micro-transfusions during uterine contractions and absorption of the virus through the infant's

digestive tract (Newell, 1998), as well as invasive obstetric procedures and co-infection with another sexually transmitted infection (Ryder et al, 1989; Landesman et al, 1996; Tovo et al, 1996; Mandelbrot et al, 1998; European Collaborative Study 1999; The European Mode of Delivery Collaboration, 1999; Van Dyke et al, 1999). Fifteen – twenty percent of postnatal transmissions may occur via breastmilk (Van de Perre et al, 1991; Dunn et al, 1992; Luzuriaga and Sullivan, 2002).

The onset of perinatally acquired HIV infection is early with most infected infants showing signs of disease by six months of age. By one year, children are symptomatic with frequent occurrence of neurological abnormalities (Bobat et al, 1998).

2.2 Development of the Central Nervous System

The brain appears as early as the third week after conception and develops rapidly, so that by the end of the seventh month of pregnancy, all the neurons of the adult brain are basically formed and in place (Nowakowski, 1987).

Postnatal cortical development is divided into 2 phases:

Phase 1: birth to one year decline in neuronal density, increases in synaptic density, number of synapses per neuron, dendritic growth and total cerebral volume.

Phase 2: one year to adolescence slow decline in synaptic and neuronal density, increases in dendritic growth and decrease of synaptic density along dendrites (Huttenlocher, 1979).

There is a period of rapid synapse formation that begins before birth, rapid growth, especially in the two to four month age period, and by six months of age, the infant's brain has more synapses than an adult brain (Rakic et al, 1986; Huttenlocher, 1990). Peaks in quantity of synapses occur during the first year of life throughout the cortex due to the interaction between innate genetic programmes and environmental stimulation via the senses (Catherwood, 1999; Stiles, 2000).

The initial overproduction of synapses in the cortex may be related to the functional property of the immature brain to allow recovery and adaptation after focal injury of malformation (Huttenlocher 1984). It may also be the mechanism by which the brain is made ready to receive specific input from the environment. There are developmental increases of synapses in the postnatal period, and therefore this is important for the onset of cognitive function (Goldman-Rakic, 1987).

Pruning (loss of synapses in the absence of cell death) refers to environmentally regulated changes in the density of synapses per unit of dendritic length, and not the loss of the whole neuron. Pruning follows a period of rapid synaptogenesis during infancy and plateau in childhood. It is likely that only inappropriate synapses and their branches disappear as a result of experience or learning (Catherwood, 1999; Stiles, 2000; Webb and Monk, 2001), and only the synapses which are stabilised or consolidated through usage will be maintained (Changeux and Dehaene, 1989; Stiles, 2000).

During the first postnatal year, growth of dendritic trees and spines are seen in all six layers of the cortex, although they are still immature. Peak production of pyramidal neuron dendrites reaches a maximum during the second year of life. In the prefrontal cortex dendrites of pyramidal neurons undergo a rapid growth phase until about one year of age, with increasing branching until early adulthood (Koenderick et al, 1995). The formation of appropriate axonal projections may be disrupted in a number of ways, for example in encephalopathy (Webb and Monk, 2001).

White matter volume increases throughout childhood and well into adulthood (Reiss et al, 1996; Huppi et al, 1998), with increase in the dorsal, frontal and parietal regions through adolescence (Sowell et al, 1999). The prefrontal cortex appears to be one of the last brain regions to mature, particularly the dorsolateral prefrontal cortex. Cognitive processes that have been attributed to the prefrontal cortex include working memory, response inhibition and attention allocation (Diamond et al, 1988). Memory, inhibition, and attention are often treated as three distinct psychological constructs. Aspects of these

cognitive processes may be part of a single construct or common underlying circuitry (Diamond et al, 1998).

Evidence of prolonged development and organisation of the prefrontal cortex throughout childhood and adolescence may suggest a parallel between brain development and cognitive development (Chugani, 1987; Diamond et al, 1988, Rakic et al, 1994). Mature cortical organisation depends on relocation or retraction (or both) of cortico-cortical axons, the elimination of excessive synapses and eventually on naturally occurring cell death (Kostovic, 1990).

Learning favours some synapses over others, with only preferred synapses surviving. This process of competition amongst synapses begins at around one year of age for most brain areas and continues up until ten years of age (later for areas involved in abstract aspects of thought). This pattern accounts for the critical periods found for many aspects of early development (Catherwood, 1999). Infancy is a critical period of development, in which rapidly growing structures are more sensitive to damage (Huttenlocher 1984). The infant brain demonstrates a greater ability to recover from some types of injury than seen in later development. As long as there are spare synapses, the brain can take on new learning and recover from injury or damage, but when this extra allowance of synapses disappears, learning may be less readily established and recovery from brain injury is more difficult. Stimulation from the environment results in learning either by stabilising existing networks in the brain, or by forging new ones. These appear to be the fundamental mechanisms by which cognitive capacities develop (Catherwood, 1999).

Genetic information plays a role in the determination of brain development. The area-specific characteristics of the neocortex are partially based on properties laid down at the time of neurogenesis (O'Leary, 1989). Another indication that genetic information contributes significantly to brain development is the fact that 50% of tissue-specific human genes are expressed in the brain (Evans, 1998).

Development is an active, dynamic process that involves cognitive and affective processing of environmental events and experiences, and adds meaning to these experiences. This takes into account the emerging cognitive and language functions, behavioural repertoire, social and emotional processes, as well as changes occurring in anatomical structures and physiologic processes of the brain during development (Sroufe et al, 1984). It is characterised by a continual reorganisation of old and new skills, as individuals adapt to new experiences and environments (Sroufe et al, 1984).

Development throughout the lifespan is a function of interactions between the individual and changing environments in which the individual lives and interacts (Culbertson et al, 2003). These include the settings of family, friends, and school, and also the larger social contexts in which these settings are embedded (Bronfenbrenner, 1977).

Development proceeds as well-defined systems awaiting an external trigger, and neural development is an active, reciprocal process. The structure and organisation of the mature normal brain is the product of synaptogenesis and pruning. Functional plasticity refers to the dynamic and adaptive processes that underlie brain development and function, and the normally developing brain is both dynamic and plastic (Stiles, 2000). The capacity for plastic change is never completely lost, as plasticity is a central feature of brain development, and not a response to pathological insult. After early injury specific neural resources are lost, and there should be consequent impairment of the system. The magnitude and duration of initial impairment may depend on a range of factors, such as the timing of insult, extent and location of injury and specificity of the neural substrate for the function under consideration. Early damage to the neural substrate ensures that neural organisation will differ from that observed following normal development, but the processes by which that organisation is achieved need not be fundamentally different (Stiles, 2000).

2.3 Cognitive Development

In development, there is a progression away from dependence on immediate stimulus input towards dependence on rules that combine perceptual information with information from memory: this is known as cognitive development (Bower, 1982). Elementary cognitive processes are in place by early childhood; however, the capacity for abstract thought, planning, and cognitive flexibility develop throughout adolescence (Levin, 1991). Concurrent with cognitive development are important brain maturational events that continue into early adulthood, including synaptic pruning, elaboration of dendritic arborisation (Huttenlocher, 1990), and increased myelination (Paus et al, 1999). Cognitive development during late childhood and adolescence is subserved primarily by the late incorporation of the prefrontal cortex, either by its intrinsic late structural maturation (Sowell et al, 1999) or by the maturation of other neocortical regions (Chugani et al, 1998) that influence their functional integration with the prefrontal cortex (Thatcher, 1987).

Psychological perspectives on cognitive development have undergone a change over the last two decades, moving from a 'stage' account of the growth of children's abilities and competence (as developed by Piaget), and incorporating the factors of children's knowledge, interest or learning context in most accounts of early cognition (Catherwood, 1999).

Detecting categorical similarities among objects begins as early as three to four months (Behl-Chadha, 1996), indicating that Piagetian characterisations vastly underestimate infant cognitive competencies (Catherwood, 1999). By nine to fourteen months of age, infants are sensitive to a range of conceptual spatial contrasts, only some of which may be relevant to the language they eventually learn (Mc Donough et al, 2003) and they are able to perform tasks involving the interaction of memory, spatial understanding, object identity and object permanence (Moore and Meltzoff, 2004). Children with focal brain lesions may learn to perform these tasks, although the processes they use differ from the normal population. These deficits in process provide evidence

of subtle, persistent spatial cognitive deficits, following early brain injury in children (Stiles, 2000).

A basic goal in studying cognitive development is to understand the origins of knowledge by assessing what infants know. Means-end behaviour, often defined as the ability to link action on one object (the means) to its effect on other objects (the end) is used from about seven months (Munakata et al 1997). Before that time infants learn various sensory-motor routines on how to uncover objects and obtain out-of reach objects by pulling, but have not developed the conceptual processes required to work out a complex goal path by thought alone. Exposing infants to varying environments has a significant impact on their development and rates of learning. In the first year of life, infants have the potential to develop means-end skills to solve problems by manipulation and exploration if given the opportunity, and are able to apply what they learn in one situation to other situations. Increased motor capacity could also have important ramifications for the development of means-end behaviours, other problem solving tasks, and overall cognitive development (Bojczk and Corbetta, 2004).

The rudiments of declarative memory are seen in infants as young as six months, (Collie et al, 1999) and by nine months, recall memory is robust (Carver et al, 2001). By ten or eleven months, infants can recall sequences after a delay of several months (Carver et al, 2001). Memory consolidation processes are essential to the development of an accessible conceptual system, which is the basis for language, hence the finding that thought comes before language (Mandler, 2004).

Mothers do not necessarily raise their children as they were raised; instead, they raise them (unconsciously) to adapt to the changed social conditions under which their children will function as adults, and therefore, children's representational skills do not necessarily replicate those of their parents. The patterns of cognitive development of a new generation change in response to a changing world, but always respecting constant patterns of basic cognitive development (Greenfield et al, 2003).

2.4 Language Development

Before language becomes well established, conceptual differentiation plays a larger role in word learning than word learning plays in conceptual differentiation (Booth and Waxman, 2002). When children start to acquire language, the conceptual representations they set up in their first year for objects, relations, properties and events provide a broad cognitive basis onto which they can map words from child-directed speech. By nine months of age, infants have developed a conceptual system rich enough to allow language to begin. This is shown by categorisation of objects above and beyond their perceptual appearance, problem-solving, long-term recall of events, and inductive inferences. This speech draws their attention to specific categories and properties of those categories, as well as to grammatical distinctions which are not yet represented (Clark, 2004). At the time when language takes off, concepts are often still less specific than many words in daily use, and the mismatch between concept and word accounts for the phenomenon of overextension of word meaning (Mandler, 2004).

Children learn their first words at about twelve months and by sixteen to eighteen months, are proficient. At twenty-one to thirty months, children should learn about two new words a day (Bloom et al, 1998). Early vocabularies include personal pronouns, proper names, prepositions, adjectives and many classes of nouns (Nelson et al, 1993). The second year of life heralds advances in expressive and receptive language abilities. At thirteen to seventeen months, infants use left and right hemispheres, and broadly distributed anterior and posterior regions when hearing comprehended and unknown words (Mills et al, 1997). In contrast, at twenty months these effects are limited to temporal and parietal regions of the left hemisphere (Mills et al, 1997). This might be linked to changes in lexical development that occur between thirteen and twenty months. Therefore language experience rather than age is a determining factor for increasing cerebral specialisation for language (Mills et al, 1997).

Word retrieval and the rapid recognition of words and utterances which are nearly automatic occur at about eighteen months to two-and-a-half years old

(time of brain re-organisation). The process of learning words, word order, and semantic cues of language reside in several areas of the brain, including the right and left parietotemporal and the frontal areas. As a word or phrase is learned and becomes part of the established language bank, the left temporal area becomes the site for this ongoing use of language, particularly for the essential elements of grammar (Mills et al, 1997).

Biology, as well as environment affects how language is learned, and the amount and variety of babbling and imitative speech production at nine to eighteen months is to some extent, a reflection of the amount of the mother's speech the child has experienced (Bishop, 2000). During the infancy-toddler period, subsequent growth in language competency is dependent on the amount and variety of responsive speech (Snow, 1972). The size of a two year-old's vocabulary is dependent on how much the mother speaks to her. Therefore the development of language is built on early interactions with caregivers and is augmented later by the presence of a rich, conversational environment (Bishop, 2000).

There is an association between motor and language impairment in school-aged children (Johnston et al, 1981; Bishop and Edmundson, 1987; Robinson, 1991; Powell and Bishop, 1992; Schwartz and Regan, 1996; Hill, 1998; Rintala et al, 1998; Hill, 2001), and children with language delays may have fine motor or gross motor delays (Bishop and Edmunson, 1987; Robinson, 1991; Schwartz and Regan, 1996). Given the motor complexity of speech, factors common to gross motor function and communication may be associated with language impairment (Webster et al, 2005). Therefore, a common pathogenesis may underlie both motor and language impairment (Webster et al, 2005).

The acquisition of language depends on different neural systems to those used by proficient language users. In the early stages of acquisition, language is affected by lesions to widely distributed brain regions; and by lesions to areas that do not affect adult language. The initial distribution of processing may provide options, which allow for the development of alternative patterns of

neural mediation for language (Stiles, 2000). Receptive language deficits are more common with right-sided lesions, and expressive deficits are seen in left-sided lesions (Stiles, 2000). Region-specific effects on language development have been resolved by five to six years of age, presumably due to the emergence of alternative forms of brain organisation for language (Stiles, 2000).

2.5 Motor Development

Variation is crucial for normal development, and developmental variation is not random, but determined by genetic evolution. Motor development is characterised by two phases of variation: the phases of primary (not geared to external conditions) and secondary variability (in which motor performance can be adapted to specific situations) (Hadders-Algra, 2000a). In both forms of variability, selection on the basis of afferent information plays a significant role.

Motor development starts during early foetal life with the phase of primary variability, which continues during infancy. Motility during early development is characterised by profuse variation, such as variation in movement trajectories, and in temporal and quantitative aspects of motility (Vles et al 1989). These variations in motor activity are not neatly tuned to environmental conditions, but the variations themselves constitute a fundamental developmental phenomenon (Hadders-Algra, 2002). Abnormal motor development due to a lesion of the brain at an early age is characterised by a limited repertoire of motor strategies and difficulties in adaptation of motor behaviour to task-specific conditions (Hadders-Algra, 2002).

Motor behaviour is one of the best indicators of well being in the first year of life (Santos et al, 2001). Knowledge of the organisation of motor control is a pre-requisite for the understanding of motor development. Motility is regarded as the net result of the activity of complex spinal or brainstem machineries, which are modulated by segmental afferent information and controlled by supraspinal networks (Grillner et al, 1995). Motor control of rhythmical movements like locomotion, respiration, sucking and mastication is based on

Central Pattern Generators (CPGs) (Calancie et al 1994; Dietz et al 1994). These are neuronal networks which can generate complex basic activation patterns of the muscles without any sensory signals, yet, the sensory information of the movement is important in adapting the movement to the environment. The activity of the networks which are usually located in the spinal cord or brain stem, is controlled from supraspinal areas via descending motor pathways (Grillner et al, 1995). The supraspinal activity itself is also organised in large-scale networks, in which cortical areas are functionally connected through direct recursive interaction or through intermediary cortical or subcortical (striatal, cerebellar) structures (Hikosaka et al, 1999). The supraspinal motor networks are the circuitries which expanded in particular during phylogeny, and which determine human motor ontogeny to a large extent (Hikosaka et al, 1999).

A lesion of the brain at an early age results in (a) a loss or a reduction of neuronal repertoires and (b) impaired selection (Hadders-Algra, 2000b). Large lesions of the brain induce a complete loss of primary neuronal repertoires resulting in a failure to develop specific functions. Less extensive lesions result in a reduction of the primary neuronal repertoires and a reduced variation in motor behaviour. One of the major signs of infants with brain damage is motility with little variation (Hadders-Algra, 2002). The presence of motor impairment, with its effects on participation in extracurricular recreational activities, is likely to have an impact on social, emotional, as well as academic function (Webster et al, 2005).

Maturation of the corticospinal (CS) tract and hand motor function provides a visible paradigm for the maturation of the central nervous system (Thelen, 1995). Various aspects of hand motor performance such as independent finger movements, precision grip, or the speed of movement serve as paradigms of hand motor function development and demonstrate the importance of neuronal structures presumed to be involved, such as the CS tract (Watts et al, 1992).

The rate of motor development within normally developing infants is not stable; there may be periods of development when no new motor skills appear,

and times when a number of motor skills are mastered simultaneously (Thelen, 1995; Darrah et al, 1998). The rate of emergence of motor development within an individual infant may be variable, depending on internal and external factors such as the CNS and the environment (Darrah et al, 1998).

2.6 Socioeconomic Effects on Development

Developmental research has clearly established that both socioeconomic status and aspects of home environment account for a significant proportion of the variance in cognitive functioning of healthy and preterm children (Bradley et al, 1989; Brooks-Gunn et al, 1996). Aspects of a child's home environment and their associations with CNS factors may explain some of the variability in the cognitive functioning of children with HIV-1 infection. That is, despite CNS pathology, protective mechanisms may promote cognitive development in children with HIV-1 infection or, conversely, risk factors may result in greater vulnerability to cognitive dysfunction (Coscia et al, 2001). As the child matures the effects of poverty begin to snowball and there may be a decline in mental, motor and social/emotional development. Higher family income is associated with a more cognitively stimulating home environment, less maternal emotional stress and more positive parenting practices, which in turn are associated with higher cognitive outcomes (Linver and Brooks-Gunn, 2002).

In the formative years of development, malnourishment affects all dimensions of health and development (Spurr, 1983). For children growing up in poverty, physical and mental development is intertwined. Measures such as weight, height, and head circumference are predictors of cognitive abilities, whilst morbidity is negatively associated with cognitive test scores (Bhargava, 1998).

2.7 HIV and the Central Nervous System (CNS)

HIV-1 associated CNS dysfunction may complicate the course of HIV-1 disease in infants and children with vertically acquired infection (Belman et al, 1985; Ho et al, 1985; Ultmann et al, 1985; Epstein et al, 1986; Sharer et al, 1986; Epstein et al, 1987; Belman et al, 1988). Twenty years have elapsed since the original description of the assault of HIV on the CNS (Epstein et al,

1985). The nervous system is among the most frequent and serious targets of HIV (Simpson et al, 1996). The incidence of CNS involvement is not known, although it is thought to occur in most HIV infected children (Fragoso et al, 1999), and its incidence in children is at least three times greater than in adults only for the first year, and is similar thereafter, as early encephalopathy may be related to the occurrence of pathological events during late foetal life (Tardieu et al, 2000; Rausch and Stover, 2001).

Neurological and developmental abnormalities are frequent complications of HIV infection in children, especially in younger perinatally affected children (Belman, 1992; Nozyce et al, 1994; Raskino et al, 1999). In children with vertically transmitted HIV, infection of the CNS may occur early in the disease process whilst the CNS is still immature. Although it is believed that CNS infection occurs early in the course of HIV, the stage of brain development when CNS infection occurs varies amongst children; therefore there are varying patterns of disease seen (Belman, 1990).

Involvement of the nervous system in HIV-infected patients can come about as a result of direct HIV action, opportunistic infection caused by the immunodeficiency, or both (Fragoso et al, 1999). In children, CNS effects usually result directly from HIV-1 infection and not from opportunistic infections (Belman, 1992). The pathogenesis of brain injury in HIV-1 infected patients remains incompletely understood and is confounded by factors such as timing of infection, variable treatments, and lack of access to brain tissue for evaluation (Fuller et al, 2004). Studies have shown that significantly more children under three years of age show evidence of CNS disease, compared to children who have survived to over six years of age (Blanche et al, 1990).

The CNS is a viral reservoir for HIV-1 (Kolson, 2002). The invasion of the CNS by HIV-1 occurs early after infection, and HIV has been found in the cerebrospinal fluid (CSF) at or near the time of seroconversion (Ho et al, 1985; Resnick et al, 1985; Goudsmit et al, 1986; Epstein et al, 1987; Davis et al, 1992; Spector et al, 1993), as well as in the aborted foetuses of HIV infected mothers as early as fifteen weeks of gestation (Lyman et al, 1990).

Once inside the CNS, virus replication occurs (Davis et al, 1992; Lipton et al, 1995). The neurodegenerative process is unleashed by HIV itself and once inside the CNS, HIV produces distinctive pathological changes (Masliah et al, 2000).

There is little evidence for direct invasion of the CNS by cell-free virus (Epstein and Gendelman, 1993; Brouwers et al, 1995). The primary immune cell targets of HIV infection within the CNS are microglia/macrophage cells derived from monocytes (Koenig et al, 1986; Wiley et al, 1986; Tardieu et al, 1992; Takahashi et al, 1996; Williams et al, 2001). In the periphery, HIV infects T Lymphocytes (T-cells) and monocytes through virus interaction with the CD4 receptor and co-receptors on the surface of these cells. HIV infection of T-cells results in cell lysis and death, yet HIV infection of monocytes, while productive, does not kill these cells. Actively infected monocytes in the blood traffic into the brain, whereupon they differentiate into a host of CNS cell types, most notably perivascular macrophages, perivascular microglia and resident microglia (Hickey and Williams, 1999). The transport of HIV into the CNS within infected monocytes is known as the 'Trojan Horse' hypothesis, so called for its stealth in invading the brain (Peluso et al, 1985). Once inside the brain, HIV particles and proteins can be localised within monocyte derived cells (Gabudza et al, 1986; Wiley et al, 1986).

Primary HIV infection of the CNS results in neural tissue damage (Navia et al, 1986; Sharer et al, 1986; Wiley et al, 1986; Davis et al, 1992; Brouwers et al, 1995) and neuron dysfunction and death are the indirect consequences of HIV infection of microglia and macrophages (Pulliam et al, 1991; Epstein and Gendelman, 1993). These infected cells secrete a battery of proinflammatory cytokines and other soluble factors including HIV proteins, which, over a sustained period and in high concentrations, are toxic to nearby neurons. Pro-inflammatory cytokines, neurotoxic metabolites and viral gene products, which may cause damage to cells, are expressed in the brain parenchyma shortly after infection and throughout the course of infection. Therefore neuronal cell damage may begin long before neurological symptoms appear (Kolson, 2002). Infected or activated T-lymphocytes trafficking into the CNS

may also contribute to the cytotoxic cascade (Pulliam et al, 1991). HIV-1 infection of brain macrophages may limit the proliferation of nearby astrocytes (Tardieu et al, 1992). While HIV to a limited extent can infect astroctyes and endothelial cells (the cell types that form the blood brain barrier), HIV does not productively infect neurons (Wiley et al, 1986; Takahashi et al, 1996). Neurons and astrocytes can be destroyed by HIV-1 infected monocytic cells after adhesion of these cells to their membranes (Tardieu et al, 1992).

The pathological hallmarks of HIV include the multi-nucleated giant cell, which is formed by fusion of infected cells of monocyte lineage (Navia et al, 1986; Price et al, 1988). Other pathological features of CNS infection include perivascular infiltration of immune cells, white matter pallor, reactive astrocytosis (proliferation of astrocytes), microglial nodules, inflammation of the choroid plexus and various degrees of neuronal loss and damage to dendrites (Belman et al, 1988; Price et al, 1988; Wiley et al, 1991; Masliah et al, 1997).

In summary, the neuropathological findings in HIV-1 infected brain tissue can be explained by the following process: The HIV-infected monocyte (macrophage/microglia) is the initiator of the pathological process (Sharer et al, 1986). There is cell-to cell communication between the HIV-infected monocytes and astrocytes, which establish an interaction that amplifies production of glial proliferatory and neurotoxic factors (Wiley et al, 1986; Brouwers et al, 1995).

A final common pathway in neuronal damage is due to excitatory amino acids, mediated through activation of the NMDA receptor. Implicating the NMDA receptor as the final common pathway for neuronal dysfunction, and ultimate loss, offers an explanation for the selection of a subpopulation of neurons responsible for the ‘subcortical’ dementia as well as for the reversibility of neurological signs seen early in the course of the disease in adults and children (Epstein and Gendelman, 1993). The changes are localised to sub-cortical structures, including deep white matter and basal ganglia, but may be found to some extent in the cortex (Belman et al, 1988; Rausch and Stover, 2001). A

striking finding in the brains of infected children is the presence of mineralisations consisting of calcium salts and iron in the basal ganglia and cerebral white matter (Belman et al, 1988; Rausch and Stover, 2001). Vascular inflammation is found frequently in children, and is characterised by lesions consisting of cuffing and infiltration of lymphocytes, monocytes and multinucleated giant cells into the walls of the small and medium sized parenchymal vessels (Rausch and Stover, 2001).

2.8 HIV Encephalopathy and Neurodevelopmental delay

HIV Encephalopathy and Neurodevelopmental delay in HIV will be discussed together, as there is no distinct difference in the literature reviewed, and the terms are used interchangeably in many instances.

The majority of HIV-infected children have developmental delay and deficits in cognitive functions, language and motor skills, impaired brain growth and loss of developmental milestones, as well as cerebellar, sensory and primitive reflex dysfunction (Belman et al, 1985; Ultmann et al, 1985; Epstein et al, 1986; Belman et al, 1988; Belman, 1992; Nozyce et al, 1994; Chase et al, 1995; Belman et al, 1996; Pollack et al, 1996; Drotar et al, 1997; Wolters et al, 1997; Fragoso et al, 1999; Pearson et al, 2000; Blanchette et al, 2001; Udgikar et al, 2003).

Neurological and developmental signs are often markers of HIV-1 disease in infants which may precede other signs of disease progression (Belman, 1992, Bisiacchi et al, 2000). HIV-1 infection of the developing CNS of infants and children is characterised by either a progressive or static loss of previously acquired developmental milestones with cognitive, behavioural and motor manifestations (Belman et al, 1985; Epstein et al, 1986; Sharer et al, 1986; Belman et al, 1988; Udgikar et al, 2003) Significant delays in mental and motor development of HIV-infected infants have been found over the first two years of life (Gay et al, 1995; Chase et al, 2000; Smith et al, 2000; Blanchette et al, 2001). Such impairments are likely to become more severe as the children are expected to reach more complex and integrative milestones (Belman, 1992; Blanchette et al, 2001). Neural development does not cease

after two years of age, and therefore further delays can be expected to evolve over time, which may be important indicators of disease progression (Gay et al, 1995; Chase et al, 2000; Blanchette et al, 2001).

A variety of CNS abnormalities are associated with HIV infection. These include cortical atrophy, calcification of the basal ganglia and frontal white matter, ventricular enlargement, and white matter low attenuation (DeCarli et al, 1993; Wolters et al, 1995). The most important finding from a developmental perspective is that of myelinopathy. During infancy the brain is still experiencing a period of rapid myelination, which coincides with the attainment of significant motor, cognitive, and behavioural milestones. Any disruption in this process can be expected to produce developmental delays that may become more significant over time. In particular, myelination of the frontal and parietal regions of the brain continues throughout childhood and even into early adulthood. These regions are responsible for higher cortical functions, such as language, sequence and the integration of multiple stimuli, and destruction of the myelination processes of these areas by HIV will cause significant delays in higher functioning (Gay et al, 1995; Blanchette et al, 2001). The range of developmental deficits associated with subcortical damage is not yet well defined, but language deficits have been reported (Aram et al 1983; Belman, 1992). Since many of the more advanced developmental skills do not develop until after two years of age, delays can be expected in areas such as visual–motor processing, verbal memory, processing speed, and sequential processing.

Development of encephalopathy is one of the most severe complications of HIV, but its frequency at different ages has long been disputed (Tardieu et al, 1992). HIV encephalopathy can occur very early in the course of HIV infection, and 88.1% of children who develop it do so within first two years of life (Newell et al, 1998). This is more common in HIV-infected children who present in early infancy and have rapid progression, as they may have been infected in utero during the last weeks of pregnancy, which is the period of fastest brain growth (Newell et al, 1998).

A current definition of encephalopathy in paediatric HIV disease is: “The failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scales or neurophysiological tests” (Brady et al, 1995).

Several patterns of encephalopathy are recognised. a) A subacute progressive course (the most severe), b) plateau (followed by deterioration or improvement) or c) static/stable course (Belman, 1994).

Progressive encephalopathy (PE) appears as early as 6 months after birth and is one of the first manifestations of HIV disease in children (Schmitt et al, 1991; Working group of the American Academy of Neurology AIDS Task Force, 1991). PE consists of a well-characterised triad of symptoms: 1) impaired brain growth 2) progressive motor dysfunction 3) loss, plateau or inadequate rate of acquisition of neurodevelopmental milestones (Belman et al, 1988). There is a tremendous range in the manifestations of PE, much of which is due to timing of entry into the CNS in relation to brain development, viral virulence and host factors (Belman et al, 1988).

If the encephalopathic course is static, poor maternal nutrition, disturbed home environment, repeated periods of illness and hospital admissions all contribute to developmental delay and motor deficits (Ultmann et al, 1985). Since the most rapid brain growth occurs in the first four years of life, children infected at an older age are less likely to suffer the major neurocognitive deficits seen among HIV infected infants and young children. In general, there is strong evidence of neuropsychological deficits associated with symptomatic paediatric HIV disease (Fowler, 1994).

An initial pathophysiological hypothesis is that early encephalopathy may be the consequence of pre-natal HIV-1 infection of the brain, inducing a reduction in brain cell proliferation during late pregnancy, leading to decreases in intrauterine brain growth and parenchymal atrophy (Tornatore et al, 1994; Tardieu et al, 2000). Neurodevelopmental impairment may be a marker of overall host susceptibility (Ellis et al, 1997), as some infants may be more

susceptible to HIV-related CNS disease, resulting in faster progression and greater mortality rate. Infected monocytes with the ability to cross the blood-brain-barrier and adhere to neural cells may play a major role in the induction of HIV-1 related encephalopathy (Tardieu et al, 1992). An accumulation of the HIV-1 *nef* protein has been described in astrocytes from brains of children with early encephalopathy (Epstein and Gendelman, 1993), and the presence of viral protein in developing astrocytes may also limit their proliferation during late pregnancy.

A lower CD4 count and higher viral RNA load are associated with increased severity of disability, growth failure and slower attainment in milestones in infants and children with vertically transmitted HIV (Chase et al, 1995; Belman et al, 1996; Pollack et al, 1996; Pearson et al, 2000). Those children with AIDS defining illnesses in the first two years of life display very severe neurological and neurodevelopmental abnormalities (Nozyce et al, 1994; Belman et al, 1996; Chase et al, 2000; Pearson et al, 2000). The presence of hepatomegaly, splenomegaly, or lymphadenopathy in the first three months of life increase the likelihood of HIV encephalopathy and the risk of death 28-fold (Laufer et al, 2000).

2.9 Growth Delays and Neurodevelopment

There is an association between delays in growth and neurodevelopment, which are manifestations of perinatal HIV disease, particularly in children with symptomatic disease (Pollack et al, 1996). Infants with the most pronounced growth failure have the most marked cognitive and motor delay, which only become apparent later (Pollack et al, 1996). Growth delay seen in these children is directly related to HIV infection. The delays in linear growth and neurodevelopment occur at different times suggesting that they represent two separate effects of high HIV viral burden or load. When formally assessed, growth hormone (GH) levels in HIV infected children, even in those with growth failure, are usually normal (Laue et al, 1990; Lepage et al, 1991). Potential causes of altered growth in HIV-infected infants may be due to decreased peripheral sensitivity to GH, decreased levels of insulin-like growth factors (Matarazzo et al, 1994), or the release of cytokines secondary to HIV-1

infection which may then lead to an ineffective action of growth hormone (Pollack et al, 1996). Cytokines are especially attractive as mediators of decreased growth because of their rapid appearance during active HIV infection. IL-6 and MIP-1a have both been shown to be elevated during periods of rapid viral replication and also to have effects on bone activity (Cocchi et al, 1995; Fuller et al, 1995; Udagawa et al, 1995).

2.10 Indirect Effects of HIV Infection on Development

HIV infections may have an indirect effect on development in children. HIV infection may lead to a variety of problems which include gastrointestinal and nutritional manifestations (Winter & Miller, 1994). Gastrointestinal and nutrional manifestations are recognised as part of the clinical course of HIV. After deterioration of immune function from malnutrition or HIV, enteric pathogens may injure the intestinal mucosa causing malabsorption. Prolonged malabsorption leads to malnutrition that causes immunodeficiency, more rapid progression to AIDS, and increased infection by opportunistic pathogens (Winter & Miller, 1994). The most common reasons for hospital admissions in children with HIV are due to pneumonia and gastroenteritis (Meyers et al, 2000). Increased hospital admissions and length of hospital stay may lead to developmental delay in these children (Fiser et al, 2000; Cooper et al, 2004).

2.11 HIV and Cognitive Delay

HIV infected infants have cognitive impairment, CNS dysfunction and deficits in neuropsychological functioning, and often present with microcephally and mental retardation, with impairment in one or more functions (Belman et al, 1985; Ultmann et al, 1985; Epstein et al, 1986; Belman et al, 1988; Diamond et al, 1990; Belman, 1992; Fowler, 1994; Belman et al, 1996; Henry et al, 1996; Fragoso et al, 1999; Mazzoni et al, 2000). Only selective impairment of executive functions during the first stages of infection have been observed, followed by subsequent jeopardy of memory and visuopraxic functions in children with full-blown AIDS (Bisiacchi et al, 2000). This supports the idea that memory deficits are subsequent to attention deficits and not the result of memory impairments in themselves (Bisiacchi et al, 2000).

Deficits in visual scanning, academic achievement, cognitive flexibility and psychomotor speed have been found (Cohen et al, 1991), however, information processing abilities may be spared (Persaud et al, 1992; Tovo et al, 1996; Drotar et al, 1997). Cognitive developmental skills, for example, vocalisation, comprehension and puzzle performance are less powerfully affected showing effects at certain ages (Drotar et al, 1997).

Infected children with brain abnormalities perform worse than those without observable brain abnormalities on measures of cognitive and motor development. Common abnormalities are calcification of the basal ganglia, and the presence of intracerebral calcifications is associated with significantly greater delays in neurocognitive development (Brouwers et al, 1995). Further, it may be an indication that these children were infected in utero rather than during the intrapartum period (DeCarli et al, 1993; Brouwers et al, 1995).

2.12 HIV and Motor Delay

Motor function is compromised early in development in infants with HIV (Nozyce et al, 1994; Chase et al, 1995), and delays in motor development in HIV-infected children are seen as early as the first few months of life (Chase et al, 1995). Young children's motor development, coordination, muscle tone, reflexes and strength are most consistently and strongly affected by HIV infection, and may result in spastic quadraparesis (Chase et al, 1995; Drotar et al, 1997). Dystonia, ataxia, tremor and rigor indicate extrapyramidal and cerebellar involvement (Belman et al, 1988, Chase et al, 1995). Focal motor deficits including diparesis, and mild spastic diparesis and diplegia with progressive long tract signs are seen (Belman et al, 1985; Belman et al, 1988; Belman, 1992; Belman et al, 1996; Fragoso et al, 1999; Mazzoni et al, 2000).

Children with early motor delays are at risk for disease progression, although motor delays have less impact on developmental outcome than early cognitive and language delays (Pearson et al, 2000). Children infected with HIV have lower motor strength, which may be related to CD4 count (Blanchette et al, 2002). Gross motor skills are delayed in HIV positive children, which may be due to the fact that gross movements require muscle groups and some degree

of physical effort, whereas fine movements are associated with more precise outputs but lower force. Therefore gross motor performance deficits may be related to an overall loss of strength (Parks and Danoff, 1999).

2.13 HIV and Language Delay

The neuropathogenesis of language problems in HIV is unknown (Wolters et al, 1995). Language is a complex construct, comprised of many interrelated components, any of which are subject to dysfunction (Rapin and Allen, 1983). Speech and language acquisition are sensitive to a variety of neurodevelopmental insults, including global cognitive delay, central disorders of language function or auditory perception, central or bulbar disorders of motor function (oromotor apraxia, dysarthria), and hearing loss. Thus, language acquisition in young children is a good barometer of CNS integrity in general (Coplan et al, 1998).

Language and social function are affected later in life and to a lesser degree than gross motor function in HIV infected infants, and these delays are either a reflection of the chronicity of the disease or a direct expression of CNS involvement (Msellati et al, 1993; Bisiacchi et al, 2000). HIV CNS disease in children is associated with deficits in both receptive and expressive language, although expressive language skills are more severely impaired (Epstein et al, 1986; Pizzo et al, 1988; Papola et al, 1994; Tardieu et al, 1995; Wolters et al, 1995; 1997). The impairments progress from weakness in expressive language in non-encephalopathic children to severe impairments in both receptive and expressive language in encephalopathic children. Damage to the basal ganglia may be associated with language dysfunction, particularly in the expressive modalities (Brunner et al, 1982; Wallesch et al, 1983; Wolters et al, 1997).

Language impairments are most likely associated with direct effects of HIV related CNS disease rather than the influence of environmental factors. Verbal expression is highly correlated with motor function, and therefore motor deficits, including those in muscle coordination and motor programming may affect oral-motor skills and contribute to feeding problems, articulation errors and speech difficulties (Wolters et al, 1997).

2.14 Bayley Scales of Infant Development

The Bayley Scales of Infant Development (BSID) were first published in 1969, with the age range for assessment being 2 – 30 months. The 2nd edition (BSID II) was published in 1993, when the age range was extended down to 1 month, and up to 42 months of age. The goals of the revision of the BSID were to incorporate research-based items that demonstrate predictive validity, to update the stimulus materials, to conduct reliability and validity studies, to report data from clinical populations of children, and to ensure a standardised assessment of children's motor and mental performances (Black and Matula, 2000).

The BSID I and II provide overall standard scores for mental and motor development, although some attempts were made in the revision to provide more comprehensive coverage of all mandated areas of assessment (cognitive, language, social, self-help and motor). A revision of the norms on the BSID was needed, as there had been an upward drift of points on both the mental and motor scales, which may have indicated that the norms no longer reflected nutritional status, environmental conditions, and family relations of the time. Therefore an updated set of norms was needed, and as a result scores obtained on the BSID II are usually lower than those obtained for the same children on the BSID I (Black and Matula, 2000).

The percentage of language items has been increased in the BSID II, as language is a higher order cognitive process that plays a role in children's cognitive development. The detection of language delay can signal neurological impairment, oral-motor impairment, general cognitive delay or environmental deprivation (Black and Matula, 2000). One of the primary uses of the Bayley Scales is to examine development of infants in whom delays are suspected (Black and Matula, 2000). The Bayley Scales have been found to be sensitive to developmental changes in the first two years of life of infants who are medically fragile (Niccols et al, 2002). This supports the clinical validity of the Scales, which can be applied to those with HIV, and the BSID has been used in a number of studies which look at development in HIV positive infants (Nozyce et al, 1994; Chase et al, 1995; Belman et al, 1996; Chase et al, 2000).

Scores are obtained in three areas: Motor, Mental and Behavioural. The raw scores obtained in the motor and mental areas are converted to standard scores, which indicate the extent of the infant's development. These are the Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) scores, which have a mean of 100, and a standard deviation of 15, in keeping with most other assessments of cognitive performance (Black and Matula, 2000). The BSID II also contains Facet Scores (Appendix IV), which place items from the Mental and Motor Scales into four facets: Cognitive, Motor, Language and Social, and can be used for descriptive analysis of these skills. The item lists are found on pg 352 – 358 of the BSID II Manual (Bayley, 1993) (Appendix V), and the Facet Scores are found in the Mental Scale Record Form.

The BSID I was normed on a South African population, taken from both urban and rural areas, and was found to be suitable for use on South African infants (Richter and Griesel, 1988). The South African infants scored above the American infants up to 10 months of age on both the Mental and Motor Scales, and from 10 months, up to the middle of the second year, the groups obtained very similar raw scores (Appendix VI). The trend across the whole age range in this South African sample was for urban children to score higher than rural children on both the mental and motor scales, although this was not statistically significant across the age range (Richter and Griesel, 1988).

After examining the literature, it is clear that a need exists for more African studies to be performed, in order to look at the effects of HIV on neurodevelopment, specifically on motor, cognitive and language development. The BSID is the most widely used measure of early development (Black and Matula, 2000), and therefore this tool would be most suitable for use in such a study, allowing comparisons to be made to similar studies done in other parts of the world.

Chapter 3: METHODS

In this chapter, the methodology used in this research report will be presented. Demographic information will be presented first, followed by information on the assessment tool used. The data presented in this study is a secondary analysis of data collected for an ongoing longitudinal study namely: "A Longitudinal Study of Neurodevelopmental Delay in HIV Infected Children" conducted by Joanne Potterton.

3.1 Location

This study was conducted at the Harriet Shezi Children's HIV Clinic at Chris Hani Baragwanath Hospital, Gauteng, South Africa. Children who are suspected of being HIV positive, or who are already enrolled in the clinic, attend appointments with doctors and primary health care sisters. Patients attending this clinic are from similar socio-economic and cultural backgrounds.

3.2 Ethical Clearance

Prior to commencement of data collection, ethical clearance was obtained from the Committee for Research on Human Subjects of the University of the Witwatersrand (Clearance number: M03-05-68) (Appendix II)

3.3 Sample Selection

The data for 40 consecutive HIV Positive Infants between 18 and 30 months of age, who were not on antiretrovirals were analysed. Informed consent had been obtained from the caregivers prior to assessment (Appendix III)

3.3.1 Inclusion Criteria

- Children with vertically transmitted HIV
- 18 – 30 months of age
- Children with a primary caregiver
- Anitiretroviral naïve children

3.3.2 Exclusion Criteria

- Children with clinically apparent abnormalities
- Prematurity (<37 weeks)
- Children resident in institutions

3.4 The Study Population

The data from 40 HIV positive infants fitting the inclusion criteria, who had been assessed using the Bayley Scales of Infant Development II were analysed. The children came mainly from Soweto and surrounding areas, and thus had similar socio-economic and educational backgrounds. All children assessed were black, and most were brought to the clinic by their mothers or grandmothers.

3.5 Assessment tool

The Bayley Scales of Infant Development II (BSID II) was the assessment tool of choice, as one of its primary uses is to examine development of infants who are suspected to be delayed (Black and Matula, 2000). The BSID is sensitive to developmental changes in the first two years of life in infants who are medically fragile (Niccols et al, 2002). It has been validated for use on black South African infants (Richter and Griesel, 1988). The BSID II can be used to assess infants from birth to 42 months.

3.6 Procedure

Infants between the ages of 18 and 30 months attending the Harriet Shezi HIV clinic at Chris Hani Baragwanath Hospital were assessed in order to obtain the data analysed in this study. The infant's date of birth was obtained from the clinic folder, and suitability for recruitment was gauged from the birth history and family information. The infant and caregiver were approached and given a form, in a choice of Zulu, Sotho, or English, which explained the study and requested participation (Appendix III). Nursing staff and clinic counsellors were available for translation if required.

Once written consent had been obtained, the infant was seated at a child-sized table and chair in a separate area from the main waiting room to minimise

distractions and disruptions. The infant was first evaluated on the Mental Scale and then the Motor Scale. The infants were assessed by the same examiner in order to standardise the procedure. The test was started at the child's chronological age, and the examiner moved back to a younger age only if the child obtained less than 5 credits within the age subset.

The data collected from 40 consecutive HIV positive children were then analysed as follows: The raw score and developmental age were calculated for the Mental and Motor Scales using the table on pg. 72 – 73 of Black and Matula (2000) (Appendix VIII). The Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) were calculated from the raw scores on the Mental and Motor Scales. The Facet Scores (Appendix IV) were developed to provide information about the infant's performance in the language, cognitive, motor and social areas of development, and were used descriptively in this study, to obtain an indication of language, gross and fine motor function. Social development was not evaluated in this study due to the lack of items on the Facet Scores. Age categories were used to determine whether developmental problems begin to manifest at certain ages. The infants were divided into two groups: 18 – 24 months, and 25 – 30 months, and the age categories were compared in language, motor and cognitive function.

The infant's socio-economic and family background information was obtained from the caregiver using a short questionnaire, in a choice of English, Zulu or Sotho (Appendix VII). This was used to obtain the level of the caregiver's education, the number of people living in the household, and the monthly household income. This information was descriptively analysed.

3.7 Statistical Analysis

All the data collected were analysed by the Medical Research Council of South Africa. A sample size of 40 HIV positive children aged 18 – 30 months has at least 90% power to detect under-performance of 1 month when a standard deviation of 2 months is assumed. Descriptive analysis of language, fine motor, and gross motor function was performed using the facet scores of the BSID II. Cognitive and Motor developmental age of HIV-positive infants

were compared to age group norms using the T-test. A Fischer's Exact Test was used to compare age categories in cognitive, motor, and language function. The software was Intercooled Stata. A p-value of less than 0.05 was considered to indicate statistical significance in this research report.

The following factors may affect the generalisability of the study:
The inclusion criteria were quite specific, and the sample was homogenous (i.e. black infants from similar socioeconomic backgrounds), and therefore the results may not be generalisable to other populations. This was a single centre study undertaken in a specialised HIV unit in Soweto, Gauteng, and therefore the results may be difficult to reproduce in a setting other than an HIV unit, and cannot be generalised to multiple centres. The adequate sample size of 40 infants was arrived at through a power calculation, which may enhance the generalisability of the study.

Chapter 4: Results

In chapter 4, the results of this study will be presented. The data from 40 subjects were analysed.

4.1 Age

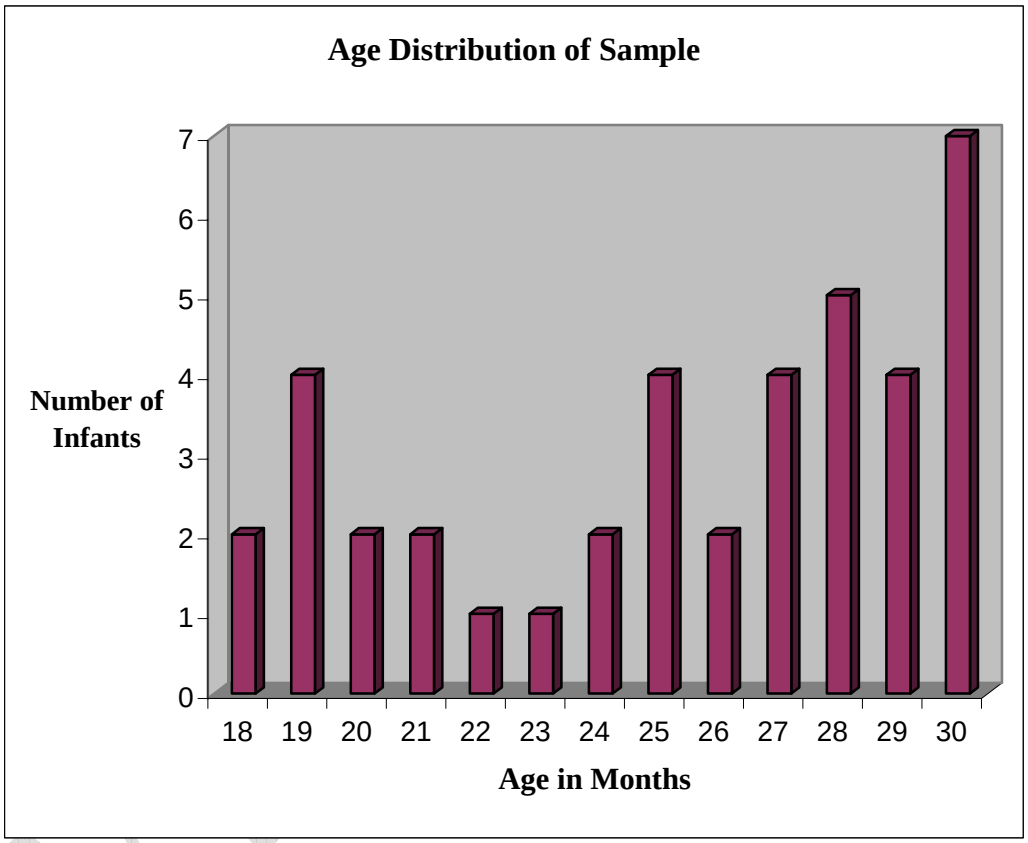

Figure 4.1: Age distribution of the sample

The age group of the sample fell between 18 and 30 months, with the mean age being 25 months.

4.2 Socioeconomic background

A demographic questionnaire was drawn up to obtain an idea of the infant's socioeconomic background (Appendix VII). The areas to be determined were: level of primary caregiver education, the number of people living in the house, and the monthly household income.

4.2.1 Level of Caregiver Education

The percentage of primary caregivers who had obtained grade 12 (matric) was only 22%. Eight percent had no education, and 13 % had not obtained an education higher than Grade 8 (Std 6).

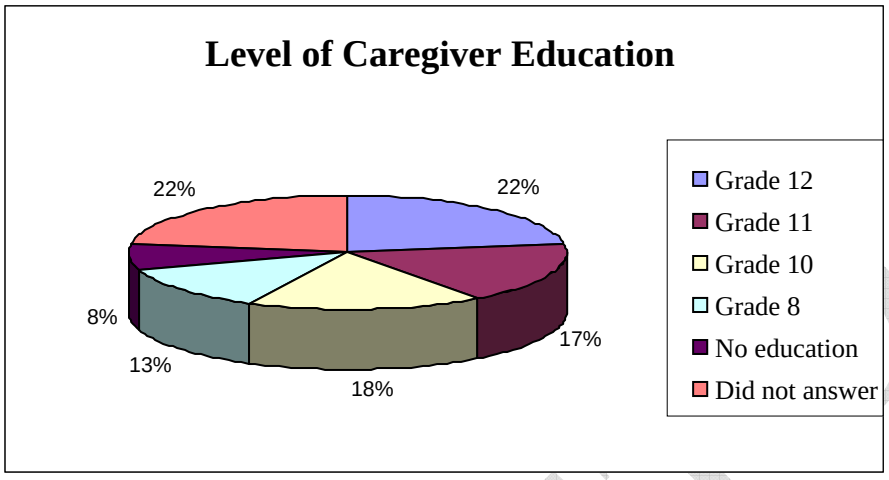

Figure 4.2: Level of Caregiver Education of the sample

4.2.2 Number of People in a Household

Ten percent of the sample had more than 10 people in a household, and the maximum number of people in one household in this sample was 16. Therefore, 48% of the sample live in households consisting of more than 5 people

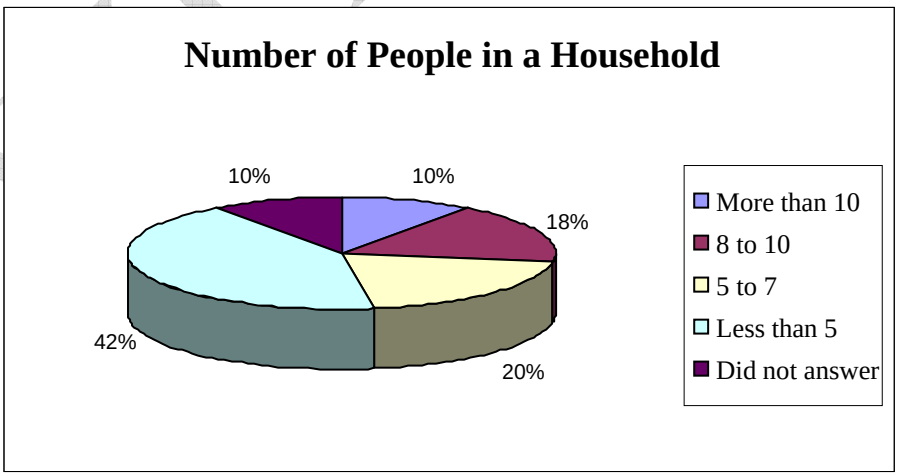

Figure 4.3: Number of people in a household

4.2.3 Monthly Household Income

As can be seen from Figure 4.4 below, only 3% have a monthly household income of more than R2000. Fifty-two percent of the sample have a monthly household income of less than R1000. When analysed together with the number of people per household, these results indicate that the socioeconomic status of the sample is very low.

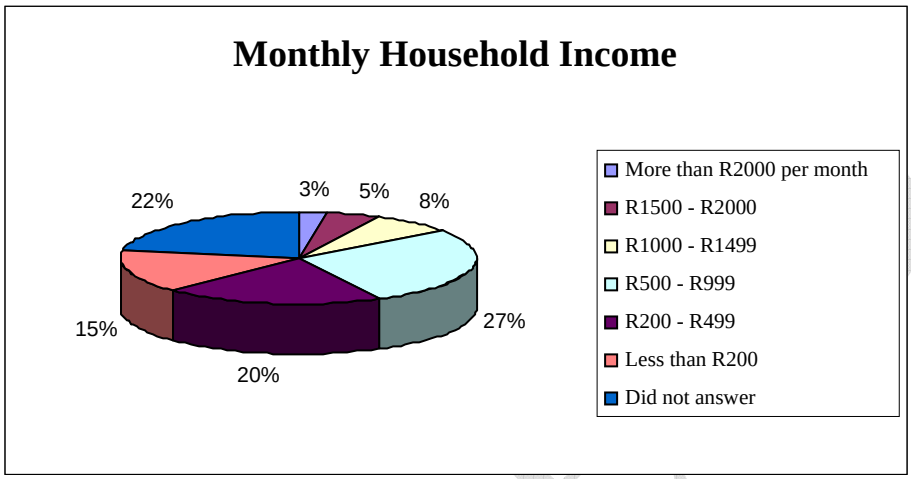

Figure 4.4: Monthly household income

4.3 Cognitive Development

The infant's cognitive developmental age was calculated from the infant's raw score obtained on the Mental Scale of the BSID II, using the table on pg 72 – 73 in Black and Matula (2000) (Appendix VIII). The cognitive developmental age was then used to calculate the infant's cognitive delay in relation to the chronological age. Mean chronological age was 25.33 months, and mean cognitive developmental age was 17.7 months, revealing that mean cognitive developmental age is 7.63 months lower than chronological age. A paired T-test was performed between the chronological age, and cognitive developmental age of all 40 infants, and the difference was statistically significant ($p<0.001$), indicating that cognitive developmental age is significantly lower than chronological age.

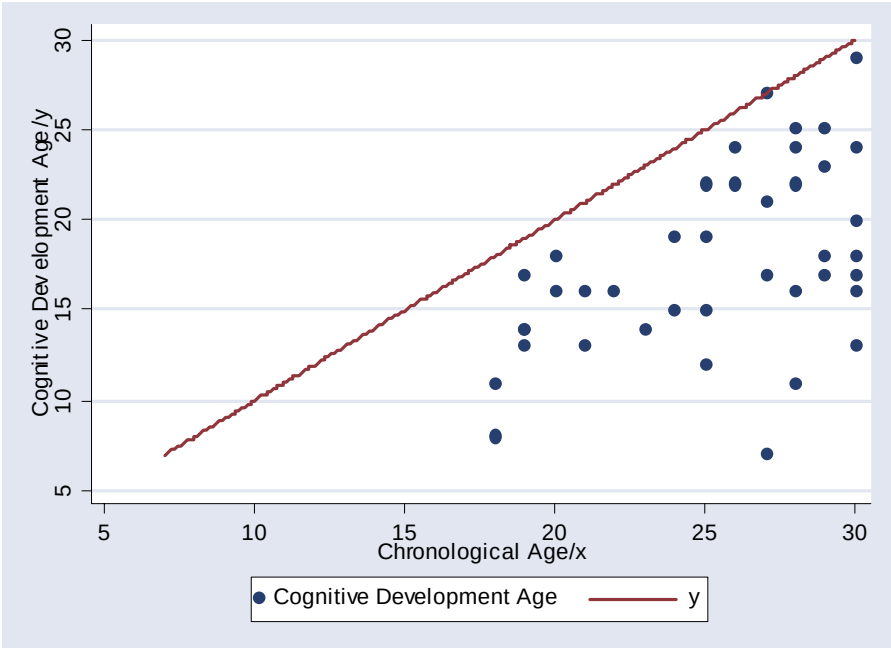

Figure 4.5: Cognitive Developmental age vs. chronological age

As can be seen on the above graph, the cognitive developmental age of almost all the infants in the sample lies below the chronological age. This indicates that 39 out of 40 (97.5%) infants are functioning below the expected cognitive age for their chronological age.

The infant's Mental Developmental Index (MDI) score was calculated from the raw score obtained by the infant on the mental scale of the BSID II. This is done by turning to Appendix A in the BSID II manual (Bayley, 1993), and using the Norm Table that corresponds to the infant's chronological age. In cases where the MDI fell below 50, the table on pg. 75 of Black and Matula, (2000) (Appendix IX) which contains extrapolated scores for an MDI of <50, was used to calculate the MDI. The MDI score can be used to place the child's development on a Bell Curve in terms of extent of delay as shown below.

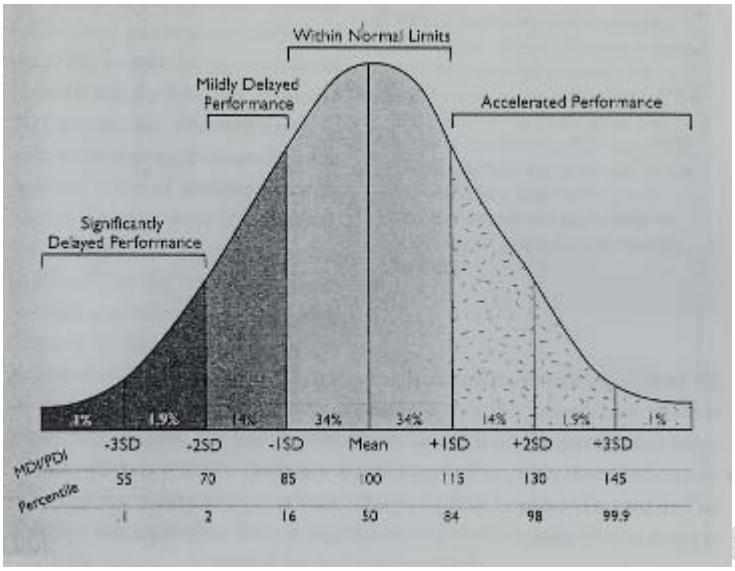

Figure 4.6: Normal Distribution of Mental and Motor Development (Black & Matula, 2000)

The results obtained are illustrated by the pie chart below:
4 children (10%) were developing within normal limits,
8 infants (20%) were mildly delayed and
28 infants (70%) were significantly delayed.

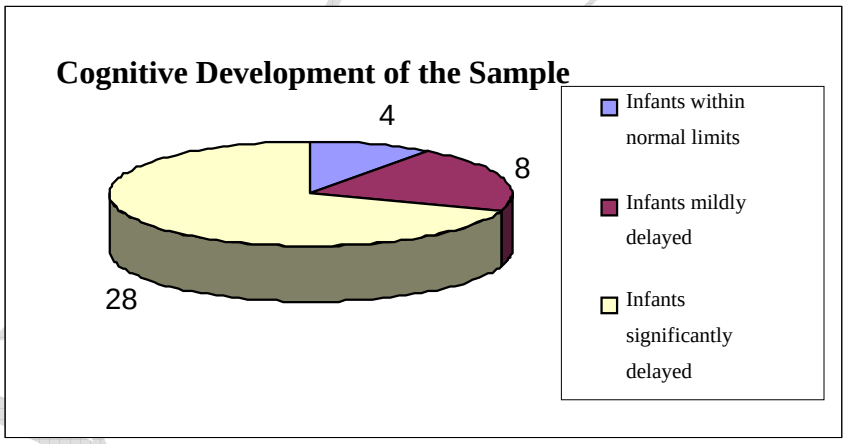

Figure 4.7: Breakdown of cognitive development of the sample

An attempt was made to analyse mental development in terms of age group, in order to determine the age at which developmental problems begin to manifest. The sample was divided into two age categories: 18 – 24 months and 25 – 30 months. It was not possible to analyse this within cognitive development, as the variation in mental developmental ages was too great to perform a Fischer's Exact Test.

4.4 Motor Development

Motor developmental age was calculated from the raw score obtained on the Motor Scale of the BSID II, using the table on pg 72-73 of Black and Matula (2000) (Appendix VIII). Mean chronological age was 25.33 months, and mean motor developmental age was 15.675 months, indicating that motor age is delayed by 9.65 months. The results of the paired T-test are statistically significant ($p<0.001$) indicating that motor developmental age is significantly lower than chronological age. Motor development is more delayed than cognitive development.

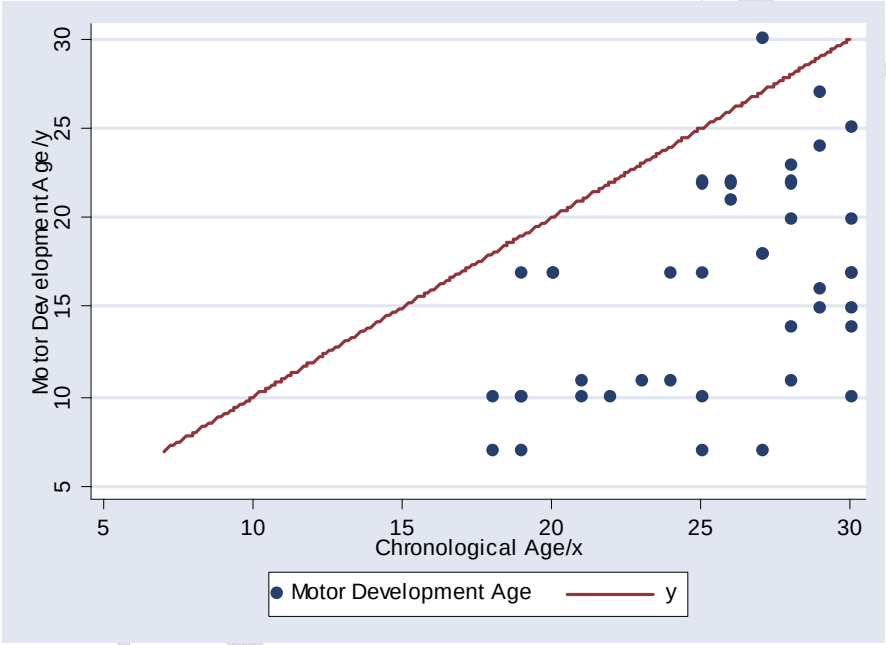

Figure 4.8: Motor developmental age vs. chronological age

The graph shows that all but one infant's motor developmental ages lie below chronological age. Therefore, 97.5% of the infants have motor developmental ages that are below chronological age.

The infant's Psychomotor Developmental Index (PDI) score was calculated from the raw score obtained by the infant on the motor scale of the BSID II. This is found in the Norms table in Appendix A, of the BSID-II manual (Bayley, 1993). In cases where the PDI fell below 50, the table on pg. 76 of Black and Matula, (2000) (Appendix IX), which contains extrapolated scores for a PDI<50, was used to calculate the PDI. The PDI score is then placed on

the Bell Curve (Figure 4.6), in order to analyse the severity of motor developmental delay.

1 infant (2.5%) showed accelerated performance
4 infants (10%) were developing within normal limits
4 infants (10%) were mildly delayed and
31 infants (77.5%) were significantly delayed

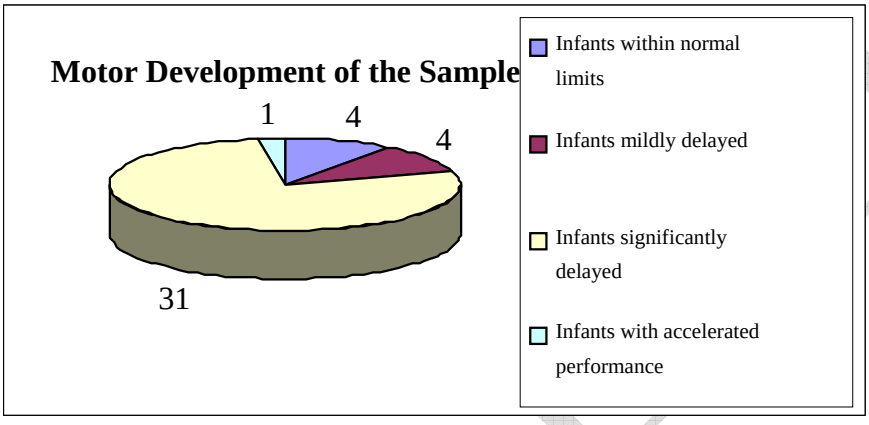

Figure 4.9: Breakdown of motor development of the sample

An attempt was made to analyse motor development in terms of age group in order to determine the age at which developmental problems begin to manifest. The sample was divided into two age categories: 18 – 24 months and 25 – 30 months. It was not possible to analyse this within motor development, as the variation in motor developmental ages was too great to perform a Fischer's Exact Test.

Motor development was further analysed in terms of fine motor development and gross motor development. This was analysed descriptively using the facet scores of the BSID II, which place items from the BSID II into language, motor, and mental scales for further analysis (Appendix IV).

The results were as follows:

1 (2.5%) child was not delayed in gross or fine motor development at all

5 (12.5%) children were delayed in fine motor skills

34 (85%) delayed in gross motor skills

Therefore gross motor delay seemed to be prominent in this sample.

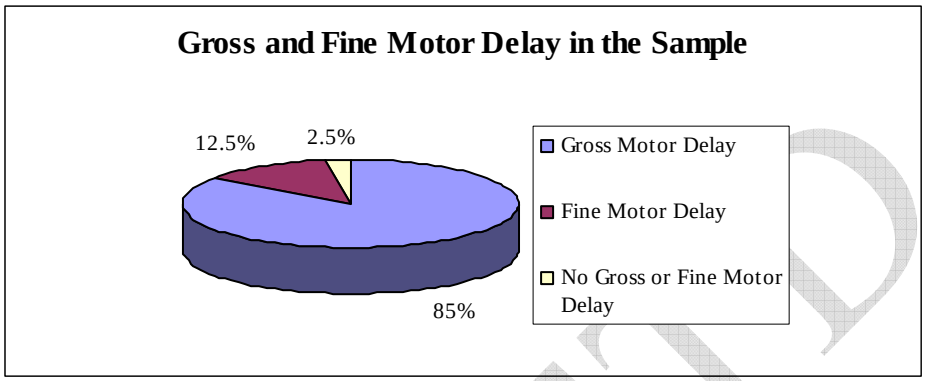

Figure 4.10: Gross and Fine Motor Delay in the Sample

An attempt was made to analyse gross motor function in terms of chronological age categories, in order to determine whether delays manifest at certain ages. The sample was divided into 2 categories of 18 – 24 months, and 25 – 30 months. A Fischer's Exact Test was performed between the age categories, for gross motor ability and there was no statistical significance ($p = 0.296$) indicating that there is no difference in onset of gross motor delay between earlier and later age groups

4.5 Language development

Language delay was descriptively analysed using language items from the BSID II Mental Scale, and placing them on the Facet Scores (Appendix IV and V). It was possible to descriptively analyse global language delay, but it was not possible to break language down into expressive and receptive components, as there are too few specific items on the BSID II to accurately analyse this. Out of 40 infants, 33 were delayed in global language development, i.e. 82.5% of the sample.

Language development was analysed in terms of age category (18 – 24 months vs. 25 – 30 months), in order to determine whether delays begin to manifest at

certain ages, by performing a Fischer's Exact Test. Again, there was no statistical significance (p=0.529), indicating that there is no difference in language delays between earlier and later age groups.

Chapter 5: DISCUSSION

In this chapter, the results obtained in this study are discussed. The results will be compared to those recorded in previous studies. The implications and limitations of this study are highlighted, and recommendations are made.

5.1 Bayley Scales of Infant Development II

One of the primary uses of the Bayley Scales is to examine development of infants who are suspected of being delayed (Black and Matula, 2000). The BSID is the most widely used tool for developmental assessment in studies, and has been shown to be valid and reliable (Long & Cintas, 1995). The Bayley Scale has been found to be sensitive to developmental changes in the first two years of life of infants who are medically fragile (Niccols et al, 2002). The scale is clinically valid, and can be applied to those with HIV (Black and Matula, 2000, Niccols et al, 2002). The BSID has been used in a number of studies which looked at development in HIV positive infants (Nozyce et al, 1994; Chase et al, 1995; Belman, 1996; Chase 2000; Llorente 2003).

In this study, the BSID II was used on a group of infants who were suspected of being delayed, and the results confirm that they are delayed in language, motor and cognitive development. The BSID II is a sensitive, valid and reliable developmental assessment tool, and therefore was the most appropriate tool to employ in order to look at motor and mental development. The BSID was normed on a group of South African infants in 1988 by Richter and Griesel, who obtained very similar raw scores to the American norms on both mental and motor scales, which indicates that this scale is suitable for use in South Africa. Although the BSID II has an increased number of language items, it is not primarily a language assessment tool, and therefore could not be used to look at language development in more depth.

5.2 The Effect of HIV on development

5.2.1 Cognitive Development

HIV infected infants have cognitive impairment, CNS dysfunction and deficits in neuropsychological functioning, and often present with microcephally and mental retardation, with impairment in one or more functions (Belman et al, 1985; Ultmann et al, 1985; Epstein et al, 1986; Belman et al, 1988; Diamond et al, 1990; Belman, 1992; Fowler, 1994; Belman et al, 1996; Henry et al, 1996; Fragoso et al, 1999; Mazzoni et al, 2000). Infected children with brain abnormalities perform worse on measures of cognitive and motor development (Brouwers et al, 1995). Further, it may be an indication that these children were infected in utero rather than during the intrapartum period (DeCarli et al, 1993; Brouwers et al, 1995).

Exposing infants to varying environments has a significant impact on their development and rates of learning. In the first year of life, infants have the potential to develop means-end skills to solve problems by manipulation and exploration if given the opportunity. Increased motor capacity could have important ramifications for the development of tool use, means-end behaviours and other problem solving tasks, or overall cognitive development. Children are able to apply what they learn in one situation to other situations (Bojczk and Corbetta, 2004)

The results of this study show that cognitive development was delayed, which was statistically significant ($p<0.001$), and mean cognitive developmental age was 7.63 months below mean chronological age. Furthermore 70% of this population was significantly delayed according to their MDI scores, although cognitive development is not as delayed as motor function. There are two factors which could explain the cognitive delay seen in this population:

1) The impact of HIV on the CNS could lead to structural changes in the brain, and therefore lead to cognitive delay. It was not within the scope of this study to look at brain imaging, and therefore, although it has been widely found that HIV infects the CNS at or near the time of seroconversion, it is not possible to state this as a definitive cause for cognitive delay.

2) The second factor could be due to the socioeconomic backgrounds of these infants, and the unstimulating homes that the infants find themselves in. This is explained in the findings of Bojczk and Corbetta, (2004), in that infants need to be exposed to situations and tasks in order to learn how to perform them, and to apply these skills to other situations. Many of the tasks in the BSID II are problem-solving based, and therefore, because the task is brand new, the infant does not have the skills to solve the problem. It would be interesting to re-test the infants after exposing them to the task once, and teaching them to solve the problem, to note whether the inability to complete the task is due to cognitive delay or lack of means-end skills. The direct effect of socioeconomics on development is discussed in more detail below.

5.2.2 Motor Development

Young children's motor development, coordination, muscle tone and reflexes are most consistently and strongly affected by HIV infection (Drotar, 1997). The delay is either a reflection of the chronicity of the disease or a direct expression of CNS involvement (Msellati et al, 1993, Bisiacchi et al, 2000). Motor function is compromised early in development in infants with HIV and it is mainly gross motor skills that are delayed (Nozyce et al, 1994; Chase et al, 1995). This may be that gross movements require muscle groups and some degree of physical effort, whereas fine movements are associated with more precise outputs but lower force. Therefore gross motor performance deficits may be related to an overall loss of strength (Parks et al, 1999).

It was determined in this study that infants were delayed in motor development, which was statistically significant ($p<0.001$), and mean motor developmental age was 9.65 months below mean chronological age. Furthermore, 77.5% of the sample is significantly delayed according to their PDI scores. These results are in agreement with those obtained by Chase et al, (1995), Nozyce et al, (1994) and Parks et al, (1999). On descriptive analysis, gross motor function was found to be affected in 85% of the population, whereas fine motor function was only affected in 12.5%. This is in agreement with the results found by Parks et al, (1999). Activities involving anti-gravity muscle strength were particularly delayed, such as jumping, stair-climbing and

standing up from sitting. These results could be due to decreased overall strength, or due to repeated hospital admissions from illness, leading to set-backs in development.

5.2.3 Language Development

The neuropathogenesis of language problems in HIV is unknown (Wolters et al, 1995). Speech and language acquisition are sensitive to a variety of neurodevelopmental insults, including global cognitive delay, central disorders of language function or auditory perception, central or bulbar disorders of motor function (oromotor apraxia, dysarthria), and hearing loss. Language acquisition in young children is therefore a good barometer of CNS integrity in general (Coplan et al, 1998). HIV CNS disease in children is associated with deficits in both receptive and expressive language, although expressive language skills are more severely impaired (Epstein, 1986; Pizzo, 1988; Nozyce et al, 1994; Papola, 1994; Tardieu, 1995; Wolters, 1995; Blanchette et al, 2001). Verbal expression is highly correlated to motor function, thus motor deficits, including those in muscle coordination and motor programming may affect oral-motor skills and contribute to feeding problems, articulation errors and speech difficulties (Wolters et al, 1997).

The results of this study confirm that children with HIV have language delays, and descriptive analysis of the data revealed that 82.5% of the sample have delays in language development. Language delay can signal neurological impairment, oral-motor impairment, general cognitive delay or environmental deprivation (Black and Matula, 2000). In this study, the language delays could be attributed to any one of the above-mentioned factors. The infants may have structural damage to the brain caused by HIV CNS infection, and there is cognitive impairment in this sample (discussed above), which may interfere with language development.

The results of this study are similar to findings by Webster et al, (2005), who found a relationship between gross motor and communication performance, suggesting that factors critical to gross motor function may also lead to language impairment.

The development of language is built on early interactions with caregivers and is augmented later by the presence of a rich, conversational environment (Bishop, 2000). The findings by Bishop, (2000) indicate that the size of a two-year old's vocabulary is dependent on how much of the mother's speech the infant has sampled. This population was globally delayed in language, which could be due to the fact that the caregivers may not be at home with the child due to work, or are too ill to interact much with the child, and therefore the child is not hearing enough speech to increase vocabulary size.

The nature of the BSID II is such, that it is not possible to break language into expressive and receptive components, as there are too few items. Therefore, it was not possible to determine which component was more affected in this sample, but based on the work of Wolters et al, (1995) and (1997), one would expect that expressive language would be more affected than receptive language.

5.3 Age

The age range used in this study (18 – 30 months) was not as wide as those in similar studies (Msellati 1993; Nozyce et al, 1994; Chase et al, 1995; Drotar et al, 1997; Chase et al, 2000; Llorente et al, 2003), as most of these studies were long-term follow up studies and therefore had a wide age range for continuous assessment. The nature of the present study was a once-off assessment format, and the age-range was chosen to ensure that the objectives could be met. It was an objective of this study to try to determine whether developmental problems manifest at certain ages, and therefore age categories were drawn up: (18 – 24 months) and (25 – 30 months), and a Fischer's Exact Test was used to compare these two groups. There was no statistical significance for language ($p=0.529$) and gross motor delays ($p=0.296$), indicating that delays are present throughout the age categories. It was not possible to determine this objective within Cognitive and overall Motor development, as there were too many factors for analysis by Fischer's Exact Test. One reason for the lack of significance in language and gross motor delays may be due to the fact that the

distribution of the ages was not equal and therefore, there were more children in the 25 – 30 month category. A wider age-range on a larger sample is needed in order to determine this objective.

5.4 Skill Most Adversely Affected

Motor Development, specifically gross motor, was found to be the skill most adversely affected in infants with HIV; which is in agreement with results from previous studies (Msellati, 1993; Chase et al, 1995; Nozyce et al, 1994, Drotar, 1997). As discussed above, this could be attributed to an overall loss of strength due to illness.

5.5 Other Factors Affecting Development

Coscia et al, (2001) found that home environment was found to mediate the association between socioeconomic status and child Intelligence Quotient (IQ), and therefore home environment can either serve as a protective factor or risk factor for the negative effects of poverty on cognitive functioning. It has also been found that children with HIV-1 living in poverty also live in less stimulating and supportive home environments and, therefore, are more at risk for developmental problems (Coscia et al, 2001). Disease severity also appears to magnify the effects of the environment on child cognitive functioning. Specific aspects of disease severity, such as CNS integrity may account for the stronger association between the home environment and cognitive function of the child. Therefore, children who have CNS impairment may be at greater risk for more negative secondary cognitive outcome secondary to a less stimulating environment (Coscia et al, 2001). Duncan et al, (1994) found that family income is a far more powerful correlate of IQ at age 5 than measures such as maternal education and ethnicity. The effects of persistent poverty on IQ are twice as large as the effects of transient poverty.

As indicated in Fig. 4.4, the socioeconomic status of this sample is low, which clearly has an effect on cognitive development. Most households consisted of more than 5 people, and the household income per month is very low in all cases. The home environment in this sample may serve as a risk factor for the

negative effects of poverty on cognitive function which, in addition to disease severity, will have a huge impact on development. Only 22% of caregivers had obtained matric and no caregivers had tertiary qualifications, showing that educational level in this sample is very low. This could indicate a poor home learning environment which would affect cognitive development. This would need to be further investigated with home visits. In addition to a poor socioeconomic set-up, and home environment, none of these infants were on antiretrovirals, which could indicate that disease progression is occurring. All of these factors are likely to impact hugely on cognitive development.

For children growing up in poverty, physical and mental development is intertwined (Bhargava, 1998). As this study has clearly shown, both mental and motor development are delayed which could also be affected by the socioeconomic factors affecting these infants.

5.6 Limitations of the study

- Language barriers could affect some of the items and the child's understanding of what is being asked of them.
- The BSID II is not primarily a language tool, and therefore it is not possible to look at expressive and receptive language, as has been done in the literature.
- The age range was not wide enough or equally distributed to determine at which ages problems begin to manifest.
- It would be interesting to look at CNS involvement in these children to see whether the delays are due to strength, socioeconomics or structural problems.
- The BSID I has been validated and normed for black South African children, but the BSID II has not, therefore it would be of value to have the BSID II normed for this population.

5.7 Implications of the Findings

The results of this study indicate that HIV positive children are delayed in at least three areas of development: motor, cognitive and language. These problems are seen from as early as 18 months of age and most infants are significantly delayed in these areas. This indicates a need for early

developmental assessment in this population, as it can be expected that most infants with HIV are delayed. In the clinic where the data were collected there is no involvement of allied health professionals aside from speech therapists, who have set up a screening programme. These results indicate that physiotherapists and possibly psychologists should also be involved in order to facilitate motor and cognitive development in these infants.

Due to the poor socioeconomic situations of many of the infants, parents cannot be expected to provide cognitively stimulating homes for these children due to financial and educational constraints, and therefore could benefit from assistance in this area.

5.8 Recommendations Based on Results

- Infants with HIV are known to be delayed in motor, cognitive and language development and should therefore be screened early for signs of delay.
- Therapists, including educational psychologists, should be involved in wards and clinics that these children attend in order to provide developmental assistance and education to parents in gross motor, language and cognitive capacities. This indicates a need for government policy change, as, at present, there is no staffing requirement for allied health professionals in HIV units, which indicates a lack of awareness in this aspect. There is a comprehensive treatment plan (Department of Health, 2003) which covers opportunistic infections, nutrition, life skills and education, but there is no mention of developmental problems in children. This research could assist in increasing awareness on this subject, and indicate the need for policy change regarding this subject.
- Simple home programmes could be effective in this population in making parents more aware of what milestones their infants should be reaching and assisting them in achieving them.

5.9 Recommendations in terms of further research

- A prospective neurological study would be useful to determine the progression of delay in a sample similar to this one.
- There have been few studies targeting HIV positive children of school-going age to determine their neurological status and whether the effects HIV on the CNS lead to academic and neurological problems in older children.
- A study which incorporates developmental assessment as well as brain imaging to determine the effects of HIV on the CNS would be useful in isolating the causes of the delays seen.

Chapter 6: Conclusion

The purpose of this study was to examine motor, mental and language development in 40 HIV positive infants between the ages of 18 and 30 months. All subjects were from similar socioeconomic backgrounds, and attend the Harriet Shezi HIV clinic at Baragwanath Hospital, Soweto. The assessment tool used was the motor and mental scales of the Bayley Scales of Infant Development.

The findings of this study support previous research which has shown that children with HIV have significant delays in mental and motor development. In addition, language is delayed in most children with HIV. It was not within the scope of this study to determine the effects of HIV on the brain matter of these infants, and therefore it is not possible to say whether the results are due to encephalopathy or other factors such as weakness, socioeconomic background or limitations of the assessment tool.

Motor development is most severely affected, specifically gross motor development which could be due to decreased strength in these children. Problems with language development are also seen, which could be due to CNS involvement, or due to oral-motor problems which stem from decreased muscle strength. Cognitive delays could be affected by CNS involvement, as well as socioeconomic problems encountered in this population. These findings are in keeping with studies done in other parts of the world. Therefore, this indicates that developmental delay in HIV positive infants is a global problem, and early developmental assessment, and intervention based on the results is crucial in the management of these patients. The results of this study are important for therapists, particularly those involved in motor and language rehabilitation, as an awareness of potential problems in these infants is needed in order to provide them with the best management and care possible.

Chapter 7: References

Aram D, Rose D, Rekate H, Whitaker H 1983 Acquired Capsular/Striatal Aphasia in Childhood. *Archives of Neurology* **40:**614–617

Bayley N 1993 Manual for the Bayley Scales of Infant Development (2nd Edition). San Antonio, TX: Psychological Corporation

Behl-Chada G 1996 Superordinate-like Categorical Representations in Early Infancy. *Cognition* **60:** 104- 141

Belman A, Ultmann H, Horoupian D, Novick B, Spiro A, Rubinstein A, Kurtzberg D, Cone-Wesson B 1985 Neurological Complications in Infants and Children with Acquired Immune Deficiency Syndrome. *Annals of Neurology* **18:** 560 – 566

Belman A, Diamond G, Dickson D, Horoupian D, Llena J, Lantos G, Rubinstein A 1988 Pediatric Acquired Immunodeficiency Syndrome: Neurologic Syndromes. *American Journal of Disease in Childhood* **142:** 29 – 35

Belman A 1990 AIDS and Pediatric Neurology. *Neurology Clinics* **8 (3):** 571 – 603

Belman A 1992 Acquired Immunodeficiency Syndrome and the Child's Central Nervous System. *Pediatric Clinics of North America* **39 (4):** 691 – 713

Belman A 1994 HIV-1 Associated CNS Disease in Infants and Children. In: *HIV, AIDS and the Brain* (R.W. Price and S.W Perry, eds), Raven Press, New York pp 289 – 310

Belman A, Muenz L, Marcus J, Goedert J, Landesman S, Rubinstein A, Goodwin S, Durako S, Willoughby A 1996 Neurologic Status of Human Immunodeficiency Virus –1 Infected Infants and their Controls: A Prospective Study from Birth to 2 Years. *Pediatrics* **98 (6):** 1109 – 1118

Bhargava A 1998 A Dynamic Model for the Cognitive Development of Kenyan Schoolchildren. *Journal of Educational Psychology* **90 (1):** 162–166.

Bhargava A, Fox-Kean M 2003 The Effects of Maternal Education versus Cognitive Test Scores on Child Nutrition in Kenya. *Economics and Human Biology* **1:** 309 – 319

Bishop D, Edmundson A 1987 Specific Language Impairment as a Maturational lag: Evidence from Longitudinal Data on Language and Motor Development. *Developmental Medicine and Child Neurology* **29:**442-59.

Bishop D 2000 How does the Brain Learn Language? Insights from the Study of Children with and without Language Impairment. *Developmental Medicine and Child Neurology* **42:** 133 – 142

Bissiachi P, Suppiej A, Laverda A 2000 Neuropsychological Evaluation of Neurologically Asymptomatic HIV-Infected Children. *Brain and Cognition* **43:** 49 - 52

Black M, Matula K 2000 Essentials of Bayley Scales of Infant Development-II Assessment. John Wiley and Sons, Inc

Blanche S, Tardieu M, Duliege A, Rouzioux C, Le Diest F, Fukunaga K, Caniglia M, Jacomet C, Messiah A, Griscelli C 1990 Longitudinal Study of 94 Symptomatic Infants with Perinatally Acquired Human Immunodeficiency Virus Infection. *American Journal of the Diseases of Children* **144: 1**210 – 1215

Blanchette N, Smith M, Fernandes-Penney A, King S, Read S 2001 Cognitive and Motor Development in Children with Vertically Transmitted HIV Infection. *Brain and Cognition* **46:** 46 - 49

Blanchette N, Smith M, King S, Fernandes-Penney A, Read S 2002 Cognitive Development in School-age Children with Vertically Transmitted HIV Infection. *Developmental Neuropsychology* **21 (3):** 223 - 241

Bloom P, Markson L 1998 Capacities Underlying Word Learning. *Trends in Cognitive Sciences* **2 (2):** 67 – 74

Bobat R, Moodley D, Coutsoudis A, Coovadia H, Gouws E 1998 The Early Natural History of Vertically Transmitted HIV-1 Infection in African Children from Durban, South Africa. *Annals of Tropical Paediatrics* **18**: 187 – 196

Bojczk K, Corbetta D 2004 Object Retrieval in the 1st Year of Life: Learning Effects of Task Exposure and Box Transparency. *Developmental Psychology* **40 (1):** 54 – 66

Booth A, Waxman S 2002 Object Names and Object Functions Serves as Cues to Categories for Infants. *Developmental Psychology* **38 (6):** 948–957

Bower T 1982 Cognitive Development; in: Development in Infancy 2nd edition. W.H Freeman and Co. 195 – 254

Bradley R, Caldwell B, Rock S, Barnard K, Gray C, Hammond M, Mitchell S, Siegel L, Ramey C, Gottfried A, Johnson D 1989 Home Environment and Cognitive Development in the First Three Years of Life: A Collaborative Study Involving Six Sites and Three Ethnic Groups in North America. *Developmental Psychology* **25:** 217 – 235

Brady M, McGrath N, Brouwers P, Gelber R, Glenn-Fowler M, Yogev R, Hutton N, Bryson Y, Mitchell C, Fikrig S, Borkowsky W, Jiminez E, McSherry G, Rubinstein A, Wilfert C, McIntosh K, Elkins M, Weintrub P and the Pediatric AIDS Clinical Trials Group 1995 Randomized Study of the Tolerance and Efficacy of High-versus-Low Dose Zidovudine in Human Immunodeficiency Virus-Infected Children with Mild to Moderate Symptoms. *Journal of Infectious Disease* **173:** 1097 – 1106

Bretherton I 1992 The Origin of the Attachment Theory: John Bowlby and Mary Ainsworth, *Developmental Psychology* **28 (5):**759

Brody B, Kinney H, Kloman A, Gilles F 1987 Sequence of Central Nervous System Myelination in Human Infancy: I. An Autopsy Study of Myelination. *Journal of Neuropathology and Experimental Neurology* **46 (3):** 283 – 301

Bronfenbrenner U 1977 Toward an Experimental Ecology of Human Development. *American Psychologist* **32:** 513– 31

Brooks-Gunn J, Klebanov K, Duncan G 1996 Ethnic Differences in Children's Intelligence Test Scores: Role of Economic Deprivation, Home Environment and Maternal Characteristics. *Child Development* **67:** 396 - 408

Brouwers P, DeCarli C, Civatello L, Moss H, Wolters P, Pizzo P 1995 Correlations between CT-Brain Scan Abnormalities and Neuropsychological Function in Children with Symptomatic HIV Disease. *Archives of Neurology* **52:** 39 – 44

Brunner R, Kornhuber H, Seemuller E, Sugar G, Wallesch C 1982 Basal Ganglia Participation in Language Pathology. *Brain and Language* **16:** 281 – 299

Burnett C, Johnson E 1971 Development of Gait in Children: Parts I and II. *Developmental Medicine and Child Neurology* **13:**196 - 215

Bushnell E, Boudreau J 1993 Motor Development and the Mind: The Potential Role of Motor Abilities as a Determinant of Aspects of Perceptual Development. *Child Development* **64:**1005-1021

Calancie B, Needham-Shropshire B, Jacobs P, Willer K, Zych G, Green B 1994 Involuntary Stepping after Chronic Spinal Cord Injury. Evidence for a Central Rhythm Generator for Locomotion in Man. *Brain* **117:** 1143–1159.

Caplan P, Kinsborne M 1976 Baby Drops the Rattle: Asymmetry of Duration of Grasp in Infants. *Child Development* **47:** 532-534

Capute A, Shapiro B, Palmer F, Ross A, Wachtel R 1985 Normal Gross Motor Development: the Influences of Race, Sex and Socio-economic Status. *Developmental Medicine and Child Neurology* **27:** 635 - 643

Capute A, Palmer F, Shapiro B, Wachtel R, Schmidt S, Ross A 1986 Clinical Linguistic and Auditory Milestone Scale: Prediction of Cognition in Infancy. *Developmental Medicine and Child Neurology* **28:** 762 - 771

Carver L and Bauer P 2001 The Dawning of a Past: the Emergence of Long-Term Explicit Memory in Infancy. *Journal of Experimental Psychology: General* **130 (4):** 726–745

Case R 1974 Structures and Strictures: Some functional Limitations on the Course of Cognitive Growth. *Cognitive Psychology* **6:** 544-574

Casey B, Giedd J, Thomas K 2000 Structural and Functional Brain Development and its Relation to Cognitive Development. *Biological Psychology* **54:** 241 – 257

Catherwood D 1993 The Robustness of Infant Haptic Memory: Testing its Capacity to Withstand Delay and Haptic Inference. *Child Development* **64:** 702 – 710

Catherwood D 1999 New Views on the Young Brain: Offerings from Developmental Psychology to Early Childhood Education. *Contemporary Issues in Early Childhood* **1 (1):** 23 – 35

Changeux J, Dehaene S 1989 Neuronal Models of Cognitive Functioning. *Cognition* **33:** 63 – 109

Chase C, Vibbert M, Pelton S, Coulter D, Cabral H 1995 Early Neurodevelopmental Growth in Children with Vertically Transmitted Human Immunodeficiency Virus Infection. *Archives of Pediatric and Adolescent Medicine* **149:** 850 – 855

Chase C, Ware J, Hittelman J, Blasini I, Smith R, Llorente A, Anisfield E, Diaz C, Fowler M, Moye J, Kaligh L 2000 Early Cognitive and Motor Development amongst Infants Born to Women Infected with Human Immunodeficiency Virus. *Pediatrics*; **106 (2):** e25 (accessed 04/04)

Chugani H, Phelps M, Mazziotta J 1987 Positron Emission Tomography Study of Human Brain Functional Development. *Annals of Neurology*. **22:** 487–497.

Chugani H 1998 A Critical Period of Brain Development: Studies of Cerebral Glucose Utilization with PET. *Preventative Medicine* **27:** 184–188

Clark C 2004 How Language Acquisition Builds on Cognitive Development. *Trends in Cognitive Sciences* **8 (10):** 472 – 479

Cocchi F, DeVico A, Garzino-Demo A, Arya S, Gallo R, Lusso P 1995 Identification of RANTES, MIP-1 a / MIP-1 b as the Major HIV-Suppressive Factors Produced by CD8/ T cells. *Science* **270:** 1811–1815.

Cohen S, Mundy T, Karassik B, Lieb L, Ludwig D, Ward J 1991 Neuropsychological Functioning in Human Immunodeficiency Virus Type 1 Seropositive Children Infected through Neonatal Blood Transfusions. *Pediatrics* **88:** 58 – 68

Collie R and Hayne H 1999 Deferred Imitation by 6- and 9-Month old Infants: More Evidence for Declarative Memory. *Developmental Psychobiology* **35:** 83–90

Condon W, Sander L 1994 Neonate Movement is Synchronized with Adult Speech: Interactional Participation and Language Acquisition. *Science* **183:** 99 – 101

Cooper S, Lyall H, Walters S, Tudor-Williams G, Habibi G, de Munter C, Britto J, Nadel S 2004 Children with Human Immunodeficiency Virus Admitted to a Paediatric Intensive Care Unit in the United Kingdom over a 10-year Period. *Intensive Care Medicine* **30 (1):** 113 - 118

Coplan J, Contello K, Cunningham C, Weiner L, Dye T, Roberge L, Wojtowycz M, Kirkwood K 1998 Early Language Development in Children Exposed to or Infected with Human Immunodeficiency Virus. *Pediatrics* **102 (1):** e8 http://www.pediatrics.org/cgi/content/full/102/1/e8 (accessed 05/04)

Coscia J, Christenson B, Henry R, Wallston K, Radcliffe J, Rutstein R 2001 Effects of Home Environment, Socio-Economic Status, and Health Status on Cognitive Functioning in Children with HIV-1 Infection. *Journal of Pediatric Psychology* **26 (6):** 321 - 329

Culbertson J, Newman J, Willis D 2003 Childhood and Adolescent Psychologic Development. *Pediatric Clinics of North America* **50:** 741 – 764

Darrah J, Redfern L, Maguire T, Beaulne P, Watt J 1998 Intra-individual Stability of Rate of Gross Motor Development in Full-Term Infants. *Early Human Development* **52:** 169 – 179

Davis L, Hjelle B, Miller V, Palmer D, Llewellyn A, Merlin T, Young S, Mills R, Wachsman W, Wiley C 1992 Early Viral Brain Invasion in Iatrogenic Human Immunodeficiency Virus Infection. *Neurology* **42:** 1736 – 9

DeCarli C, Civitello A, Brouwers P, Pizzo P 1993 The Prevalence of Computed Tomographic Abnormalities of the Cerebrum in 100 Consecutive Children Symptomatic with the Human Immune Deficiency Virus. *Annals of Neurology*, **34,** 198–205

Department of Health: Operational Plan for Comprehensive HIV and AIDS Care and Treatment for South Africa. 19th November 2003. http://www.info.gov.za/otherdocs/2003/aidsplan.pdf (accessed 11/05)

Department of Health National HIV and Syphilis Antenatal Sero-Prevalence Survey in South Africa 2004 www.health.gov.co.za (Accessed 08/05)

De Rossi A, Ometto L, Zanotto C, Salvatori F, Mastero S, Mammano F, Chieco-Bianci L 1994 Mother-to-Child HIV-1 Transmission: A Quantatative Assessment of Viral Burden as a Diagnostic Tool and Prognostic Parameter in HIV-1 Infected Children. *Acta Paediatrica Supplementa* **400:** 25-28

Diamond A 1988 Abilities and Neural Mechanisms Underlying A not B Performance. *Child Development* **59:** 523–527

Diamond G, Gurdin P, Wiznia A, Belman A, Rubinstein A, Cohen H 1990 Effects of Congenital HIV Infection on Neurodevelopmental Status of Babies in Foster Care. *Developmental Medicine and Child Neurology* **32:** 999 – 1005

Dietz V, Colombo G, Jensen L 1994 Locomotor Activity in Spinal Man. *Lancet*: **344:** 1260–1263.

Drotar D, Olness K, Wizniter M, Guay L, Marum L, Svilar G, Hom D, Fagan J, Ndugwa C, Kiziri – Mayengo R 1997 Neurodevelopmental Outcomes of Ugandan Infants with Human Immunodeficiency Virus Type 1 Infection. *Pediatrics* **100 (1):** e5 http://www.pediatrics.org/cgi/content/full/100/1/e5 (accessed 06/04)

Duncan G, Brooks-Gunn J, Klebanov P 1994 Economic Deprivation and Early Childhood Development. *Child Development* **65:** 296 - 318

Dunn D, Newell M, Ades A, Peckham C 1992 Risk of Human Immunodeficiency Virus Type 1 Transmission Through Breastfeeding. *Lancet* **340:** 585–8.

Ellis R, Deutsch R, Heaton R, Marcotte T, McCutchan J, Nelson J, Abramson I, Thal L, Atkinson J, Wallace M, Grant I and the San Diego HIV Neurobehavioural Research Centre Group 1997 Neurocognitive Impairment is an Indepenedent Risk Factor for Death in HIV Infection. *Achives of Neurology* **54:** 416 – 24

Epstein L, Sharer L, Joshi V, Fojas M, Koeningsberger M, Oleske J 1985 Progressive Encephalopathy in Children with Acquired Immune deficiency. *Annals of Neurology* **17:** 488 – 496

Epstein L, Sharer L, Oleske J, Connor E, Goudsmit J, Bagdon L, Robert-Guroff M, Koeningsberger R 1986 Neurologic Manifestations of Human Immunodeficiency Virus Infection in Children. *Pediatrics* **78:** 678 – 687

Epstein L, Goudsmit J, Paul D, Morrison S, Connor E, Oleske J, Holland B 1987 Expression of Human Immunodeficiency Virus in Cerebrospinal Fluid of Children with Progressive Encephalopathy. *Annals of Neurology* **21:** 397 – 406

Epstein L, Gendelman H 1993. Human Immunodeficiency Virus Type 1 Infection of the Nervous System: Pathogenetic Mechanisms. *Annals of Neurology* **33:** 429 – 436

European Collaborative Study 1996 Vertical transmission of HIV-1: maternal immune status and obstetric factors. *AIDS* **10:**1675–81.

European Collaborative Study 1999 Maternal Viral Load and Vertical Transmission of HIV-1: an Important Factor but not the Only One. *AIDS* **13:**1377–85

The European Mode of Delivery Collaboration 1999 Elective Caesarean Section versus Vaginal Delivery in Preventing Vertical HIV-1 Transmission: a Randomised Clinical Trial. *Lancet* **353:**1035–9.

Evans G 1998 The Human Genome Project. *Archives of Neurology* **55:** 1287-1290.

Fietzek U, Heinen F, Berweck S, Maute S, Hufschmidt A, Schulte-Monting J, Lucking C, Korithinthenberg R 2000 Development of the Corticospinal System and Hand Motor Function: Central Conduction Times and Motor Performance Tests. *Developmental Medicine and Child Neurology* **42:** 220 – 227

Fischer K 1987 Relations Between Brain and Cognitive Development. *Child Development* **58:** 623 – 632

Fiser D, Tilford J, Roberson P 2000 Relastionship of Illness Severity and Length of Stay to Functional Outcomes in the Pediatric Intensive Care Unit: A Multi-Institutional Study. *Critical Care Medicine* **28 (4)** 1173 - 1179

Flavell J 1971 Stage-related Properties of Cognitive Development. *Cognitive Psychology* **2:** 421-453

Forssberg H, Hirschfeld H 1994 Postural Adjustments in Sitting Humans Following External Perturbations: Muscle Activity and Kinematics. *Experimental Brain Research* **97:** 515–527.

Fowler M 1994 Paediatric HIV Infection: Neurologic and Neuropsychological findings. *Acta Paediatra Supplementa* **400:** 59 – 62

Fragoso Y, Andalat R, Adamo A, Lopes de Fonseca N, Moryiama M 1999 Neurologic Manifestations of AIDS in Children and Adolescents: A review of cases in Santos, Brazil. *Medscape General Medicine* 24:E3 www.medscape.com/viewarticles/408010 (accessed 09/4/04)

Frazier J, Giedd J, Hamburger S, Albus K, Kaysen D, Vaituzis C, Rajapakse J, Lenane M, McKenna K, Jacobson L, Gordon C, Breier A, Rapaport K 1996 Brain Anatomic Magnetic Resonance Imaging in Childhood-onset Schizophrenia. *Archives of General Psychiatry* **53:** 617 - 624

Fuller K, Owens J, Chambers T 1995 Macrophage Inflammatory Protein 1a and IL-8 Stimulate the Motility but Suppress the Resorption of Isolated Rat Osteoclasts. *Journal of Immunology* **154:** 6065–6071.

Fuller R, Westmoreland S, Ratai E, Greco J, Kim J, Lentz M, He J, Prabhat S, Masliah E, Halpern E, Lackner A, Gonzalez G 2004 A Prospective Longitudinal In Vivo H MR Spectroscopy study of the SIV/Macaque Model of NeuroAIDS. *BMC Neuroscience* **5:**10 www.biomedcentral.com/1471-2202/5/10 (accessed 7/9/04)

Gabiano C, Tovo P, de Martino M, Galli L, Gianquito C, Loy A, Schoeller M, Giovanini M, Ferranti G, Rancilo L, Caselli D, Segni G, Livadiotti S, Conte A, Rizzi M, Viggiano M, Mazza A, Ferrazin A, Tozzi A, Cappello N 1992 Mother-to-Child

Transmission of Human Immunodeficiency Virus Type 1: Risk of Infection and Correlates of Transmission. *Pediatrics* **90:** 369 - 374

Gabudza D, Ho D, De la Monte S, Hirsch M, Rota T, Sobel R 1986 Immunohistochemical Identification of HTLV-III Antigen in Brains of Patients with AIDS. *Annals of Neurology* **20:** 289 – 295

Ganger J, Brent M 2004 Re-examining the Vocabulary Spurt. *Developmental Psychology* **40 (4):** 621- 632

Gay C, Armstrong D, Cohen D, Lai S, Hardy M, Swales T, Morrow C, Scott G 1995 The Effects of HIV on Cognitive and Motor Development in Children Born to HIV-Seropositive Women with no Reported Drug Use: Birth to 24 months. *Pediatrics* **96:** 1078 – 1082

Goldman –Rakic P 1987 Development of Cortical Circuitry and Cognitive Function. *Child Development* **58:** 601 - 622

Goudsmit J, de Wolf F, Paul D, Lange J, Speelman H, Van der Noordaa J, Van der Helm H, Epstein G, Krone W, Wolters E, Oleske J, Coutinho R 1986 Expression of Human Immunodeficiency Virus Antigen (HIV-ag) in Serum and Cerebrospinal Fluid during Acute and Chronic Infection. *Lancet* **2:** 177 – 180

Greenfield P, Maynard A, Childs C 2003 Historical Change, Cultural Learning, and Cognitive Representation in Zinacantec Maya Children. *Cognitive Development* **18:** 455 – 487

Greenough W, Black J, Wallace C 1987 Experience and Brain Development. *Child Development* **58:** 539 - 559

Grillner S, Deliagina T, Ekeberg Ö, El Manira A, Hill R, Lansner A, Orlovsky G, Wallén P 1995 Neural Networks that Coordinate Locomotion and Body Orientation in Lamprey. *Trends in Neurosciences* **18:** 270–279

Guilian D, Vaca K, Noonan C 1990 Secretion of Neurotoxins by Mononuclear Phagocytes Infected with HIV-1. *Science* **250:** 1593 – 1596

Hadders-Algra M 2000a The Neuronal Group Selection Theory: A Framework to Explain Variation in Normal Motor Development. *Developmental Medicine* & *Child Neurology* **42:** 566–572.

Hadders-Algra M 2000b The Neuronal Group Selection Theory: Promising Principles for Understanding and Treating Developmental Motor Disorders. *Developmental Medicine* & *Child Neurology* **42:** 707–715

Hadders-Algra M 2002 Variability in Infant Motor Behavior: A Hallmark of the Healthy Nervous System. *Infant Behaviour and Development* **25:** 433 – 451

Halford G, Wilson W 1980 A Category Theory Approach to Cognitive Development *Cognitive Psychology* **12:** 356-411

Henry R, Christensen, B, Coscia J, Cohen F, Moore E 1996 Relationship Between Cognitive and Immune Functioning in Children Born to HIV-Seropositive Women. *Developmental Neuropsychology* **12**(3): 283–298.

Hickey W, Williams K 1999 Leukocyte Traffic in the Central Nervous System: The Participants and Their Roles. *Seminars in Immunology* **11:** 125 – 137

Hikosaka O, Nakahara H, Rand M, Sakai K, Lu X, Nakamura K, Miyachi S, Doya K 1999 Parallel Neural Networks for Learning Sequential Procedures. *Trends in Neurosciences* **22:** 464–471.

Hill E 1998 A Dyspraxic Defect in Specific Language Impairment and Developmental Coordination Disorder? Evidence From Hand and Arm Movements. *Developmental Medicine and Child Neurology* **40:** 388-395.

Hill E 2001 Non-Specific Nature of Specific Language Impairment: a Review of the Literature with Regard to Concomitant Motor Impairments. *International Journal of Language and Communication Disorders* **36 (2):**149-71.

Ho D, Rota T, Schooley T, Kaplan J, Allan D, Groopman J, Resnick L, Felsenstein D, Andrews C, Hirsch M 1985 Isolation of HTLV-III from Cerebrospinal Fluid and Neural Tissues of Patients with Neurologic Syndromes Related to the Acquired Immunodeficiency Syndrome *New England Journal of Medicine* **313:** 1493 - 1497

Holt K 1991 Child Development. Butterworth Heinemann Ltd. Oxford 41 - 169

Horak F, Nashner L 1986 Central Programming of Postural Movements: Adaptation to Altered Support-Surface Configurations. *Journal of Neurophysiology* **55 (6):** 1369–1381

Huppi P, Warfield S, Klikinis R, Barnes P, Zientara G, Jolesz F, Tsuji M, Volpe J 1998 Quantitative Magnetic Resonance Imaging of Brain Development in Premature and Mature Newborns. *Annals of Neurology* **43:** 224 – 235

Huston A, McLoyd V, Coll C 1992 Children and Poverty: Issues in Contemporary Research. *Child Development* **65:** 275 – 282

Huttenlocher P 1979 Synaptic Density in the Human Frontal Cortex – Developmental Changes and the Effects of Ageing. *Brain Research* **163:** 195 – 205

Huttenlocher P 1984 Synapse Elimination and Plasticity in Developing Human Cortex. *American Journal of Mental Deficiency* **88 (5):** 488 – 496

Huttenlocher P 1990. Morphometric Study of Human Cerebral Cortex Development. *Neuropsychologia* **28 (6):** 517–527

Jernigan T, Zisook S, Heaton R, Moranville J, Hesselink J, Braff D 1991 Magnetic Resonance Imaging Abnormalities in Lenticular Nuclei and Cerebral Cortex in Schizophrenia. *Archives of General Psychiatry* **48**: 881–890.

Johnston R, Stark R, Mellits E, Tallal P 1981 Neurological Status of Language-Impaired and Normal Children. *Annals of Neurology* **10:**159-63.

Koendrick M, Uylings H 1995 Postnatal Maturation of Layer V Pyramidal Neurons in the Human Prefrontal Cortex. A Quantitative Golgi Analysis. *Brain Research* **678:** 233 – 243

Koenig S, Gendelman H, Orenstein J, Dal Canto M, Pezeshkpour G, Yungbluth M, Janotta F, Aksamit, Martin M, Fauci A 1986 Detection of AIDS Virus in Macrophages in Brain Tissue from AIDS Patients with Encephalopathy. *Science* **233:**1089-1093

Kolson D 2002 Neuropathogenesis of Central Nervous System HIV-1 Infection. *Clinical Laboratory Medicine* **22:** 703 – 717

Kostovic 1990 Structural and Histochemical Reorganization of the Human Prefrontal Cortex during Perinatal and Postnatal life. *Progress in Brain Research* **85:** 223 – 239.

Landesman S, Kalish L, Burns D, Minkoff H, Fox H, Zorrilla C, Garcia P, Fowler MG, Mofenson L, Tuomala R for the Women and Infants Transmission Study 1996 Obstetrical Factors and the Transmission of Human Immunodeficiency Virus Type 1 from Mother-to-Child. *New England Journal of Medicine* **334 (25):**1617–23.

Lantz C, Melen K, Forsberg H 1996 Early Infant Grasping Involves Radial Fingers. *Developmental Medicine and Child Neurology* **38:** 668-675

Largo R, Molinari L, Comenale Pinto L, Weber M, Duc G 1986 Language Development of Term and Preterm Children during the First Five years of Life. *Developmental Medicine and Child Neurology* **28:** 333 - 350

Laue L, Pizzo P, Butler K, Cutler G 1990 Growth and Neuroendocrine Dysfunction in Children with Acquired Immunodeficiency Syndrome. *Journal of Pediatrics* **117:** 541–545.

Laufer M, Scott G 2000 Medical Management of HIV Disease in Children. *Pediatric Clinics of North America* **47 (1):** 127-153

Lepage P, Van de Perre P, Van Vliet G, Nsengumuremyi F, Van Goethem C, Kestelyn P, Msellati P, Hitimana D 1991 Clinical and Endocrinologic Manifestations in Perinatally Human Immunodeficiency Virus type-1 Infected Children aged 5 years or older. *American Journal of Diseases in Childhood* **145:** 1248–1251.

Levin H, Culhane K, Hartmann J, Evankovich K, Mattson A 1991 Developmental Changes in Performance on Tests of Purported Frontal Lobe Functioning. *Developmental Neuropsychology* **7 (3):** 377–395.

Linver M, Brooks – Gunn J 2002 Family Processes as Pathways from Income to Young Children's Development. *Developmental Psychology* **38 (5):** 719 – 734

Lipton S, Gendelman H 1995 Dementia Associated with the Acquired Immunodeficiency Syndrome. *New England Journal of Medicine* **332:** 934-940

Llorente A, Brouwers P, Magder L, Mellins C, Ware J, Hittleman J, Mofenson L, Velez-Borras J, Adeniyi-Jones S 2003 Early Neurodevelopmental Markers Predictive of Mortality in Infants Infected with HIV-1 *Developmental Medicine and Child Neurology* **45:** 76 – 84

Luna B, Thulborn K, Munoz D, Merriam E, Garva K, Minshew N, Keshavan M, Genovese C, Eddy W, Sweeney J 2001 Maturation of Widely Distributed Brain Function Subserves Cognitive Development. *NeuroImage* **13:** 786 – 793

Luzuriaga K, Sullivan J 2002. Pediatric HIV-1 Infection: Advances and Remaining Challenges. *AIDS Review* **4:** 21 - 26

Lyman W, Kress Y, Kure K, Rashbaum W, Rubinstein A, Soeiro R 1990 Detection of HIV in Fetal Central Nervous System Tissue. *AIDS* 4: 917 – 920

Lyon G, Arita F, Le Galloudec E, Valee L, Misson J, Ferriere G 1990 A Disorder of Axonal Development, Necrotising, Myopathy, Cardiomyopathy and Cataracts: A New Familiar Disease. *Annals of Neurology* **27:** 193 – 199

Mandelbrot L, Le Chenadec J, Berrebi A, Bongain A, Benifla J, Delfraissy J, Blanche S, Mayaux M for the French Perinatal Cohort 1998 Perinatal HIV-1 Transmission-Interaction between Zidovudine Prophylaxis and Mode of Delivery in the French Perinatal Cohort. *Journal of the American Medical Association* **280 (1):** 55–60.

Mandler J 2004 Thought Before Language. *Trends in Cognitive Sciences* **8 (11):** 508 – 514

Masliah E, Heaton R, Marcotte T, Ellis R, Wiley C, Mallory M, Achim C, McCutchan J, Nelson J, Atkinson J, Grant I and the HNRC Group 1997 Dendritic Injury is a Pathological Substrate for Human Immunodeficiency Virus-related Cognitive Disorders. HNRC Group. *Annals of Neurology* **42:** 963 – 972

Masliah E, Deteresa R, Mallory M, Hansen L 2000 Changes in Pathological Findings at Autopsy in AIDS Cases for the last 15 Years. *AIDS* **14:** 69 – 74

Matarazzo P, Palomba E, Lala R, Ciuti E, Altare F, deSanctis L, Tovo P 1994 Growth Impairment, IGF-1 Hyposecretion and Thyroid Dysfunction in Children with Perinatal HIV-1 Infection. *Acta Paediatrica* **83:** 1029–1034.

Mazzoni P, Chiriboga C, Millar W, Rogers A 2000 Intracerebral Aneurysms in Human Immuno-deficiency Virus Infection: Case Report and Literature Review. *Pediatric Neurology* **23:** 252- 255

McDonough L, Choi S, Mandler J 2003 Understanding Spatial Relations: Flexible Infants, Lexical Adults. *Cognitive Psychology* **46:** 229–259

Meltzoff A 1988 Infant Imitation and Memory: Nine-Month-Olds in Immediate and Deferred Tests. *Child Development* **59**: 217–225

Meyers T, Pettifor J, Gray G, Crewe-Brown H, Galpin J 2000 Pediatric Admissions with Human Immunodeficiency Virus Infection at a Regional Hospital in Soweto, South Africa. *Journal of Tropical Pediatrics* **46 (4)** 224 - 230

Mills D, Coffey-Corina S, Neville H 1997 Language Comprehension and Cerebral Specialization from 13-20 months. *Developmental Neuropsychology* **13 (3):**397- 445

Mills D, Plunkett K, Prat C, Schafer G 2005 Watching the Infant Brain Learn Words: effects of Vocabulary Size and Experience. *Cognitive Development* **20 (1)** 19 - 31 www.sciencedirect.com (accessed 02/05)

Moore K, Meltzoff A 2004 Object Permanence After a 24-Hour Delay and Leaving the Locale of Disappearance: The Role of Memory, Space and Identity. *Developmental Psychology* **40 (4):** 606 – 620

Msellati P, Lepage P, Hihama D, Van Goetham C, Van de Perre P, Dabis F 1993 Neurodevelopmental Testing of Children born to Human Immunodeficiency Virus Type 1 Seropositive and Seronegative Mothers: A Prospective Cohort in Kigali, Rwanda. *Pediatrics* **92 (6):** 843 – 848

Munakata Y, McClelland J, Johnson M, Siegler R 1997 Rethinking Infant Knowledge: Toward an Adaptive Process Account of Successes and Failures in Object Permanence Tasks. *Psychological Review* **104 (4):** 686–713.

Munakata Y, Bauer D, Stackhouse T, Landgraf L, Huddleston J 2002 Rich Interpretation vs. Deflationary Accounts in Cognitive Development: the Case of Means-end Skills in 7-Month-old Infants. *Cognition* **83:** B43 – B53 www.elsevier.com/locate/cognit (accessed 09/04)

Navia B, Cho E, Petito C, Price R 1986 The AIDS Dementia Complex: II. Neuropathology. *Annals of Neurology* **19:** 525 – 535

Nelson K, Hampson J, Shaw L 1993 Nouns in Early Lexicons: Evidence, Explanations, and Extensions. *Journal of Child Language* **20:** 61–84

Newell M 1998 Mechanisms and Timing of Mother-to-Child Transmission of HIV-1. *AIDS* **12:** 831–7.

Niccols A, Latchman A 2002 Stability of the Bayley Mental Scale of Infant Development with High Risk Infants. *The British Journal of Developmental Disabilities* **48 (94):** 3 – 13

Nowakowski R 1987 Basic Concepts of CNS Development. *Child Development* **58**: 568 – 595

Nozyce M, Hitteman J, Muenz L, Durako C, Fischer M, Willoughby A 1994 Effect of Perinatally Acquired Human Immunodeficiency Virus Infection on Neurodevelopment in children during the first two years of life. *Pediatrics* **94 (6)**:883 – 91

O'Leary D 1989 Do Cortical Areas Emerge from a Protocortex? *Trends in Neurosciences* **12 (10):** 400–406.

Oliver B, Dale P, Plomin R 2004 Verbal and Non-Verbal Predictors of Early Language Problems: an Analysis of Twins in Early Childhood back to Infancy. *Journal of Child Language* **31:** 609 - 631

Papola P, Alvarez M, Cohen H 1994 Developmental and Service Needs of School-Age Children with Human Immunodeficiency Virus Infection: A Descriptive Study. *Pediatrics* **94(6):**914–918

Parks R, Danoff J 1999 Motor Performance Changes in Children Testing Positive for HIV over 2 Years. *American Journal of Occupational Therapy* **53:** 524 – 528

Paus T, Zijdenbos A, Worsley K, Collins D, Blumenthal J, Evans A 1999 Structural Maturation of Neural Pathways in Children and Adolescents: *In vivo* study. *Science* **283:** 1908–1911.

Pearson D, McGrath N, Nozyce M, Nichols S, Raskino C, Brouwers P, Lifschitz M, Baker C, Englund J 2000 Predicting HIV Disease Progression in Children Using Measures of Neuropsychological And Neurological Functioning. *Pediatrics* **106:** e76 http://www.pediatrics.org/cgi/content/full/106/6/e76 (accessed April 2004)

Peluso R, Haase A, Stowring L, Edwards M, Ventrura P 1985 A Trojan Horse Mechanism for Spread of Visna Virus in Monocytes. *Virology* **147:** 231 – 236

Persaud D, Chandwani S, Rigaud M, Leibovitz E, Kaul A, Lawrence R, Pollack H, Dijohn D, Krasinski K, Borkosky W 1992 Delayed Recognition of Human Immunodeficiency Virus Infection in Preadolescent Children. *Pediatrics* **90:** 688 – 691

Pfefferbaum A, Mathalon D, Sullivan E, Rawles J, Zipursky R, Lim K 1994 A Quantitative Magnetic Resonance Imaging Study of Changes in Brain Morphology from Infancy to Late Adulthood. *Archives of Neurology* **51**: 874–887.

Pizzo P, Eddy J, Falloon J, Balis F, Murphy R, Moss H, Wolters P, Brouwers P, Jarosinski P, Rubin M, Broder S, Yarchoan R, Brunetti A, Maha M, Nusinoff-Lehrman S, Poplack D 1988 Effect of Continuous Intravenous Infusion of Zidovudine (AZT) in Children with Symptomatic HIV Infection. *New England Journal of Medicine* **319 (14)**:889–896

Winter H, Miller T 1994 *Gastrointestinal and Nutritional Problems in Pediatric HIV Disease* in Pediatric AIDS: the challenge of HIV Infection in Infants, Children and adolescents by Pizzo P, Wilfert C (eds). 2nd Edition pg 513 - 515. Williams and Wilkins. Baltimore, Maryland.

Pollack H, Kuckuk A, Cowan L, Hacimamutoglu S, Glasberg H, David R, Krasinski K, Borkowsky W, Oberfield S 1996 Neurodevelopment, Growth and Viral Load in HIV-1 Infected Infants. *Brain, Behaviour and Immunity* **10:** 298 – 312

Powell R, Bishop D 1992 Clumsiness and Perceptual Problems in Children with Specific Language Impairment. *Developmental Medicine and Child Neurology* **34:** 755 – 765

Pratt R 2003 *Retroviruses, the cause of AIDS* in HIV and AIDS: A Foundation for Nursing and Healthcare Practise. 5th Edition pg 25, 27. Arnold, London

Pressman H 1992 Communication Disorders and Dysphagia in Pediatric AIDS. *American Speech-language Hearing Association* **34:** 45 – 47

Price R, Brew B, Sidtis J, Rosenblum M, Scheck A, Cleary P 1988 The Brain in AIDS: Central Nervous System HIV-1 Infection and AIDS Dementia Complex. *Science* **239:** 586 – 592

Pulliam L, Herndier B, Tang N, McGrath M 1991 Human Immunodeficiency Virus-Infected Macrophages Produce Soluble Factors that cause Histological and Neurochemical Alterations in Cultured Human Brains. *Journal of Clinical Investigation* **87:** 503 – 512

Rakic P, Bourgeois J, Eckenhoff M, Zecevic N, Goldman-Rakic P 1986 Concurrent Overproduction of Synapses in Diverse Regions of the Primate Cerebral Cortex. *Science* **232**: 232–235.

Rakic P, Bourgeois J, Goldman-Rakic P 1994 Synaptic Development of the Cerebral Cortex: Implications for Learning, Memory, and Mental Illness. *Progress in Brain Research* **102:** 227–243.

Rapin I, Allen D 1983 Developmental Language Disorders: Nosologic Considerations: In: *Neuropsychology of Language, Reading and Spelling* (Kirk U, Ed) Orlando: Academic Press; 155 – 184

Raskino C, Pearson D, Baker C, Lifschitz M, O'Donnell T, Nozyce M, Brouwers P, McKinney R, Jiminez E, Englund J 1999 Neurologic, Neurocognitive and Brain Growth Outcomes in Human Immuno-Deficiency Virus-Infected Children Receiving Different Nucleoside Antiretroviral Regimens. *Pediatrics* **104:** e32 http://www.pediatrics.org/cgi/content/full/104/3/e32 (Accessed 08/04)

Rausch D, Stover E 2001 Neuroscience Research in AIDS. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **25:** 231 – 257

Reiss A, Abrams M, Singer H, Ross J, Denckla M 1996 Brain Development, Gender and IQ in Children. A Volumetric Imaging Study. *Brain* **119:** 1763–1774.

Resnick L, Veronese F, Schupbach J, Tourtellotte W, Ho D, Muller F, Shashak P, Vogt M, Groopman J, Markham P, Gallo R 1985 Intra-Blood-Brain-Barrier synthesis of HTLV-III-Specific IgG in Patients with Neurologic Symptoms associated with AIDS or AIDS-related complex. *New England Journal of Medicine* **313:** 1498 – 1504

Richter LM, Griesel RD 1988 BSID Norms for Interpreting the Performance of Black South African Infants.Pretoria, University of South Africa.

Rintala P, Pienimaki K, Ahonen T, Cantell M, Kooistra L 1998 The Effects of a Psychomotor Training Programme on Motor Skill Development in Children with Developmental Language Disorders. *Human Movement Science* **17:** 721-37

Robinson R 1991 Causes and Associations of Severe and Persistent Specific Speech and Language Disorders in Children. *Developmental Medicine and Child Neurology* **33:** 943-62.

Rutter M, O'Connor T, and the English and Romanian Adoptees (ERA) study team 2004 Are there Biological Programming Effects for Psychological Development? Findings from a Study of Romanian Adoptees. *Developmental Psychology* **40 (1):** 81 - 94

Ryder R, Nsa W, Hassig S, Behets F, Rayfield M, Ekungola B, Nelson A, Mulenda U, Francis H, Mwandagalirwa K, Davachi F, Rogers M, Nzilambi N, Greenberg A, Mann J, Quinn T, Piot P, Curran J 1989 Perinatal Transmission of the Human Immunodeficiency Virus Type 1 to Infants of Seropositive Women in Zaire. *New England Journal of Medicine* **320 (25):**1637–42.

Santos D, Gabbard C, Goncalves V 2001 Motor Development in the First year: A Comparative Study. *The Journal of Genetic Psychology* **162(2):** 143 – 153

Schmidtmaerova H, Notter H, Nuovo G, Raabe T, Flanagan C, Dubrovsky L, Gendelman H, Cerami A, Bukrinsky M, Sherry B 1996 Human Immunodeficiency Virus Type 1 Infection Alters Chemokine Peptide Expression in Human Monocytes: Implication for Recruitment of Leukocytes in Brain and Lymph Nodes. *Proceedings of the National Academy of Science USA* **93:** 700–704.

Schmitt B, Seeger J, Kreuz W, Erenkel S, Jacobi G 1991 Central Nervous System Involvement of Children with HIV Infection. *Developmental Medicine and Child Neurology* **33:** 535 – 540

Schwartz M, Regan V 1996 Sequencing, Timing and Rate Relationships Between Language and Motor Skill in Children with Receptive Language Delay. *Developmental Neuropsychology* **12(3):**255-70.

Scott G, Hutto C, Makuch R, Mastrucci M, O'Connor T, Mitchell C, Trapido E, Parks W 1989 Survival in Children with Perintallay Acquired Human Immunodeficiency Virus Type 1 Infection. *New England Journal of Medicine* **321 (26):** 1791- 1796

Shaklee H 1979 Bounded Rationality and Cognitive Development: Upper Limits on Growth. *Cognitive Psychology* **11:** 327-345

Sharer L, Epstein L, Cho E, Joshi V, Meyenhofer M, Rankin L, Petito C 1986 Pathologic Features of AIDS Encephalopathy in Children: Evidence of LAV/HTLV-III Infection of Brain. *Human Pathology* **17:** . 271– 284

Siegler R 1976 Three Aspects of Cognitive Development. *Cognitive Psychology* **8:** 481-520

Simpson D, Berger J 1996 Neurologic Manifestations of HIV Infection. *Medical Clinics of North America* **80 (6):** 1363 – 94

Smith R, Malee K, Charurat Magder L, Mellins C, Macmillan C, Hittleman J, Lasky T, Llorente A, Moye J 2000 Timing of Perinatal Human Immunodeficiency Virus type 1 Infection and Rate of Neurodevelopment. *The Pediatric Infectious Disease Journal* **19 (9):** 862-871

Snow C 1972 Mothers' Speech to Children Learning Language. *Child Development* **43**: 549-565

Sowell E, Thompson P, Holmes C, Batth R, Jerrigan T, Toga A 1999 Localising Age-Related Changes in Brain Structure Between Childhood and Adolescence using Statistical Parametric Mapping. *Neuroimage* **9:** 587 – 597

Spector S, Hsia K, Pratt D, Lathey J, McCutchan J, Alcaraz J, Atkinson J, Gulevich S, Wallace M, Grant I 1993 Virologic Markers of Human Immunodeficiency Virus Type 1 in Cerebrospinal Fluid. The HIV Neurobehavioral Research Centre Group. *Journal of Infectious Diseases* **168:** 68 – 74

Spurr G 1983 Nutritional Status and Physical Work Capacity. *Yearbook of Physical Anthropology* 1–35.

Sroufe L, Rutter M 1984 The Domain of Developmental Psychopathology. *Child Development* **55:**17 –29.

Stiles J 2000 Neural Plasticity and Cognitive Development. *Developmental Neuropsychology* **18 (2):** 237 - 272

Stoneburner R, Sato P, Burton A, Mertens T 1994 The Global HIV Pandemic. *Acta Pediatrica Supplementa* **400:** 1 - 4

Takahashi K, Wesselingh S, Griffin D, McArthur J, Johnson R, Glass J 1996 Localisation of HIV-1 in Human Brain using Polymerase Chain Reaction/in situ Hybridization and Immunocytochemistry. *Annals of Neurology* **39:** 705 - 711

Tardieu M, Hery C, Peudenier S, Boespflug O, Montagnier L 1992 Human Immunodeficiency Virus Type-1-infected Monocytic Cells can Destroy Human Neural Cells after Cell-to-cell adhesion. *Annals of Neurology* **32:** 11 – 17

Tardieu M, Mayaux M, Seibel N, Funck-Brentano I, Straub E, Teglas J, Blanche S 1995 Cognitive Assessment of School-age Children Infected with Maternally Transmitted Human Immunodeficiency Virus Type 1. J*ournal of Pediatrics* **126:** 375 – 9

Tardieu M, Le Chenadec M, Persoz A, Meyer L, Blanche S, Mayaux M 2000 HIV-1 related Encephalopathy in Infants Compared With Children and Adults. *Neurology* **54:** 1089 – 1095

Thal D, Bates E, Goodman J, Jahn-Samilo J 1997 Continuity of Language Abilities: an Exploratory Study of Late- and Early-talking Toddlers. *Developmental Neuropsychology* **13 (3):** 239 - 273

Thal D, Reilly J 1997 Origins of Language Disorders. *Developmental Neuropsychology* **13 (3):** 233- 237

Thatcher R, Walker R, Giudice S 1987 Human Cerebral Hemispheres Develop at different Rates and Ages. *Science* **236:** 1110–1113.

Thelen E, Corbetta D, Kamm K, Spencer J, Schneider K, Zernicke R 1993 The Transition to Reaching: Mapping Intention and Intrinsic Dynamics. *Child Development* **64:**1058 - 1098

Thelen E 1995 Motor Development: a New Synthesis, *American Psychologist* **50 (2):**79-91

Thorne C, Newell N 2000 Epidemiology of HIV Infection in the Newborn. *Early Human Development* **58:** 1 - 16

Tomasello M, Stahl D 1995 Sampling Children's Spontaneous Speech: How much is enough? *Cognitive Development:* **10:** 131 - 156

Tornatore C, Chandra R, Berger J, Major E 1994 HIV-1 Infection of Subcortical Astrocytes in the Pediatric Central Nervous System. *Neurology* **44:** 481 – 487

Tovo P-A, de Martino M, Gabiano C, Galli L, Cappello N, Ruga E 1996. Mode of Delivery and Gestational Age influence Perinatal HIV-1 Transmission. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* **11:** 88–94

Udagawa N, Takahashi N, Katagiri T, Tamura T, Wada S, Findlay D, Martin T, Hirota H, Taga T, Kishimoto T, Suda T 1995 Interleukin (IL)-6 Induction of Osteoclast Differentiation Depends on IL-6 Receptors Expressed on Osteoblastic cells but not on Osteoclast Progenitors. *Journal of Experimental Medicine* **182:** 1461–1468.

Udgirkar V, Tullu M, Bavdekar S, Shaharao V, Kamat J, Hira P 2003 Neurological Manifestations of HIV Infection. *Indian Pediatrics* **40**:230-234

Ultmann M, Belman A, Ruff H 1985 Developmental Abnormalities in Infants and Children with Acquired Immune Deficiency Syndrome (AIDS) and AIDS-related Complex. *Developmental Medicine and Child Neurology* **27:** 563 – 571

UNAIDS Update 2004 AIDS Epidemic Update http://www.unaids.org/wad2004/report.html (accessed 08/05)

Van de Perre P, Simonon A, Msellati P, Hitimana D-G, Vaira D, Bazubagira A, van Goethem C, Stevens A, Karita E, Sondag-Thull D, Dabis F, Lepage P 1991 Postnatal Transmission of Human Immunodeficiency Virus Type 1 from Mother to Infant: a Prospective Cohort Study in Kigali, Rwanda. *New England Journal of Medicine* **325 (9):** 593–8.

Van Dyke R, Korber B, Popek E, Macken C, Widmayer A, Bardeguez A, Hanson C, Wiznia A, Luzuriaga K, Viscarello R, Wolinsky S and the Ariel Core Investigators 1999 The Ariel Project: A Prospective Cohort Study of Maternal–Child Transmission of Human Immunodeficiency Virus Type 1 in the era of Maternal Antiretroviral Therapy. *Journal of Infectious Diseases* **179:** 319–28.

Vles J, Kingma H, Caberg H, Daniels H, Casaer P 1989 Posture of Low-risk Pre-term Infants between 32 and 36 weeks postmenstrual age. *Developmental Medicine & Child Neurology* **31:** 191–195.

Von Hofsten C 1989 Motor Development as the Development of Systems. *Developmental Psychology* **25 (6):** 950 - 953

Wallesch C, Kornhuber H, Brunner R, Kunz T, Hollerbach B, Suger G 1983 Lesions of the Basal Ganglia, Thalamus and Deep White Matter: Differential Effects on Language Functions. *Brain and Language* **20:** 286 – 304

Watts C, Eyre JA, Kelly S, Ramesh V. (1992) Development of the Pincer Grasp and its Relationship to the Development of Adult Corticospinal Delays in Man. *Journal of Physiology (London)* 452: 273.

Webb S, Monk C 2001 Mechanisms of Postnatal Neurobiological Development: Implications for Human Development. *Developmental Neuropsychology* **19 (2):** 147 – 171

Webster R, Majnemer A, Platt R, Shevell M 2005 Motor Function at School Age in Children with a Preschool Diagnosis of Developmental Language Impairment. *Journal of Pediatrics* **146:** 80 - 85

Whitall J, Getchell N 1995 From Walking to Running: Applying a Dynamical Systems Approach to the Development of Locomotor Skills. *Child Development* **66:**1541-1553

Wiley C, Schrier R, Nelson J, Lampert P, Oldstone M 1986 Cellular Localization of Human Immunodeficiency Virus Infection within the Brains of Acquired Immune Deficiency Syndrome Patients. *Proceedings of the National Academy of Science U.S.A* **83:**7089 - 7093

Wiley C, Masliah E, Morey M, Lemere C, Deteresa R, Grafe M, Hansen L, Terry R 1991 Neocortical Damage During HIV Infection. *Annals of Neurology* **29:** 651 – 657

Williams K, Corey S, Westmoreland S, Pauley D, Knight H, deBakker C, Alvarez X, Lackner A 2001 Perivascular Macrophages are the Primary Cell Type productively Infected by Simian Immunodeficiency Virus in the Brains of Macaques: Implications for the Neuropathogenesis of AIDS. *Journal of Experimental Medicine* **193 (8):** 905 – 915

Witelson S 1987 Neurobiological Aspects of Language in Children. *Child Development* **58:** 653 - 688

Wiznia A, Lambert G, Pavlakis S 1996 Pediatric HIV Infection. *Medical Clinics of North America* **80 (6):** 1309 - 1336

Wolters P, Brouwers P, Moss H, Pizzo P 1995 Differential Receptive and Expressive Language Functioning of Children with Symptomatic HIV Disease and Relation to CT brain abnormalities. *Pediatrics* **95 (1):** 112-119

Wolters P, Brouwers P, Civitello L, Moss H 1997 Receptive and Expressive Language Function of Children with Symptomatic HIV Infection and Relationship with Disease Parameters: a Longitudinal 24-month Follow-up Study. *AIDS* **11:**1135 – 1144

Working Group of the American Academy of Neurology AIDS Task Force 1991 Nomenclature and Research Case Definition For Neurologic Manifestations of Human Immunodeficiency Virus Type-1 Infection. *Neurology* **41:** 775 – 778

APPENDIX I: Research Proposal

THE EXTENT OF DELAY OF LANGUAGE, MOTOR AND COGNITIVE DEVELOPMENT IN HIV POSITIVE INFANTS

Nicole Baillieu BSc (Physiotherapy)

Supervisors: Joanne Potterton MSc (Physiotherapy),
Lecturer: University of the Witwatersrand
Karen Rothbart MSc (Physiotherapy)

INTRODUCTION AND RATIONALE FOR THE STUDY

In 2001 it was estimated that in South Africa, 4.7 million people were living with Human Immunodeficiency Virus (HIV), of whom 189,000 were babies. Based on extrapolation of the results of this 2002 antenatal survey, the Department of Health estimated that 5.3 million South Africans were HIV positive by the end of 2002. It is estimated that 91,271 babies were infected with HIV during 2002 (250 a day) by mother-to-child transmission. (Department of Health, 2002)

Almost 20 years have elapsed since the original description of the assault of HIV on the central nervous system. (Navia et al, 1986). The nervous system is among the most frequent and serious targets of HIV (Simpson et al, 1996). Involvement of the nervous system in HIV-infected patients can come about as a result of direct HIV action, opportunistic infection caused by the immunodeficiency, or both (Fragoso et al, 1999). The pathogenesis of brain injury in HIV-1 infected patients remains incompletely understood, and is confounded by factors such as timing of infection, variable treatments, and lack of access to brain tissue for evaluation. (Fuller et al, 2004).

The most frequent manifestations of HIV-associated progressive encephalopathy are: cognitive impairment, developmental delays, corticospinal tract lesions, acquired microcephaly, movement disorders, and ataxia. Progressive motor dysfunction is common, and often results in a loss of milestones (Belman 1992).

It has been found that HIV-positive children have significantly greater neurological dysfunction in eight domains (activity, language, cranial nerve, fine motor, gross motor, cerebellar, sensory and primitive reflexes) than their HIV negative counterparts (Belman et al, 1996). Chase et al (1995) and Pearson et al (2000) found that a lower CD4 count, and viral RNA load were associated with severity of disability, and that slower attainment in milestones in both motor and mental development is associated with vertically transmitted HIV infection in infants and children younger than 30 months.

Significant delays in mental and motor development of HIV-infected infants have been found over the first two years of life (Gay et al, 1995; Smith et al, 2000). Because neural development does not cease after 2 years of age, further delays can be expected to evolve over time. In particular, myelination of the frontal and parietal regions of the brain continues throughout childhood and even into early adulthood. These regions are responsible for higher cortical functions, and destruction of the

myelination processes of these areas by HIV will cause significant delays in higher functioning.

The neuropathogenesis of language problems in HIV is unknown (Wolters et al, 1995). They found that children with HIV had language problems, with expressive language significantly lower than receptive language, and that damage to the basal ganglia may be associated with language dysfunction, particularly in the expressive modalities. They also found that verbal expression was highly correlated to motor function, thus motor deficits, including those in muscle coordination and motor programming may affect oral-motor skills and contribute to feeding problems, articulation errors and speech difficulties (Wolters et al, 1997).

Identification of HIV-1 infected infants at greatest risk for disease-related mortality is crucial to their survival, making delays in performance on early neurodevelopmental measures plausible predictors of mortality (Llorente et al, 2003). Results of their longitudinal study indicate that HIV-infected infants, with lower Mental Developmental Indices or Psychomotor Developmental Indices on neurodevelopmental Bayley Scales of Infant Development II (BSID II) scores at a baseline of 4 months of age, are at a greater risk of mortality than infants with higher scores.

The Bayley scales of Infant Development were published in 1969, and the 2nd edition in 1993, when the age range was extended down to 1 month of age, and up to 42 months. One of the primary uses of the Bayley scales is to examine development of infants who are suspected to be delayed (Black and Matula, 2000). The Bayley Scale has been found to be sensitive to developmental changes in the first two years of life of infants who are medically fragile (Niccols et al, 2002). Their findings support the clinical validity of the scale, which can be applied to those with HIV.

There has been very little research conducted in Africa regarding the extent of delay of language, motor, cognitive and social development in HIV positive infants. Overall development of HIV infected infants has been found to be delayed, but there is a need for the assessment of the above-mentioned skills to determine any emerging trends, to facilitate a better understanding of where the biggest developmental problems lie. Treatment regimens could then be formulated to target these areas specifically, in order to prevent delay and further deterioration.

GENERAL AIM OF THE STUDY:

The main aim of this study is to determine the extent of delay in acquisition of language, cognitive, social and motor skills of HIV positive children.

STUDY OBJECTIVES:

-to assess the development of language, cognitive and motor skills in HIV positive infants.
-to determine the emerging trends in neurodevelopmental delay in HIV infected children
-to determine the skill that is most adversely affected by HIV infection
-to attempt to determine the age at which developmental problems begin to manifest

HYPOTHESIS THAT WILL BE TESTED:

Null hypothesis: children will reach developmental milestones on time.
Ho: mean development=0 (null hypothesis is that mean development is delayed by 0 months)

The alternate hypothesis is that they will be delayed.
H1: mean development <-1 (alternate hypothesis, mean development is delayed by more than a month)

RESEARCH DESIGN:

The study will be cross-sectional

SUBJECTS:

Population
HIV positive children between the ages of 18 months and 30 months attending the Harriet Shezi HIV clinic at Chris Hani Baragwanath Hospital.

Inclusion Criteria:
-Children with vertically transmitted HIV
-18 – 30 months of age
-children with a primary caregiver
-Antiretroviral naïve children

Exclusion criteria:
-children with clinically apparent abnormalities
-prematurity (<37 weeks)
-children resident in institutions

Sample size determination

A sample of 40 HIV positive children aged 18 – 30 months will have at least 90% power to detect an under-performance of 1 month when a standard deviation of 2 months is assumed (i.e.12/6 = 2 where 12 months is the maximum underperformance) for their cognitive, language and motor development, when using a one-sided single sample t-test at the 0.05 level of significance.

METHODS:

Measurement instruments
Bayley Scales of Infant Development II will be used to determine performance in each section of the child's age group. These results will then be transferred to the facet scoring section. The facet scores analyse in greater detail, with respect to Cognitive, language, social and motor development.

Reliability of the study will be ensured through consistent use of the BSID II, and researchers will be trained in administration of this test. The validity of the study can be measured in the relevance of the BSID II, which is internally and externally valid.

Baseline BSID II assessments of HIV infected children currently enrolled in a longitudinal study of neurodevelopmental delay will be analysed to determine which facets of development are most delayed.

PROCEDURE:

Recruitment

The subjects who will take part in the study will be those children meeting the inclusion criteria, and who fall into the correct age group, and will be taken from the Harriet Shezi HIV clinic at Chris Hani Baragwanath Hospital in Soweto. They will form part of a sample of convenience taken from the clinic. A letter stating the purpose of the study, and asking the cargiver's permission to look at records will be given.

Data collection:

This will take place on Mondays and Fridays at the HIV clinic, and ideally, would hope to recruit 4 children a week. This would mean 10 weeks of data collection to make up the sample size of 40. The mental and motor indices of the BSID II will be administered to each child who is recruited, and will take approximately 1 hour. These results will be transferred to the facet scoring system of the BSID II, which analyse language, motor and cognitive skills in greater detail.

DATA ANALYSIS:

Statistical tests:
The primary hypothesis will be tested using a one-sided, one sample t-test at the 0.05 level of significance where:
Ho: mean development=0 (null hypothesis is that mean development is delayed by 0 months)
H1: mean development <-1 (alternate hypothesis, mean development is delayed by more than a month)
With mean development 0 meaning at least age group norm, and –1 denotes 1 month delayed.

Children will be considered to be delayed if milestones are delayed by1 month or more. The distribution of delay will be analysed using the facet scores of the BSID II.

ETHICS:

Ethical clearance has been obtained. (M03-05-68)

CONCLUSION

HIV is a serious problem in children in South Africa, and has been shown to cause developmental delay. This study aims to analyse the extent and distribution of the delay.

APPENDIX II: Ethical Clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL)
Ref: R14/49 Potterton

CLEARANCE CERTIFICATE PROTOCOL NUMBER M03-05-68

PROJECT A Longitudinal Study of Neurodevelopmental Delay in HIV Infected Children

INVESTIGATORS Ms JL Potterton

DEPARTMENT School of Therapeutic Sci, Wits Medical School.

DATE CONSIDERED 03-05-30

DECISION OF THE COMMITTEE Approved unconditionally

Unless otherwise specified the ethical clearance is valid for 5 years but may be renewed upon application
This ethical clearance will expire on 1 January 2008.

DATE 03-07-25 CHAIRMAN M Makhaetane 25/07/03 (Professor P E Cleaton-Jones)

* Guidelines for written "informed consent" attached where applicable.

c c Supervisor: Mrs A Stewart
Dept of School of Therapeutic Sci· Wits Medical School
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DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10001, 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 form. I/we agree to inform the Committee once the study is completed.

DATE .....SIGNATURE .....

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX III: Informed Consent

APPENDIX III

INFORMATION SHEET

Dear parent/caregiver
Good morning and thank you for taking the time to read this information. My name is Joanne Potterton and I am a physiotherapist. I am busy doing some research to find out more about the development of children with HIV and the stress of the person caring for the child with HIV. If your child meets the criteria for the study then I would like to ask you whether you and your child would join my study. I am doing this study to try to find the best way to treat children who have got HIV and to see whether we can do anything to make your stress about caring for your child less.

I will do an assessment of what your child can do every 6 months from now until your child is 3 and a half years old. This will tell me how well your child is developing. I will also ask you to fill in a questionnaire to find out more about the stress you feel as a parent/caregiver. I will do this at your normal clinic visits. The assessment of your child will take about one hour and it will take you about 15 minutes to fill in the questionnaire. I will also look in your child's file to get the results of their last blood tests.

I will divide the children into 2 groups. Both groups will come to see me every 3 months. I will pay transport for the extra visits. Group one will have their height, weight and their heads measured. Group 2 will also have their height, weight and their heads measured. their parent/caregiver will also be given a programme to do with their child at home to stimulate them. I am doing this to try and find out the best way to care for children who have got HIV.

Nothing that I do will hurt your child and all your information will be kept private. If you do not want to be part of this study you do not have to, and you will still get all the other services at the clinic. If you do join the study, you may change your mind and may take your child out of the study at any time, without any prejudice being held against you.

If you agree for you and your child to be in this study please sign the form below.

Thank you for your help.

Joanne Potterton.

.....

I.....agree that I and my child.....will join this study. I agree that Joanne Potterton may look at my child's file to get their blood results. I understand that we may withdraw from the study at any time.

Signed.....
Date.....
Researcher.....

IKHASI ELINIKEZA ULWAZI

Mzali/mbheki wengane

Ngiyakubingelela futhi ngiyabonga ukuthi uzinike ithuba lokufunda lolu lwazi. Igama lami nguJoanne Potterton kanti ngingumluli wamathambo, phecelezi i-*physiotherapist*. Ngimatasatasa nocwaningo ngoba ngifuna ukuthola ulwazi oluthe xaxa ngokukhula kwezingane ezinegciwane leSandulela-Ngculazi (I-HIV) kanye nokukhathazeka umuntu onakekela ingane eneSandulela-Ngculazi aba nakho. Uma ingane yakho ihlangabezana nezidingo zocwaningo ngizocela ukwazi ukuthi wena nengane yakho ningathanda yini ukungena ocwaningweni lwami. Ngenza lolu cwaningo ngoba ngizama ukuthola indlela engcono yokwelapha izingane ezineSandulela-Ngculazi nokubona ukuthi kukhona yini esingakwenza ukunciphisa ukukhathazeka onakho ngokunakekela ingane yakho.

Ngizohlola ukuthi yini ingane yakho esikwazi ukuyenza njalo emva kwezinyanga eziyisithupha kusukela manje ize ibe neminyaka emithathu nohhafu ingane yakho. Lokhu kuzongibonisa ukuthi ingane yakho ikhula kahle kangakanani. Ngizobuye ngikucele futhi ukuba uphendule imibuzo ezobe imayelana nokukhathazeka onakho njengomzali/umbheki wengane. Ukuhlolwa kwengane yakho kuyothatha cishe ihora elilodwa kanti ukuphendula imibuzo kuyokuthatha cishe imizuzu eyi-15. Ngiyobuye ngibheke nasefayeleni lengane yakho ukuze ngibone imiphumela yokuhlolwa kwegazi layo kwakamuva.

Ngizozahlukanisa zibe ngamaqembu amabili izingane. Amaqembu womabili azoza azongibona njalo emva kwezinyanga ezintathu. Ngizoyikhokha imali yokugibela uma kudingeka zize ngezikhathi ezevile. Iqembu lokuqala lizokalwa ubude, isisindo somzimba bese kukalwa namakhanda abo. Iqembu lesibili nalo lizokalwa ubude, isisindo somzimba bese bekalwa namakhanda abo, kanti nabazali/ababheki babo bayonikwa uhlelo ekuzodingeka ukuba balulandele nezingane zabo emakhaya ukuze bazikhuthaze. Lokhu ngikwenza ngoba ngifuna ukuthola indlela engcono yokunakekela izingane ezineSandulela-Ngculazi.

Akukho kwengizokwenza okungalimaza ingane yakho futhi yonke into izogcinwa iyimfihlo. Uma ungathandi ukungena kulolu cwaningo awuphoqelekile, futhi usazoqhubeka nokuthola ezinye izinsizakalo emtholampilo. Uma ungena ocwaningweni, ungaguqula umqondo wakho uyikhiphe ingane yakho ocwaningweni noma ingasiphi isikhathi, ngale kokubandlululwa ngandlela thize.

Uma uvuma ukuba wena nengane yakho ningenele lolu cwaningo, ngicela usayine ifomu elilapha ngezansi.

Ngiyabonga ngosizo lwenu.

NguJoanne Potterton

Mina…….. ngiyavuma ukuthi mina nengane yami u…….. sisongena ocwaningweni. Ngiyavuma ukuba uJoanne Potterton angabheka ifayela lengane yami ukuze athole imiphumela yegazi layo. Ngiyaqonda ukuthi singaphuma ocwaningweni noma nini.

Isignesha ……
Usuku……
Umcwaningi……

PAMPITSHANA YA TSEBISO

Motswadi/mohlokomedi ya ratehang
Ke a o dumedisa ebile ke a o leboha ka ho ipha nako ya ho bala tsebiso ena. Lebitso la ka ke Joanne Potterton, mme ke mosidilli wa mesifa. Ke tshwarahane le ho etsa diphuputso tse itseng ho fumana ho eketsehileng mabapi le kgolo ya bana ba nang le HIV hammoho le kgatello moyeng ho motho ya hlokomelang ngwana ya nang le HIV. Haeba ngwana wa hao a phethahatsa ditlhoko tsa dipatlisiso tsena, teng he, ke ne nka rata ho le kopa hore na ebe wena le ngwana wa hao le ka kenela dipatlisiso tsa ka na. Ke etsa dipatlisiso tsena ho leka ho fumana tsela e molemo ka ho fetisisa ya ho tshwara bana ba nang le HIV le ho bona hore na ebe ho na le seo re ka se etsang ho fokotsa kgatello ya hao moyeng mabapi le ho hlokomela ngwana wa hao.

Ke tla etsa tshekatsheko ya hore ngwana wa hao a ka etsa eng dikgwedi tse ding le tse ding tse 6 ho tloha hona jwale ho fihlella ngwana wa hao a ba le dilemo tse 3 le halofo. Sena se tla mpolella hore ngwana wa hao o hola hantle hakae. Ke tla boela ke o kope ho tlatsa pampitshanadipotso ho fumantsha ho eketsehileng ka kgatello ya moyeng eo o e utlwang jwalo ka motswadi/mohlokomedi. Ke tla etsa sena diketelong tsa hao tse tlwaelehileng tsa tleleniking. Tshekatsheko ya ngwana wa hao e tla nka nako e ka etsang hora e le nngwe mme ho tla o nka nako e ka bang metsotso e 15 ho tlatsa pampitshanadipotso. Ke tla boela ke tadime faeleng ya ngwana wa hao ho fumana sephetho sa diteko tsa hae tsa ho qetela tsa madi.

Ke tla arola bana ho ba dihlopha tse pedi. Dihlopha ka bobedi di tla tla ho mpona dikgwedi tse ding le tse ding tse 3. Ke tla lefella teranseporoto bakeng sa diketelo tsa tlatsetso. Sehlopha sa pele se tla lekangwa bolelele, boima ba mmele le dihlooho. Sehlopha sa 2 le sona se tla lekangwa bolelele, boima ba mmele le dihlooho, mme batswadi/bahlokomedi ba bona le bona ba tla nehwa lenaneo leo ba tlang ho le etsa le bana ba bona malapeng ho ba tsosollosa. Ke etsa sena ho leka ho fumantsha tsela e molemo ka ho fetisisa ya ho hlokomela bana ba nang le HIV.

Ha ho letho leo ke le etsang le tlang ho utlwisa ngwana wa hao bohloko mme tsebiso ya hao kaofela e tla bolokwa e le lekunutu. Haeba ha o batle ho ba karolo ya dipatlisiso tsena, ha o a qobellwa, mme o tla nne o fumane ditshebeletso tse ding tsohle tleleniking. Ha ho ka etsahala o ikamahanye le dipatlisiso tsena, o ka nna wa fetola mohopolo wa hao mme o ka ntsha ngwana wa hao dipatlisisong nako efe kapa efe, ntle le hore o tadingwe ka mahlo a mabe.

Haeba o dumela hore wena le ngwana wa hao le kenele dipatlisiso tsena, o kopjwa ho saena foromo e ka tlase ka mona.

Joanne Potterton.

……

Nna, …… ke a dumela hore ngwana wa ka …… o tla kenela dipatlisiso tsena. Ke dumela hore Joanne Potterton a ka nna a tadima faele ya ngwana wa ka ho fumana sephetho sa hae sa teko ya madi. Ke utlwisisa hore re ka ikhula dipatlisisong tsena nako efe kapa efe.

E saennwe:……
Letsatsi:……
Mofuputsi:……

APPENDIX IV: Facet Scores

Dev. Age	Cognitive Mental	Cognitive Motor	Language Mental	Language Motor	Social Mental	Social Motor	Motor Mental	Motor Motor	Dev. Age
12	155, 156, 157, 158, 159, 160 161, 162, 163, 164, 165, 166, 167 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178	104, 105, 111	155, 156, 159 164, 166, 167, 172, 177		158	98	165, 169	98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111	42
11	154		154						41
10								97	40
9			153						39
8	152		148, 152						38
7									37
6	151	96						96	36
5	150		149						35
4	146, 147, 150		146						34
3								95	33
2	145	92						92, 93, 94	32
1									31
0	141, 143		141			91		91	30
9									29
8									28
7	144	88						88	27
6	137, 138, 139		140				139	86, 89, 90	26
5								87	25
4	135		136				135		24
3								83, 84, 85	23
2	130		134				130		22
1	132		129, 133				132	80, 82	21
0	128		126, 127						20
9	117, 123, 124, 125, 131		121, 124, 131				112, 123	79, 81	19
8	119, 120, 122		117				119, 120		18
7	115, 116, 118		114, 118, 122				115, 116	75	17
6			113					74, 78	16
5		76	111					76, 77	15
4	99		99, 106, 108, 109, 110					73	14
3	90, 102, 103, 104, 105		107				60, 103	71, 72	13
2	87, 93, 96, 97, 98		100, 101				87, 93, 97, 98	65, 67, 68, 69, 70	12
1	91, 92, 95		94				91, 92	66	11
0	88, 89						89	63, 64	10
9	82, 83, 84, 85, 86		79		53		82	58, 59, 61, 62	9
8	73, 75, 77, 79, 80		71, 78, 81				73, 75, 77, 79	60	8
7	74, 76		70				74	49, 50, 51, 52, 53, 54, 55, 56, 57	7
6	62, 64, 65, 66, 67, 69		68		64		62, 65, 66, 67	42, 43, 44, 45, 46, 47, 48	6
5	57, 59, 60, 61, 68, 69, 60		63, 67				54, 59, 60, 68, 69	34, 36, 37, 38, 39, 40, 41	5
4	43, 44, 45, 46, 48 49, 50, 51, 52, 55	32			49, 50		43, 44, 45, 48, 52, 55	28, 30, 31, 32, 33, 35	4
3	29, 33, 35, 36, 37, 38, 39, 40, 41, 42, 47				47		38, 39, 40, 42	19, 21, 22, 23, 24, 25, 26, 27, 29	3
2	17, 18, 20, 23, 24, 25, 26, 27, 28, 30, 32		21, 22, 31, 33		19, 20, 33		30	7, 11, 12, 13, 15, 16, 17, 18, 20	2
1	3, 5, 6, 7, 8, 9, 10, 14, 15, 19		3, 10		1, 2, 3, 5, 7, 12, 13, 14			1, 2, 3, 4, 5, 6, 8, 9, 10, 14	1

APPENDIX V: Item Classification: Mental and Motor Scales

MENTAL SCALE

Item Number	Skill
	Acquisition of cube(s)
42	Reaches for cube
44	Uses Eye-Hand Coordination in Reaching
45	Picks up cube
53	Reaches for second cube
57	Picks up cube deftly
58	Retains two cubes for 3 seconds
65	Retains two of three cubes for 3 seconds
75	Attempts to secure three cubes
	Auditory Perception
7	Habituates to rattle
8	Discriminates between bell and rattle
9	Searches with eyes for sound
23	Glances from bell to rattle
30	Turns head to sound
	Barrier
88	Retrieves toy (clear box I)
105	Retrieves toy (clear box II)
	Bell
59	Manipulates bell, showing interest in detail
66	Rings bell purposely
	Blue Board
90	Places one piece (Blue Board)
112	Places four pieces in 150 seconds (Blue Board)
130	Completes Blue Board in 75 seconds
165	Completes Blue Board in 30 seconds
	Colour Learning
128	Matches three colours
137	Matches four colours
155	Names Four colours
	Construction with Blocks
97	Builds Tower of Two Cubes
123	Builds Tower of Six Cubes
135	Builds Tower of Eight Cubes
138	Builds Train of Cubes
149	Builds Bridge
150	Builds Wall
173	Builds T
176	Builds Steps
	Counting
146	Counts (Number Names)
157	Counts (One-to-one Correspondance)
159	Counts (Stable Number Order)
164	Counts (Cardinality)
175	Counts (Order Variance)
	Cube in Cup
74	Puts one cube in cup
86	Puts three cubes in cup

95	Puts nine cubes in cup
	Interpersonal
1	Regards person momentarily
14	Smiles when examiner speaks
19	Smiles when examiner smiles
21	Vocalises when examiner speaks
33	Visually recognises caregiver
13	Reacts to disappearance of face
20	
	Expressive language
63	Imitates vocalisation
94	Imitates word
100	Uses two different words appropriately
106	Uses word(s) to make wants known
111	Combines word and gesture
113	Says eight different words
114	Uses a two-word utterance
117	Imitates a two-word sentence
127	Uses a three-word sentence
129	Makes a contingent utterance
136	Poses question(s)
148	Uses past tense
	Manipulative Behaviour-ring
37	Manipulates ring
38	Reaches for suspended ring
39	Grasps suspended ring
40	Carries ring to mouth
	Mirror
41	Approaches mirror image
49	Smiles at mirror image
50	Responds playfully to mirror image
	Naming objects
110	Names one object
126	Names three objects
	Naming and pointing to pictures
99	Points to two pictures
109	Names one picture
122	Points to five pictures
133	Names five pictures
	Object permanence-cup
55	Lifts inverted cup
67	Lifts cup by handle
84	Finds one object
96	Finds toy under reversed cups
102	Retrieves toy (visible displacements)
	Object permanence-box
72	Looks for contents of box
80	Removes lid from box
	Pegboard
79	Fingers holes in pegboard
87	Places one peg repeatedly

98	Places pegs in 70 seconds
119	Places pegs in 25 seconds
	Pink board
93	Places circle piece (pink board)
115	Completes pink board
120	Completes reversed pink board
	Pre-reading skills
69	Looks at pictures in book
73	Turns pages of book
131	Attends to story
142	Produces multiple-word utterances in response to picture book
	Pre-writing behaviour
60	Attends to scribbling
91	Scribbles spontaneously
103	Imitates crayon stroke
116	Differentiates scribble from stroke
139	Imitates vertical and horizontal strokes
	Quantitative Reasoning
141	Understands concept of one
156	Understands concept of more
	Pattern discrimination
162	Sorts pegs by colour
168	Completes patterns
	Receptive language
70	Listens selectively to two familiar words
81	Responds to spoken request
101	Shows shoe, other clothing or object
107	Follows directions (doll)
108	Points to three of doll's body parts
	Responds to being lifted
2	Quiets when picked up
11	Becomes excited in anticipation
12	Adjusts in anticipation of being lifted
	Ring/string behaviour
48	Plays with string
62	Pulls string adaptively to secure ring
82	Suspends ring by string
	Spatial problem-solving and planning
169	Finds most direct route on map
170	Finds alternate route on map
171	Picks up two friends on map
	Understands another's perspective
158	Understands another's perspective I
172	Understands another's perspective II
	Understands prepositions
140	Understands two prepositions
153	Understands four prepositions
	Visual discrimination

144	Discriminates pictures I
151	Discriminates pictures II
	Visual Learning
26	Habituates to visual stimulus
27	Discriminates novel visual pattern
28	Displays visual preference
29	Prefers novelty
	Visual tracking
6	Regards ring for 3 seconds
15	Eyes follow ring (horizontal excursion)
16	Eyes follow ring (vertical excursion)
17	Eyes follow ring (circular path)
18	Eyes follow ring (arc)
24	Head follows ring
	Vocalisation
10	Vocalises four times
22	Vocalises two different vowel sounds
31	Vocalises attitude
61	Vocalises three different vowel sounds
71	Repeats vowel-consonant combination
76	Jabbers expressively
78	Vocalises four different vowel-consonant combinations
	Ungrouped
3	Responds to voice
4	Inspects surroundings
5	Eyes follow moving person
25	Regards cube for 3 seconds
32	Eyes follow ball rolling across table
34	Inspects own hand(s)
35	Plays with rattle
36	Eyes follow rod
43	Reaches persistently
46	Fixates on disappearance of ball for 2 seconds
47	Displays awareness of novel surroundings
51	Regards pellet
52	Bangs in play
54	Transfers object from hand to hand
56	Looks for fallen spoon
64	Cooperates in game
68	Uses gesture to make wants known
77	Pushes car
83	Pats toy in imitation
85	Removes pellet from bottle
89	Puts six beads in a box
92	Closes round container
104	Uses rod to attain toy
118	Identifies objects in photograph
121	Uses pronoun(s)
124	Discriminates book, cube and key
125	Matches pictures
132	Places beads in a tube in 120 seconds
134	Displays verbal comprehension
143	Recalls geometric forms
145	Compares sizes
147	Compares masses
152	Repeats three number sentences

154	Identifies gender
160	Remembers sequence
161	Discriminates patterns
163	Discriminates sizes
166	Identifies three incomplete pictures
167	Relates temporal sequence of events
174	Classifies objects
177	Comprehends congruent and incongruent tasks
178	Solves bridge-building problem

MOTOR SCALE

Item Number	Skill
	Balance
72	Stands on right foot with help
73	Stands on left foot with help
82	Stands alone on right foot
83	Stands alone on left foot
86	Swings leg to kick ball
102	Stands alone on left foot for 4 seconds
103	Stands alone on right foot for 4 seconds
107	Hops twice on one foot
110	Hops five feet
	Drawing
96	Copies circle
104	Copies plus sign
105	Traces designs
111	Copies square
	Gaining vertical position
42	Attempts to raise self to sit
47	Raises self to sitting position
52	Raises self to standing position
59	Stands up I
68	Stands up II
94	Stands up III
	Grasping cube
31	Uses partial thumb opposition to grasp cube
37	Uses pads of fingertips to grasp cube
	Grasping pellet
32	Attempts to secure pellet
41	Uses whole hand to grasp pellet
49	Uses partial thumb opposition to grasp pellet
56	Uses pads of fingertips to grasp pellet
76	Places 10 pellets in bottle in 60 seconds
	Grasping rod
29	Uses whole hand to grasp rod
57	Uses partial thumb opposition to grasp rod
	Hands posture
6	Hands are fisted
23	Keeps hands open
	Head Control-prone
20	Maintains head at 45º and lowers with control
24	Maintains head at 90º and lowers with control

Head control – upright

3 Lifts head when held at shoulder
4 Holds head erect for 3 seconds (vertical position)
5 Adjusts posture when held at shoulder
7 Holds head erect & steady for 15 seconds
15 Holds head steady while being moved
19 Balances head

Head control – suspension

8 Lifts head (dorsal suspension)
14 Adjusts head to ventral suspension

Imitative behaviour

91 Imitates hand movements
98 Imitates postures

Jumping

78 Jumps off floor (both feet)
81 Jumps from bottom step
87 Jumps distance of 4 inches
106 Jumps over rope
109 Jumps distance of 24 inches

Lowers self

55 Sits down
65 Squats briefly

Pencil grasp and writing activities

58 Grasps pencil at farthest end
70 Grasps pencil at middle
74 Uses pad of fingertips to grasp pencil
75 Uses hand to hold paper pencil
90 Grasps pencil at nearest end
93 Manipulates pencil in hand

Pre-ambulatory skills

10 Makes crawling movements
18 Elevates self by arms
25 Shifts weight on arms
43 Moves forward, using pre-walking methods

Sitting

21 Sits with support
22 Sits with slight support for 10 seconds
28 Sits alone momentarily
34 Sits alone for 30 seconds
35 Sits alone while playing with a toy
36 Sits alone steadily
50 Rotates trunk while sitting alone
51 Moves from sitting to creeping position

Stairs

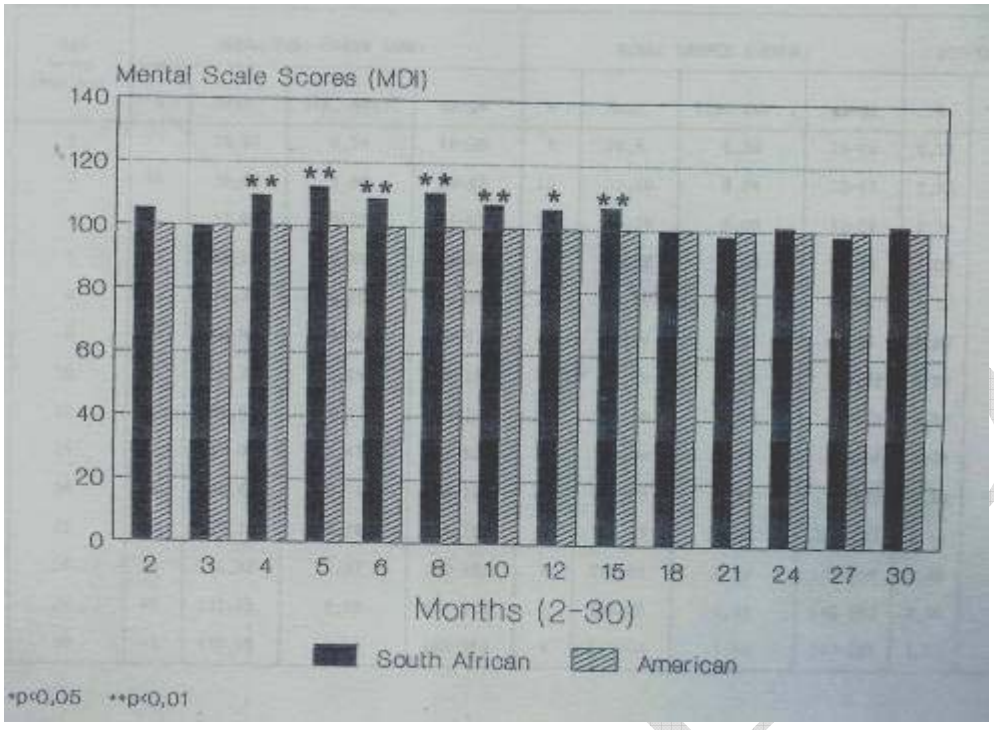
66 Walks up stairs with help
69 Walks down stairs with help
79 Walks up stairs alone, placing both feet on each step
80 Walks down stairs alone, placing both feet on each step
95 Walks up stairs, alternating feet
108 Walks down stairs, alternating feet

Rolling

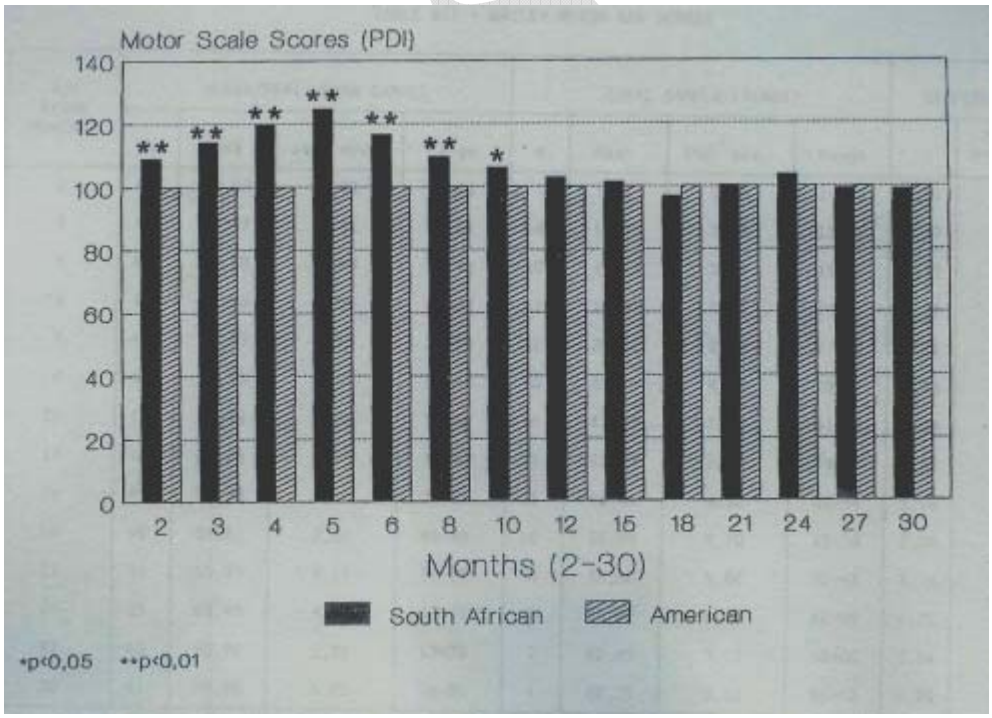
11	Turns from side to back
26	Turns from back to side
38	Turns from back to stomach
	Uses person to raise self
33	Pulls to sitting position
45	Pulls to standing position
	Walking
40	Makes early stepping movements
44	Supports weight momentarily
46	Shifts weight while standing
53	Attempts to walk
54	Walks sideways while holding onto furniture
60	Walks with help
61	Stands alone
62	Walks alone
63	Walks alone with good coordination
67	Walks backward
71	Walks sideways
77	Runs with coordination
84	Walks forward on line
85	Walks backward close to line
89	Walks on tiptoe for 4 steps
90	Walks on tiptoe for 9 feet
	Ungrouped
1	Thrusts arms in play
2	Thrusts legs in play
9	Holds legs up for 2 seconds
12	Attempts to bring hands to mouth
13	Retains ring
16	Displays symmetric movements
17	Holds head in midline position
27	Rotates wrist
30	Reaches unilaterally
39	Grasps foot with hands
48	Brings spoon or cubes to midline
64	Throws ball
88	Laces three beads
92	Tactilely discriminates shapes
97	Uses hand-eye coordination in tossing ring
100	Stops from full run
101	Buttons one button

APPENDIX VI: Differences in Scores between South African and American Infants on the BSID

Mental Scale



Motor Scale



APPENDIX VII: Demographic Questionnaire

DEMOGRAPHIC QUESTIONNAIRE

ENGLISH

Caregiver's name……
Relationship to child……...
Level of Education ……..
Number of people in household: Adults……Children…….....
Address.……..……..
Telephone Number.…….
Approximate monthly income for household…….

ZULU

IMIBIZO NGESIMO SEMPILO NENHLALO

Igama lombheki wengane……
Ubuhlobo nengane……...
Izinga lemfundo……
Inani labantu abahlala endlini: Abadala……Izingane……
Ikheli…….
Inombolo yocingo……
Isilinganiso semali engena ekhaya ngenyanga…….

SOTHO

PAMPITSHANADIPOTSO YA HO PHATLALLA HA BATHO HO YA KA DIBAKA

Lebitso la mohlokomedi……..
Kamano le ngwana……..
Maemo a thuto…….
Palo ya batho ka lapeng: Batho ba baholo……bana…….
Aterese…….
Nomoro ya mohala……..
Kakanyo ya moputso wa lapeng wa kgwedi le kgwedi……...

APPENDIX VIII: Calculation of Developmental Age from Raw Scores obtained on the Mental and Motor Scales

EXTRAPOLATED SCORES FOR MDI OR PDI <50		
Mental Scale Raw Score	**Estimated Developmental Age (in months)**	**Motor Scale Raw Score**
0 – 13	<1	0 - 10
14 - 21	1	11 - 14
22 - 31	2	15 - 21
32 - 40	3	22 - 27
41 – 51	4	28 - 32
52 – 60	5	33 - 37
61 - 65	6	38 - 43
66 - 70	7	44 - 50
71 - 74	8	51 - 55
75 – 77	9	56
78 – 80	10	57 - 60
81 – 86	11	61 - 63
87 – 90	12	64 - 66
91 – 93	13	67
94 – 97	14	68 - 69
98 – 101	15	70-71
102 – 106	16	72-73
107 – 111	17	74-75
112 – 115	18	76
116 – 119	19	77
120 – 122	20	78
123 – 125	21	79-80
126 – 128	22	81-82
129 – 131	23	83
132 – 134	24	84-85
135 – 137	25	86-87
138 – 140	26	88-89
141 – 143	27	90-91
	28	92
144 – 145	29	93
146 – 147	30	94
148	31	95
149 – 150	32	96
151	33	97
152	34	98
153 – 154	35	99
155 – 157	36	100
158 – 162	37 - 39	101-103
163 – 165	40 -42	104-105
166 - 178	>42	106-111

APPENDIX IX: Extrapolated Scores for MDI or PDI < 50

Table 4.5 Extrapolated Raw Scores for the MDI and PDI

Extrapolated Raw Scores for the MDI

	Age in Months															
MDI	2	3	4	5	6	8	10	12	15	18	21	24	27	30	36	42
50	3				38	47	55		74		99	108	117		130	140
49		8	19	30				65	73	87				122		
48	2				37	46					98	107	116		129	139
47		7	18	29			54	64	72	86				121		
46	1				36	45					97	106	115		128	138
45		6	17	28			53	63	71	85				120		
44					35	44					96	105	114		127	137
43		5	16	27			52	62	70	84				119		
42					34	43					95	104	113		126	136
41		4	15	26			51	61	69	83				118		
40					33	42					94	103	112		125	135
39		3	14	25			50	60	68	82				117		
38					32	41					93	102	111		124	134
37		2	13	24			49		67	81				116		
36					31	40		59			92	101	110		123	133
35		1	12	23			48		66	80				115		
34					30	39		58			91	100	109		122	132
33			11	22			47		65	79				114		
32					29	38		57			90	99	108		121	131
31			10	21					64	78				113		
30					28	37	46	56			89	98	107		120	130

Extrapolated Raw Scores for the PDI

	Age in Months															
PDI	2	3	4	5	6	8	10	12	15	18	21	24	27	30	36	4
50																
49		8			23			52	57		66	71	77		84	
48				17												9
47			11			35	41			62				80		
46		7			22			51							83	
45				16					56		65	70	76			
44			10			34	40									9
43		6			21					61				79	82	
42			9	15				50			64	69				
41						33	39		55				75			9
40		5			20										81	
39				14						60				78		
38			8			32	38	49				68				
37		4			19				54		63		74		80	
36				13												8
35			-			31	37			59				77		
34		3			18			48				67			79	
33			6	12			36		53		62		73			
32						30										8
31		2			17					58				76	78	
30			5	11		29	35	47				66				